



The International Symposium on
Ocular Pharmacology and Therapeutics

www.isopt.net

10th ISOPT *Clinical*

March 7-10, 2013, Paris, France

Program & Abstracts



ISOPT is Celebrating its 10th Anniversary



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Dear Colleague,

ISOPT is Celebrating its 10th Anniversary!

Over the years ISOPT has become a place for formal updates of medical ophthalmology and drug utilization combined with informal meetings of clinicians and drug developers.

ISOPT's vision is to increase knowledge and awareness of drug usage in ophthalmology, reflecting innovations and their utilization in practice. ISOPT's vision will be reflected in the following missions:

- Share treatment algorithms in major ophthalmic indications.
- Implement data from clinical studies for daily practice
- Facilitate innovation – connecting innovators with practitioners

ISOPT offers a relevant and updated scientific program in a relaxed atmosphere leading to direct interactions of its delegates.

We welcome you in Paris, and invite you to share experiences and insights, whether your field of interest is in retinal diseases, inflammation, cornea and external diseases, glaucoma or basic science.

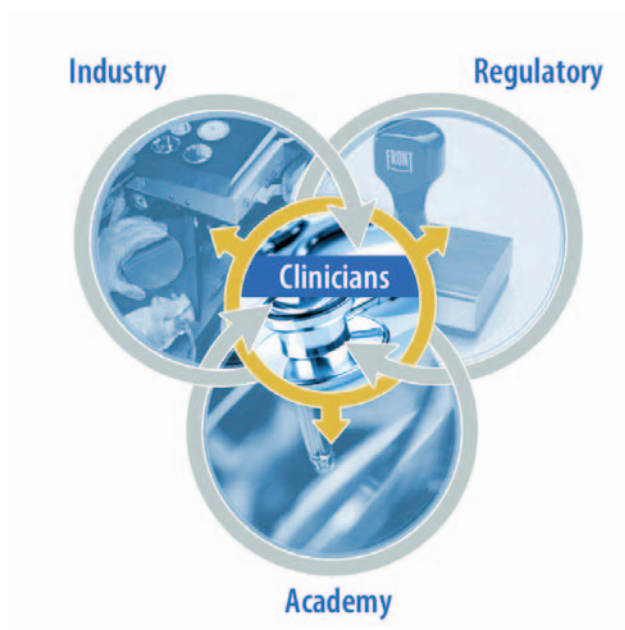
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Ron Neumann, MD

S. Krupsky

Sara Krupsky, MD

Symposium Chairpersons





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General Information

Venue

Marriott Rive Gauche Hotel & Conference Center

17 Boulevard Saint Jacques

Paris 75014,

France

Tel: +33 1 4078 7980

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Language

English is the official language of the Symposium.

Registration and Hospitality

The registration desk will be located in the entrance to the meetings halls and will be open as follows:

Thursday, 7 March	11:00 – 18:00	Saturday, 9 March	07:30 – 17:30
Friday, 8 March	07:30 – 17:30	Sunday, 10 March	07:30 – 12:00

Symposium Kit and Name Badge

Upon registering you will receive your kit, containing your personal name badge.

Please remember to wear your name badge to all symposium activities and to the Welcome Reception.

Please note there will be a charge of €30 to replace lost badges.

Internet Facilities

Free internet and e-mail facilities are located in the exhibition area and are available during exhibition opening hours. Please be considerate of fellow participants when using the facilities.

Certificate of Attendance

A certificate of attendance will be available at the registration desk on Saturday, March 9th, noon time.

Exhibition Opening Hours

All participants are invited to view the exhibition in the hotel. Exhibition opening hours are as follows:

Thursday, 7 March	13:00 - 20:00
Friday, 8 March	10:00 - 18:00
Saturday, 9 March	10:00 - 18:00

Oral Presentations

If using a **PowerPoint** presentation, please note you need to bring it on a CD or on a memory stick (using the USB port in the computer) and load it on one of the Symposium computers in the Speaker Preview Room, at least 1 hour before the start of the session.

If combining video films with PowerPoint, please make sure to check it in the session hall where your lecture is taking place during a coffee or lunch break prior to your session, at least 30 minutes before the start of the session.

Please note: You cannot use your own personal laptops for the presentation, only the computers available at the Preview room.

E-Poster Presentations

E-posters will be available for viewing throughout the Symposium in the exhibition area.

ISOPT Symposium Secretariat



Paragon Conventions

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Reception & Refreshments

Welcome Reception

18:00 – Thursday, 7 March

All participants are invited to the Welcome Reception at the exhibition area

Coffee & Refreshments

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Coffee will be served in the exhibition area at the times indicated in the Scientific Program

Lunch Sessions

Lunchboxes will be provided during the sponsored lunch sessions:

Friday, March 8th – Sponsored by



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Santen, one of the oldest ophthalmic pharmaceutical companies in the world, is Japan's pioneer and leader in ophthalmic pharmaceuticals. Today, we at Santen are focusing our research and development efforts on glaucoma, retinal, and corneal disorders. We are also accelerating our efforts towards globalization to deliver our products and our message of "A clear vision for life®" to people around the world.

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Alcon's surgical portfolio includes technologies and devices for cataract, retinal, refractive and glaucoma surgery, such as the INFINTI® vision system for cataract procedures, the CONSTELLATION® vitreoretinal system for retinal operations, and the AcrySof® family of intraocular lenses (IOLs) to treat cataract and refractive errors like presbyopia and astigmatism.

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Heidelberg Engineering is a high tech medical device company which designs, manufactures and distributes diagnostic instruments for eye care professionals. The core technologies include confocal microscopy, scanning lasers and optics, optical coherence tomography and software image analysis



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Belgium

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EVER, the European Association for Vision and Eye Research, is the leading non-profit ophthalmological research association in Europe which covers all areas of ophthalmology and visual sciences. Membership is open to individuals of any nationality engaging in or with an interest in ophthalmic and vision research. EVER currently has over 850 members from 48 countries all over the world and represented by 11 scientific sections, ranging from epidemiology to optics, the cornea to the retina, and immunology to genetics. One of the main activities of EVER is organizing a high quality research meeting. The next meeting will be held in Nice, France from September 18-21, 2013.

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Alimera Sciences, a biopharmaceutical company, has received marketing authorisation for ILUVIEN® (fluocinolone acetonide intravitreal implant) for chronic DME in Austria, France, Germany, Portugal, Spain and the United Kingdom. Italy national phase is ongoing. ILUVIEN is an investigational drug in the U.S.

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Imagine Eyes provides advanced ophthalmic devices for high-precision wavefront analysis of the eye's refractive errors and cellular-level retinal imaging.



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Headquartered in Japan with operations also in the US, China, and Europe, Santen is a leader in ophthalmic research, development, regulatory management, and marketing. Our global vision is to develop innovative products to serve the needs of people worldwide. We are committed to applying our unique capabilities to contribute to the health and quality of life for patients, their families, and society as a whole. Santen's strategic focus is retina, glaucoma, and cornea. The company will continue to contribute to society, working primarily for the benefit of patients and their loved ones throughout the world.

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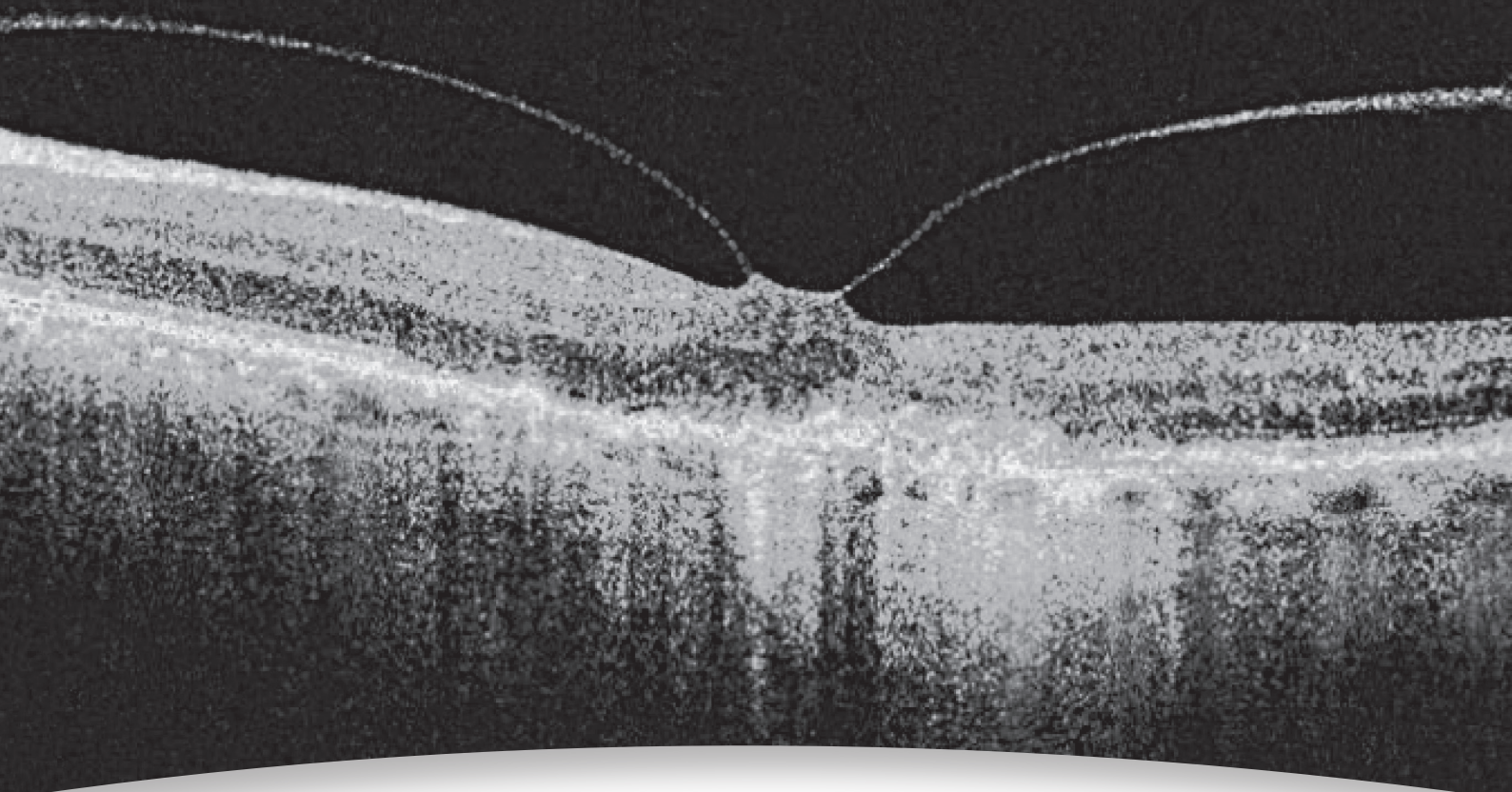
10th ISOPT *Clinical*

March 7-10, 2013, Paris, France

Scientific Program



rethink VMT



Patients with **vitreomacular traction (VMT)** are at risk for **macular hole** and suffer visual impairment that can affect their daily lives.¹⁻³ If unresolved, VMT can progress and can lead ultimately to central vision loss.^{4,5}

In recent years, optical coherence tomography (OCT) has brought greater clarity to VMT, advancing both diagnosis and understanding of the condition.⁵ Today, there is more to know about VMT, and there may be more you can do, as well.

References: 1. Sebag J, Wang MY. Combined spectral-domain optical coherence tomography/scanning laser ophthalmoscopy imaging of vitreous and the vitreo-retinal interface. Holz FG, Spaide RF, eds. *Medical Retina: Focus on Retinal Imaging*. Berlin, Germany: Springer-Verlag; 2010:157-168. 2. Bottós J, Elizalde J, Arevalo JF, Rodrigues EB, Maia M. Vitreomacular traction syndrome. *J Ophthalmic Vis Res*. 2012;7(2):148-161. 3. Mojon-Azzi SM, Sousa-Poza A, Mojon DS. Impact of low vision on well-being in 10 European countries. *Ophthalmologica*. 2008;222:205-212. 4. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Idiopathic Macular Hole. San Francisco, CA: American Academy of Ophthalmology; 2008. <http://www.aao.org/ppp>. Accessed October 24, 2012. 5. Barak Y, Ihnen MA, Schaal S. Spectral domain optical coherence tomography in the diagnosis and management of vitreoretinal interface pathologies. *J Ophthalmol*. 2012:Article ID 876472. doi: 10.1155/2012/876472.

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Chair: **Barry Kuppermann, USA & Paolo Lanzetta, Italy**

In dedication to the memory of Ephraim Friedman

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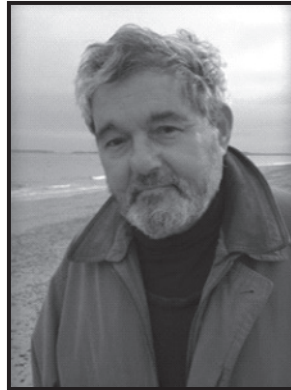
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*The 10th ISOPT Retina section is devoted to
Prof. Ephraim Friedman
1930 -2011*



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



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Thursday, March 07, 2013

Afternoon Sessions - Hall A

14:00-15:30	Diabetic Macular Edema Chairs: <u>Michaella Goldstein</u> , Israel & <u>Albert Augustin</u> , Germany	Hall A
14:00	Subthreshold MicroPulse Laser for Diabetic Macular Edema: Basic Science and Clinical Results <u>Giorgio Dorin</u> , USA	
14:15	36 Month RISE and RIDE <u>David Boyer</u> , USA	
14:30	Latest Outcomes of Aflibercept for DME Trials <u>Patricia Udaondo</u> , Spain	
14:45	Latest Outcomes of Steroid Implants for DME <u>Michaella Goldstein</u> , Israel	
15:00	Combination Therapy for Diabetic Macular Edema <u>Albert Augustin</u> , Germany	
15:15	Experimental Treatments of Diabetic Retinopathy <u>David Boyer</u> , USA	
15:30-16:00	Coffee Break - Sponsored by Santen	Exhibition Hall
16:00-17:30	Diabetic Macular Edema Chairs: <u>David Boyer</u> , USA & <u>Francesco Bandello</u> , Italy	Hall A
16:00	Guidelines for the Use of Laser, anti-VEGF, or Steroids in DME <u>Francesco Bandello</u> , Italy	
16:15	A Comprehensive Patient-Level Meta-Analysis Evaluating Systemic Safety Profiles of Marketed Formulations of Ranibizumab in AMD, RVO and DME <u>Baruch Kuppermann</u> , USA	
16:30	Comparison of Outcomes from DME Trials <u>Barry Kuppermann</u> , USA	
16:45	DME Case Discussion Panel: <u>Francesco Bandello</u> , Italy, <u>David Boyer</u> , USA & <u>Michaella Goldstein</u> , Israel	
18:00	Welcome Reception	Exhibition Hall

Thursday, March 07, 2013

Afternoon Sessions - Hall B

14:00-15:30	On the Use of Corticosteroids for Retinal Diseases Chairs: <u>Francine Behar-Cohen</u> , France & <u>Barry Kuppermann</u> , USA	Hall B
14:00	Mechanisms of Action of Corticoid Hormones: Gluco and Mineralocorticoid Receptors <u>Nicolette Farman</u> , France	
14:15	The Potency of Glucocorticoids: is the Actual Classification Adapted for the Eye? <u>Francine Behar-Cohen</u> , France	
14:30	Ocular Toxicity of Different Glucocorticoids <u>Alicia Torriglia</u> , France	
14:45	Anti-Edematous Effects of Glucocorticoids: Mechanisms of Action <u>Min Zhao</u> , France	
15:00	Formulations and Routes of Administration: Differential Effects <u>Barry Kuppermann</u> , USA	
15:15	Discussion <u>All Speakers</u>	
15:30-16:00	Coffee Break - Sponsored by Santen	Exhibition Hall
16:00-17:30	Gene Therapy Chair: <u>Francine Behar-Cohen</u> , France	Hall B
16:00	RPE 65 from Bench to Bedside <u>Michel Weber</u> , France	
16:15	Update on Clinical Trials <u>Bart Leroy</u> , Belgium	
16:30	The Choice of the Optimal Viral Vector for Severe Retinal dystrophies <u>Yvan Arsenijevic</u> , Switzerland	
16:45	Gene Therapy for the Cornea <u>François Jean Malecaze</u> , France	
17:00	The Place of Non-Viral Vectors <u>Elodie Touchard</u> , France	
17:15	Discussion <u>All Speakers</u>	
18:00	Welcome Reception	Exhibition Hall

Thursday, March 07, 2013

Afternoon Sessions - Hall C

14:00-14:45	Intraocular Strategies Chair: <u>B. Bodaghi</u> , France	Hall C
14:00	Intraocular Utilization of Steroids <u>Elisabetta Miserocchi</u> , Italy	
14:15	The Theory of Cell Therapy for Uveitis <u>Benoit Salomon</u> , France	
14:30	Initial Efforts and Future Directions in Cell Therapy for Uveitis <u>Bahram Bodaghi</u> , France	
14:45-15:30	Rational and Pragmatic Use of Diagnostic Procedures for Patients' Management Chair: <u>Ramin Tadayoni</u> , USA	Hall C
14:45	Pragmatic Use of Diagnostic Procedures Before Treatment of CNV in AMD <u>Jonathan Dowler</u> , United Kingdom	
15:00	How Intravitreal Injections Change the Imaging Strategies for Diagnosis and Follow-Up of RVO <u>Michel Paques</u> , France	
15:15	Rational Follow-Up Strategies for Treated DME <u>Bénédicte Dupas</u> , France	
15:30-16:00	Coffee Break - Sponsored by Santen	Exhibition Hall
16:00-17:30	Anterior Segment Imaging Chairs: <u>P. Asbell</u> , USA & <u>Jodhbir S. Mehta</u> , Singapore	Hall C
16:00	Corneal Imaging in Dry Eye <u>Christophe Baudouin</u> , France	
16:12	The Basis of Staining by Topical Dyes and its Relevance to Clinical Practice <u>Anthony Bron</u> , United Kingdom	
16:24	OCT of Surface Eye Tumors <u>Rick Fraunfelder</u> , USA	
16:36	Anterior Segment Optical Coherence Tomography for the Cornea <u>Jodhbir S. Mehta</u> , Singapore	
16:48	Fully Automated Quantification of Morphological Features of Different Epithelial Cell Layers in Human Corneas <u>Oliver Stachs</u> , Germany	
17:00	Scheimpflug Analysis in Corneal Ectasia <u>Ömür Uçakhan-Gündüz</u> , Turkey	
17:12	Q&A Panel <u>All Speakers</u>	
18:00	Welcome Reception	Exhibition Hall

Friday, March 08, 2013

Morning Sessions - Hall A

08:00-09:45	Dry AMD Chairs: <u>Anat Lowenstein</u> , Israel & <u>Francesco Boscia</u> , Italy	Hall A
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08:00	Alprostadiil for Dry Age Related Macular Degeneration (AMD) <u>Albert Augustin</u> , Germany
08:10	New Approaches to Screening for AMD <u>Anat Loewenstein</u> , Israel
08:20	The Role of Imaging in the Management of Dry AMD <u>Gisele Soubrane</u> , France
08:30	AREDS2: The Rationale of Supplement Integration and the Role of Macular Pigment Measurement <u>Paul Bernstein</u> , USA
08:40	The Role of Genetic Testing in the Management of AMD <u>Itay Chowers</u> , Israel
08:50	The TOGA Study: A Phase II/III Study Evaluating the Treatment with ORACEA doxycycline for Geographic Atrophy <u>Elias Reichel</u> , USA
09:00	The Complement System in Dry AMD: a Therapeutic Target <u>Jordi Mones</u> , Spain
09:10	Progress in the Development of Emixustat Hydrochloride for the Treatment of Dry AMD <u>Nathan Mata</u> , USA
09:20	Pathophysiology of Dry AMD <u>Francesco Boscia</u> , Italy
09:30	New Insights in the Pathogenesis of Dry AMD <u>Jayakrishna Ambati</u> , USA

09:45-10:30	Basic Science, Nanotechnology and Drug Delivery Chairs: <u>Jayakrishna Ambati</u> , USA & <u>Marco Zarbin</u> , USA	Hall A
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09:45	New Therapeutic Targets in CNV <u>Jayakrishna Ambati</u> , USA
09:54	Nanotechnology and Posterior Segment Diseases <u>Marco Zarbin</u> , USA
10:03	Intravitreal Injections: an Healthcare Failure Modes and Effects Analysis <u>Daniele Veritti</u> , Italy
10:12	What's an Appropriate Dosing Interval for Intravitreal Ranibizumab? A Pharmacokinetic Model <u>Daniele Veritti</u> , Italy
10:21	Ocriplasmin for Pharmacologic Treatment of Vitreomacular Traction (VMT): Results of the MIVI-TRUST Program <u>Baruch Kuppermann</u> , USA

10:30-11:00	Coffee Break - Sponsored by Santen	Exhibition Hall
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11:00-11:45	Plenary Session - Sponsored by Santen Chair: <u>Christophe Baudouin</u> , France
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Main Presentations: Hall B
For full program please refer to page 21

Friday, March 08, 2013

Morning Sessions - Hall A

11:45-12:30	Biomarkers of Diabetic Retinopathy Progression to CSME. Relevance for Clinical Trial Design Chair: <u>Jose Cunha-Vaz</u> , Portugal	Hall A
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11:45	Recruitment Selection for NPDR Studies. Need to Identify Eyes/Patients that Show Disease Activity and are Expected to Progress During the Trial <u>Francesco Bandello</u> , Italy
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11:55	Microaneurysm Turnover and Phenotypes of Nonproliferative Diabetic Retinopathy Progression to Clinically Significant Macular Edema <u>José Cunha-Vaz</u> , Portugal
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12:05	Subclinical Macular Edema as a predictor of progression to CSME <u>Isabel Pires</u> , Portugal
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12:15	Round Table Discussion and Q&A <u>All Speakers</u>
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12:30-13:30	Lunch Session - Sponsored by Alcon - Pharmacological Treatment of Vitreomacular Traction Chair: Barry Kuppermann , USA
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Main Presentations: Hall B
For full program please refer to page 22

Friday, March 08, 2013

Morning Sessions - Hall B

08:00-09:00	Role of Intraocular Pressure, Cerebrospinal Fluid Pressure, and Blood Pressure in Glaucoma Chairs: <u>Jost Jonas</u> , Germany & <u>Alain Bron</u> , France	Hall B
08:00	Vascular Risk Factors, Ethnicity and Glaucoma <u>Alon Harris</u> , USA	
08:15	Optic Nerve Compartmentation in Normal Tension Glaucoma <u>Hanspeter E. Killer</u> , Switzerland	
08:30	Cerebrospinal Fluid Pressure and Glaucoma: Ocular Perfusion Aspects <u>Leopold Schmetterer</u> , Austria	
08:45	Cerebrospinal Fluid Pressure and Glaucoma: Anatomical Facts and Theoretical Myths <u>Jost Jonas</u> , Germany	
09:00-09:45	Toxicology Chair: <u>Rick W. Fraunfelder</u> , USA	Hall B
09:00	Adverse Ocular Drug Reactions Recently Identified by the National Registry of Drug-Induced Ocular Side Effects <u>Rick Fraunfelder</u> , USA	
09:10	Intramural Deposition of Alexidine into Heated Bausch & Lomb ReNu Plastic Bottles and the Worldwide Fusarium Keratitis Epidemic of 2004-2006 <u>John D. Bullock</u> , USA	
09:20	Drug-Related Toxic Retinopathy <u>K.V. Chalam</u> , USA	
09:30	Effects of Preservatives to the Ocular Surface <u>Christophe Baudouin</u> , France	
09:45-10:30	Gene Therapy Chair: <u>Chris Paterson</u> , USA	Hall B
09:45	AAV Gene Transfer Following Intravitreal Injection – Mice are Different from Monkeys (Man?) <u>Samuel Wadsworth</u> , USA	
10:00	An Optogenetic Approach to Establishing Light Sensitivity in the Inner Retina <u>Alan Horsager</u> , USA	
10:15	Ongoing Trials and Requirements on Usher Syndrome <u>José-Alain Sahel</u> , France	
10:30-11:00	Coffee Break - Sponsored by Santen	Exhibition Hall
11:00-11:45	Sponsored Plenary Session - Santen Chair: <u>Christophe Baudouin</u> , France	Hall B
11:00	ODISSEY - Introduction - When Signs and Symptoms Dissociate: a Key Challenge in Severe Keratoconjunctivitis Sicca <u>Christophe Baudouin</u> , France	
11:08	Establishing the Diagnosis of Keratoconjunctivitis Sicca: What to do in Clinical Practice <u>Gysbert Van Setten</u> , Sweden	
11:16	Reaching Consensus on Severe Keratoconjunctivitis Sicca: the ODISSEY Algorithm <u>Stefano Bonini</u> , Italy	
11:24	The Role of Inflammation in Keratoconjunctivitis Sicca: Perspectives for Research and Therapy <u>Pasquale Aragona</u> , Italy	
11:32	Discussion Panel <u>All Speakers</u>	

Friday, March 08, 2013

Morning Sessions - Hall B

11:45-12:30	Nutrition & Antioxidants Chair: <u>Paul Bernstein</u> , USA	Hall B
11:45	Responder Analysis of the Effect of 9-cis Beta-Carotene on ERG and Visual Field in Patients with Retinitis Pigmentosa <u>Ygal Rotenstreich</u> , Israel	
11:56	Oral Docosahexaenoic Acid in Prevention of Exudative Age-Related Macular Degeneration: the NAT2 Study <u>Eric Souied</u> , France	
12:07	Testing Therapy in a Mouse Model of Geographic Atrophy <u>Alfred Lewin</u> , USA	
12:18	Macular Carotenoids in Infant Ocular Health and Development <u>Paul Bernstein</u> , USA	
12:30-13:30	Lunch Session - Sponsored by Alcon - Pharmacological Treatment of Vitreomacular Traction Chair: <u>Barry Kuppermann</u> , USA	Hall B
12:30	Lunch Bags Distribution	
12:45	Welcome <u>Barry Kuppermann</u> , USA	
12:50	Natural History of Vitreomacular Traction (VMT) <u>Ramin Tadayoni</u> , France	
13:00	Pharmacologic Treatment of symptomatic Vitreomacular Adhesion with Ocriplasmin: Results of the MIVI-TRUST Program <u>Barry Kuppermann</u> , USA	
13:10	Predictive of Pharmacologic Vitreomacular Adhesion (VMA) Resolution in the Ocriplasmin Pivotal Studies <u>Susanne Binder</u> , Austria	
13:20	Panel Discussion - Q&A <u>All Speakers</u>	
13:25	Wrap Up, Conclusions <u>Barry Kuppermann</u> , USA	

Friday, March 08, 2013

Morning Sessions - Hall C

08:00-09:00	Cornea Cases	Hall C
09:00-10:30	Dry Eye Disease & Inflammation Chairs: Penny Asbell, USA & Jing-Feng Huang, USA	Hall C
09:00	The Role of Innate Immunity on dry Eye Pathogenesis <u>Pasquale Aragona</u> , Italy	
09:12	sPLA2-IIa and Innate Immunity of the Ocular Surface <u>Penny A. Asbell</u> , USA	
09:24	Immune Mechanisms in Dry Eye Pathogenesis <u>Reza Dana</u> , USA	
09:36	Different Underlying Inflammatory Mechanisms in Dry Eye Disease – Heterogeneity at Molecular Level <u>Jing-Feng Huang</u> , USA	
09:48	Oral Medications to Control Dry Eye Pain - Our Experience with Lyrica (Pregablin) and LDN (Low Dose Naltrexone) <u>Rolando Toyos</u> , USA	
10:00	Meibomian Gland Dysfunction <u>Greg J. Berdy</u> , USA	
10:12	Discussion Panel <u>All Speakers</u>	
10:30-11:00	Coffee Break - Sponsored by Santen	Exhibition Hall
11:00-11:45	Sponsored Plenary Session - Santen Chair: Christophe Baudouin , France	
	Main Presentations: Hall B For full program please refer to page 21	
11:45-12:30	Biomarkers in External Disease Chairs: Penny Asbell, USA & Margarita Calonge, Spain	Hall C
11:45	Biomarkers in External Disease- HLA and Cytokines <u>Penny A. Asbell</u> , USA	
11:54	The Tears as a Diagnostic Substrate for Understanding Ocular Surface Disease <u>Roger Beuerman</u> , Singapore	
12:03	Potential Biomarkers of Disease Activity in Ocular Surface Inflammation <u>Margarita Calonge</u> , Spain	
12:12	Patient Stratification - Biomarker Application in Dry Eye Clinical Trial <u>Huang Jing-Feng</u> , USA	
12:21	Discussion <u>All Speakers</u>	
12:30-13:30	Lunch Session - Sponsored by Alcon - Pharmacological Treatment of Vitreomacular Traction Chair: Barry Kuppermann , USA	
	Main Presentations: Hall B For full program please refer to page 23	

Friday, March 08, 2013

Afternoon Sessions - Hall A

14:00-15:30	Retinal Vein Occlusion Chairs: <u>Gabriel Coscas</u> , France & <u>Patricia Udaondo</u> , Spain	Hall A
14:00	Clinical Markers of Inflammation and Exudation in ME due to RVO <u>Gabriel Coscas</u> , France	
14:15	Ranibizumab for RVO: BRAVO, CRUISE, HORIZON <u>Francesco Bandello</u> , Italy	
14:30	Aflibercept for Central Retinal Vein Occlusion <u>Paolo Lanzetta</u> , Italy	
14:45	Dexamethasone Implant: GENEVA Trial's Everyday Clinical Practice <u>Patricia Udaondo</u> , Spain	
15:00	RVO Case Discussion Panel: <u>Gabriel Coscas</u> , France, <u>Barry Kuppermann</u> , USA & <u>Patricia Udaondo</u> , Spain	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:40	Dry AMD Chairs: <u>Paul Bernstein</u> , USA & <u>Eric Souied</u> , France	Hall A
16:00	Complement Inhibition Using Gene Therapy for AMD <u>Elias Reichel</u> , USA	
16:10	Stem Cells in Dry AMD <u>Marco Zarbin</u> , USA	
16:20	The Dry AMD New Drug Pipeline <u>Paul Bernstein</u> , USA	
16:30	Multimodal Functional and Morphological Aspects of Reticular Pseudodrusen <u>Giuseppe Querques</u> , France	
16:40	Toward Personalized Medicine in AMD <u>Eric Souied</u> , France	
16:50	Treatment for Acute Central Retinal Arty Occlusion by the Intravenous Drip of Prostaglandin E1 <u>Akihiro Ohira</u> , Japan	
17:00	Protective Effect of TGF-β1 in RPE Cells Upon Oxidative Stress as a Model for Oxidative Damage During Dry AMD <u>Zeev Dvashi</u> , Israel	
17:10	Case Discussion: How to Follow, Imaging Options, When to Start Nutraceuticals, Role of Complement, Role of Genetic Testing Panel: <u>Gisele Soubrane</u> , France, <u>Paul Bernstein</u> , USA, <u>Francesco Boscia</u> , Italy & <u>Itay Chowers</u> , Israel	

Friday, March 08, 2013

Afternoon Sessions - Hall B

14:00-15:30	Drug Delivery Chairs: <u>Robert Gurny</u> , Switzerland & <u>Rocio Herrero-Vanrell</u> , Spain	Hall B
14:00	Protein Delivery: is Local Route an Option? <u>Francine Behar-Cohen</u> , France	
14:15	Prolonged Intravitreal Release of the EndothelinA-Receptor Antagonist BQ123 from an Injectable Polymer System Aiming at a Retinal Vasodilator Response <u>Marieke Veurink</u> , Switzerland	
14:30	Intravitreal Concentrations of a Near-Infrared Fluorescence – Labeled Biotherapeutic Determined In Situ Using Confocal Scanning Laser Ophthalmoscopy <u>Anthony Basile</u> , USA & <u>Diane Tang-Liu</u> , USA	
14:45	Novel Micelle Carriers for Topical Ocular Delivery: a Novel Approach for Treating Dry Eye Disease <u>Claudia Di Tommaso</u> , Switzerland	
15:00	Biodegradable Microspheres as Drug Delivery Systems in the Treatment of Retinal Diseases <u>Rocio Herrero-Vanrell</u> , Spain	
15:15	Discussion <u>All Speakers</u>	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Drug Delivery Chairs: <u>Diane Tang-Liu</u> , USA & <u>Uday Kompella</u> , USA	Hall B
16:00	Sustained Protein Drug Delivery to the Eye <u>Uday Kompella</u> , USA	
16:15	Aqueous Cyclosporine A Prodrug Topical Formulation to Treat Ocular Diseases <u>Marta Rodriguez-Aller</u> , Switzerland	
16:30	Rationale for the Use of Cationic Emulsions in Ophthalmology: From Bench to Bedside <u>Frederic Lallemand</u> , France	
16:45	In Vitro Sustained-Release and Stability of Single-Chain VEGF Antibody Fragments <u>Lutz Asmus</u> , Switzerland	
17:00	Unmet Needs in Drug Delivery - Panel Speakers: <u>Robert Gurny</u> , Switzerland , <u>Diane Tang-Liu</u> , USA, <u>Francine Behar-Cohen</u> , France, <u>Rocio Herrero-Vanrell</u> , Spain, <u>Uday Kompella</u> , USA and <u>Frederic Lallemand</u> , France	

Friday, March 08, 2013

Afternoon Sessions - Hall C

14:00-15:30	Allergy and Conjunctival Cicatrization: From Trivial to Highly Destructive Entities Chair: <u>Esen K. Akpek</u> , USA	Hall C
14:00	Ocular Allergy: Magnitude of Problem <u>Esen Akpek</u> , USA	
14:15	Mouse Model of Corneal Involvement in Ocular Allergy <u>Daniel Saban</u> , USA	
14:30	Allergic Conjunctivitis: Overview of Current Classification <u>Stefano Bonini</u> , Italy	
14:45	Diagnosis and Management of Vernal Keratoconjunctivitis <u>Kathryn Colby</u> , USA	
15:00	Atopic Keratoconjunctivitis (AKC) in Pediatric Age <u>Margarita Calonge</u> , Spain	
15:15	Urge to Rub: Is there a Link Between Eye Rubbing, Atopy and Keratoconus <u>Michael W. Belin</u> , USA	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Wound Healing - Cornea Chair: <u>Penny Asbell</u> , USA & <u>Uçakhan-Gündüz Ömür</u> , Turkey	Hall C
16:00	New Approaches to Wound Healing <u>Penny A. Asbell</u> , USA	
16:10	Post-Refractive Surgery Dry Eye <u>Christophe Baudouin</u> , France	
16:20	Ocular Sensitivity. Update <u>Jesús Merayo-Llodes</u> , Spain	
16:30	Innervations of the Ocular Surface. Experimental Models and Clinical Applications <u>Jesus Merayo-Llodes</u> , Spain	
16:40	Collagen Crosslinking in Keratoconus <u>Ömür Uçakhan-Gündüz</u> , Turkey	
16:50	Photodynamic Therapy (PDT) in Infectious Keratitis <u>Berthold Seitz</u> , Germany	
17:00	The Steroids for Corneal Ulcer Trial - 5 years of SCUT <u>Thomas Lietman</u> , USA	
17:10	Q&A Panel <u>All Speakers</u>	

Saturday, March 09, 2013

Morning Sessions - Hall A

08:00-09:00	Inhibition of Diabetic Retinopathy - Novel Targets Chair: <u>Arup Das</u> , USA	Hall A
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08:00	Targeting GADPH Nuclear Translocation as a Potential Novel Therapy against Hyperglycemia-Induced Retinal Injury <u>Susanne Mohr</u> , USA
08:12	Brief Low Intensity Far-Red Light Inhibits Early Lesions that Contribute to Diabetic Retinopathy <u>Tim Kern</u> , USA, USA
08:24	Approaches Using Inhibition of Mitochondrial Damage <u>Renu Kowluru</u> , USA
08:36	Fatty Acid Elongases as Therapeutic Targets in Retinal Diseases <u>Julia Busik</u> , USA
08:48	Role of Calcium Flux, Calcineurin, and NFAT in Pathogenesis of Retinal Diseases <u>John Penn</u> , USA

09:00-10:30	OCT - New Developments and Future Chair: <u>Susanne Binder</u> , Austria	Hall A
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09:00	Latest Developments in OCT Technology <u>Wolfgang Drexler</u> , Austria
09:15	Vascular Structure of the Choroid in Health and Ocular Pathology of the Posterior Eye Examined with 3D-1060nm-OCT <u>Marieh Esmaeelpour</u> , Austria
09:30	OCT During Membrane Peeling in Macular Disease-Does it Replace Dying? <u>Susanne Binder</u> , Austria
09:45	Central Retinal Thickness Measurement and Observance of Macular Reaction using intraoperative OCT in Cataract Surgery before and after Phacoemulsification <u>Florian Zeiler</u> , Austria
10:00	Clinical Importance of OCT-3D Imaging and Future <u>Carl Glittenberg</u> , Austria
10:15	Discussion <u>All Speakers</u>

10:30-11:00	Coffee Break - Sponsored by Santen	Exhibition Hall
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11:00-12:30	Innovations Implemented in the Global Environment Chair: <u>Malvina Eydelman</u> , USA	Hall A
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11:00	EVICRnet's Contribution to Expediting Ophthalmic Innovation in Europe <u>Maria Cecilia Martinho</u> , Portugal
11:15	Ophthalmic Innovations in Japan <u>Mitsuru Sawa</u> , Japan
11:30	ISO's Contribution to Global Innovation <u>Eva Lydhal</u> , Sweden
11:45	FDA's Innovation Initiatives <u>Malvina Eydelman</u> , USA
12:00	Discussion

12:30-13:30	Lunch Session - Sponsored by Bayer HealthCare - Treatment Experience with EYLEA® for Wet AMD Chair: <u>Jean-Francois Korobelnik</u> , France
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Main Presentations: Hall B
For full program please refer to page 29

Saturday, March 09, 2013

Morning Sessions - Hall B

08:00-09:00	Ocular Inflammatory Diseases - Case Presentation Discussion Panel Moderator: <u>Christoph Deuter</u> , Germany	Hall B
08:00	Cases Presentation & Discussion Panel: <u>Christoph Deuter</u> , Germany, <u>Yosuf El-Shabrawi</u> , Austria & <u>Sofia Androudi</u> , Greece	
09:00-10:30	Treating Uveitis 2013 Chair: <u>Manfred Zierhut</u> , Germany	Hall B
09:00	Primary Endpoint Results of the SAVE Study - Sirolimus As Therapeutic Approach To Uveitis <u>Quan Dong Nguyen</u> , USA	
09:13	Evolution of our Treatment Paradigms <u>Manfred Zierhut</u> , Germany	
09:26	Local vs Systemic Therapy in Uveitis <u>Carlos Pavesio</u> , United Kingdom	
09:39	Scleritis-Differences and Similarities in Therapeutic Approach to Uveitis <u>Maite Sainz de la Maza</u> , Spain	
09:52	The Relevance of Objective Followup Criteria (Endpoints) to Patient Well Being <u>Jennifer Thorne</u> , USA	
10:05	From Cohort Studies to Individual Case Management <u>Michal Kramer</u> , Israel	
10:18	Philosophy and Goals of Uveitis Therapy <u>Phuc Le Hoang</u> , France	
10:30-11:00	Coffee Break - Sponsored by Santen	Exhibition Hall
11:00-11:45	Imaging - EVER Session Chair: <u>Leopold Schmetterer</u> , Austria	Hall B
11:00	Tear Film Imaging Using OCT <u>Gerhard Garhofer</u> , Austria	
11:15	Non-Invasive Retinal Oximetry <u>Sveinn Hakon Hardarson</u> , Iceland	
11:30	Doppler OCT <u>Leopold Schmetterer</u> , Austria	
12:30-13:30	Lunch Session - Sponsored by Bayer HealthCare - Treatment Experience with EYLEA® for Wet AMD Chair: <u>Jean-Francois Korobelnik</u> , France	Hall B
12:30	Lunch Bags Distribution	
12:45	Introduction <u>Jean-Francois Korobelnik</u> , France	
12:55	Practical Benefits of Every-Other-Month EYLEA® Treatment <u>Andrew Chang</u> , Australia	
13:05	How to Manage EYLEA® Patients Beyond 1 Year <u>Jeffrey Heier</u> , USA	
13:20	Summary <u>Jean-Francois Korobelnik</u> , France	

Saturday, March 09, 2013

Morning Sessions - Hall C

08:00-09:00	Glaucoma and Lipids Chair: <u>Alain Bron</u> , France	Hall C
08:00	What Can we Learn from Age Related Macular Degeneration? <u>Catherine Creuzot-Garcher</u> , France	
08:15	Vitamine E Tocopherols and Glaucoma <u>M Francesca Cordeiro</u> , United Kingdom	
08:30	Glaucoma and Lipids: Cholesterol and Glaucoma <u>Lionel Bretillon</u> , France	
08:45	Glaucoma and Lipids: Fatty Acids and Glaucoma <u>Niyazi Acar</u> , France	
09:00-09:45	Glaucoma Devices and Claims Chair: <u>Malvina Eydelman</u> , USA	Hall C
09:00	The FDA-American Glaucoma Society Workshop on Glaucoma Imaging Devices: Goals and Key Concepts <u>Jeffrey Liebmann</u> , USA	
09:10	Glaucoma Diagnostic Imaging Technologies in Clinical Practice <u>David Garway-Heath</u> , United Kingdom	
09:20	The FDA's View of Current Glaucoma Imaging Devices <u>Malvina Eydelman</u> , USA	
09:30	Discussion	
09:45-10:30	Improving Translation of Preclinical Studies into Approved Drugs and Devices Chairs: <u>Leonard A. Levin</u> , Canada & <u>Wolf Lagreze</u> , Germany	Hall C
09:45	Increasing the Rigor of Preclinical Studies: Academia vs. Industry <u>Wolf Lagreze</u> , Germany	
09:56	Optimizing the Choice and Use of Animal Models <u>Ceren Ergorul</u> , USA	
10:07	Decision Analysis and Proof of Concept Studies <u>Leonard Levin</u> , Canada	
10:18	Regulatory Issues: From Bedside to Bench <u>M Francesca Cordeiro</u> , United Kingdom	
10:30-11:00	Coffee Break - Sponsored by Santen	Exhibition Hall

Saturday, March 09, 2013

Morning Sessions - Hall C

11:00-12:30	Dry Eye Disease Treatment Chairs: Penny Asbell, USA & Anthony Bron, UK	Hall C
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11:00	Essential Fatty Acids (EFA) and Dry Eye Disease <u>Penny A. Asbell</u> , USA
11:10	Updating the Role of Meibomian Gland Dysfunction in Dry Eye <u>Anthony Bron</u> , United Kingdom
11:20	Artificial Tear Based on Liposomes and Hyaluronic Acid. Translational Research <u>Rocio Herrero-Vanrell</u> , Spain
11:30	Characterization of Clinical Tests Currently Used in Dry Eye Clinical Trials <u>Jing-Feng Huang</u> , USA
11:40	Outcome Analysis in Ocular Rosacea <u>Jesus Merayo-Llloves</u> , Spain
11:50	Dry Eye Syndrome after Refractive Surgery <u>Orwa Nasser</u> , Israel
12:00	Effects of Long Term Use of Topical NSAIDs in Dry Eye Patients <u>Rolando Toyos</u> , USA
12:10	Q&A Panel <u>All Speakers</u>

12:30-13:30	Lunch Session - Sponsored by Bayer HealthCare - Treatment Experience with EYLEA® for Wet AMD Chair: Jean-Francois Korobelnik, France
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Main Presentations: Hall B
For full program please refer to page XX

Saturday, March 09, 2013

Afternoon Sessions - Hall A

14:00-15:30	Wet AMD Chairs: <u>Pravin Dugel</u> , USA & <u>Paolo Lanzetta</u> , Italy	Hall A
14:00	Epimacular Brachytherapy (EMBT) for Age Related Macular Degeneration Patients <u>Pravin Dugel</u> , USA	
14:15	Different Drugs and Regimens in the Treatment of Wet-AMD: What to Choose? <u>Paolo Lanzetta</u> , Italy	
14:30	Effects of VEGF Inhibition on Vascularized Pigment Epithelium Detachment due to Occult Choroidal Neovascularization <u>Daniele Veritti</u> , Italy	
14:45	Implications of the EVEREST Study on Current Paradigms in Diagnosis and Treatment of Polypoidal Choroidal Vasculopathy <u>Adrian Koh</u> , Singapore	
15:00	Combination Therapy Targeting VEGF and PDGF for Wet AMD <u>Jordi Mones</u> , Spain	
15:15	Extracellular Matrix – CNV Interaction as a Potential Therapeutic Target for Wet AMD <u>Samir Patel</u> , USA	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:30	Wet AMD Chairs: <u>Samir Patel</u> , USA, <u>Jordi Mones</u> , Spain & <u>Gisele Soubrane</u> , France	Hall A
16:00	Inhibition of VEGF During Choroidal Neovascularization and Retinal Stresses by Gene Transfer Strategy <u>Yvan Arsenijevic</u> , Switzerland	
16:15	Targeting Complement Factor 5 in Neovascular AMD <u>Samir Patel</u> , USA	
16:30	New Drugs in Development for Wet AMD <u>Francesco Boscia</u> , Italy	
16:45	Choosing Anti-VEGF Therapy for Wet Age-Related Macular Degeneration <u>Pravin Dugel</u> , USA	
17:00	Case Discussion/Wet AMD Panel Panel: <u>Paolo Lanzetta</u> , Italy, <u>Jordi Mones</u> , Spain, <u>Gisele Soubrane</u> , France & <u>Pravin Dugel</u> , USA	

Saturday, March 09, 2013

Afternoon Sessions - Hall B

14:00-15:30	Clinical Studies for Uveitis Chair: <u>Marc De Smet</u> , The Netherlands	Hall B
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14:00	The Boundaries of Evidence Based Medicine <u>Ron Neumann</u> , Israel
14:15	Biomarkers and Their Utilization <u>Talin Barisani-Asenbauer</u> , Austria
14:30	Adaptive Protocols for Clinical Studies <u>Marc De Smet</u> , The Netherlands
14:45	Dealing with Heterogeneity in Clinical Studies for Uveitis <u>Astrid Queant</u> , France
15:00	Round Table Discussion: Endpoints and Beyond <u>All Speakers</u>

15:30-16:00	Coffee Break	Exhibition Hall
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16:00-17:30	Treating Ocular Infections 2013 Chair: <u>Irina Barequet</u> , Israel	Hall B
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16:00	An Update on Adenoviral Antivirals <u>Eric Romanowski</u> , USA
16:11	The Treatment of Conjunctivitis in Pediatric Population <u>Dominique Bremond-Gignac</u> , France
16:22	The Assessment of Anti-Acanthamoeba Solutions Using a Complete-Kill Assay <u>Regis Kowalski</u> , USA
16:33	An Update on Treatment for Bacterial Keratitis <u>Prashant Garg</u> , India
16:45	Graft-to-Host Transmission of Herpes Simplex Virus after PKP – Myth or Reality? <u>Berthold Seitz</u> , Germany
16:56	Antibiotic Resistance - A Global Problem <u>Penny A. Asbell</u> , USA
17:07	Intrastromal Amphotericin B Injection for the Management of Deep Keratomycosis <u>Pham Thi Khanh Van</u> , Vietnam
17:18	Microsporidial Stromal Keratitis - a Therapeutic Challenge <u>Prashant Garg</u> , India

Saturday, March 09, 2013

Afternoon Sessions - Hall C

14:00-15:30	Preservative Issues: From the Front to the Back of the Eye Chairs: Penny Asbell, USA & Christophe Baudouin, France	Hall C
14:00	Ocular Surface Disease Induced by Preservatives <u>Penny A. Asbell</u> , USA	
14:15	Effects of BAK on Corneal Nerves <u>Sandeep Jain</u> , USA	
14:30	Could Trabecular Meshwork be Damaged by Preservatives? <u>Christophe Baudouin</u> , France	
14:45	Benzalkonium Chloride Effects on Deep Ocular Structures <u>Françoise Brignole-Baudouin</u> , France	
15:00	Pseudophakic Preservative Maculopathy: its Updates <u>Kensaku Miyake</u> , Japan	
15:20	Discussion <u>All Speakers</u>	
15:30-16:00	Coffee Break	Exhibition Hall
16:00-17:35	Neuroprotection and Glaucoma + Free Papers Chair: Francesca Cordeiro, UK	Hall C
16:00	Methods to Evaluate Neuroprotection in the Retina <u>Manuel Vidal-Sanz</u> , Spain	
16:12	Use of High Content Screening to Identify Novel Neuroprotective Agents <u>Donald J. Zack</u> , USA	
16:24	Controversies in Glaucoma Neuroprotection <u>Leonard Levin</u> , Canada	
16:36	Neuroprotection: Where are We Now? <u>M Francesca Cordeiro</u> , United Kingdom	
16:48	Targeting RGC Axons in Glaucoma <u>Hani Levkovitch-Verbin</u> , Israel	
17:00	AntiVEGF Use in Trabeculectomy Surgery - What is its Role and the Evidence <u>Tina Wong</u> , Singapore	
17:09	IOP Lowering Effects of Single Drop Application of Five Drugs Classes in Rats With Steroid-Induced Ocular Hypertension <u>Renu Agarwal</u> , Malaysia	
17:18	Prior Prostaglandin Agonist Exposure and Conjunctival Hyperemia With Bimatoprost 0.03% Preservative-free and Bimatoprost 0.03% Solutions in a Randomized, Multicenter Study <u>Marina Bejani</u> , USA	
17:27	MRZ-99030, a β-Amyloid Aggregation Modulator, Protects Axons and RGCs in a Rodent Model of Glaucoma - PK/PD Relationship <u>Andreas Gravius</u> , Germany	

Sunday, March 10, 2013

Morning Sessions - Hall A

08:00-09:00	Therapy for Retinal and Choroidal Angiogenesis Chair: <u>Arup Das</u> , USA	Hall A
08:00	Novel Strategies for Limiting Retinal Vascular Injury and Pathological Neovascularization <u>Ruth Caldwell</u> , USA	
08:12	Therapeutic Role of AlphaB Crystallin in Retinal and Choroidal Angiogenesis <u>David Hinton</u> , USA	
08:24	Targeted Nanoparticle Therapy using Intraceptor Inhibition of Choroidal Neovascularization <u>Balamurali Ambati</u> , USA	
08:36	Notch and Jak/Stat Signaling Cascades in Astrocytes Regulate Remodeling of the Retinal Blood Vessels <u>Debasish Sinha</u> , USA	
08:48	Potential Role of CLT-28643, a Selective $\alpha 5 \beta 1$-Integrin Receptor Antagonist, in Neovascular Ophthalmic Diseases <u>Stephan Michels</u> , Switzerland	
09:00-10:30	Retinal Degeneration + Free Papers Chairs: <u>Henry Klassen</u> , USA & <u>José-Alain Sahel</u> , France	Hall A
09:00	Next Generation Sequencing for Retinal Degeneration <u>Isabelle Audo</u> , France	
09:12	Extending Cone Survival and Function in Retinal Degenerations <u>José-Alain Sahel</u> , France	
09:24	Gene Therapy for Stargardt Disease <u>José-Alain Sahel</u> , France	
09:36	PBN Inhibits RPE65 Activity and Protects the Retina from Stress-Induced Degeneration <u>Robert Anderson</u> , USA	
09:48	Cell-Based Therapeutics for the Retina <u>Henry Klassen</u> , USA	
10:00	Measuring the Intravitreal Mobility of Nanoparticles to Aid in the Rational Design of Gene Therapeutics for Retinal Disorders <u>Thomas Martens</u> , Belgium	
10:07	Nanotechnology Guided Targeting and Triggered Release of siRNA within Ocular Neovascular Lesions <u>Ashwath Jayagopal</u> , USA	
10:15	Dynamic Observation of Total VEGF Level in Hyperglycemia Mouse Eyes after Intravitreal Injection of a Novel Anti-VEGF Drug KH902 <u>Bo Lei</u> , China	
10:22	Improved Vitreous Stability and Retinal Delivery of Modified Cx43 Mimetic Peptides for the Treatment of Optic Neuropathies <u>Erica (Ying-Shan) Chen</u> , New Zealand	
10:30-11:00	Coffee Break - Sponsored by Santen	Exhibition Hall

Sunday, March 10, 2013

Morning Sessions - Hall A

11:00-12:30 Retina Free Papers		Hall A
Chairs: Jost Jonas, Germany & Akihiro Ohira, Japan		
11:00	A Comparison of On-Demand and Continuous Treatment with Bevacizumab Every Four or Eight Weeks in Age-Related Macular Degeneration <u>Sankha Amarakoon</u> , Netherlands	
11:10	Comparison of Very Low Fluence and Low Fluence Photodynamic Therapy in Chronic Central Serous Chorioretinopathy <u>Min Sagong</u> , South Korea	
11:20	Visual Acuity (VA) Outcomes with Pharmacologic Resolution of Vitreomacular Traction (VMT) or Full-Thickness Macular Hole (FTMH) Closure <u>Arnd Gandorfer</u> , Germany	
11:30	Intravitreal Bevacizumab for Retinopathy of Prematurity: Refractive Error Results <u>Jost Jonas</u> , Germany	
11:40	Anti-Inflammatory and Anti-Angiogenic Effects of NOV C-ter in Experimental Models <u>Chadi Mehanna</u> , France	
11:50	In Vivo Molecular Imaging of Retinal Vascular Diseases <u>Ashwath Jayagopal</u> , USA	
12:00	Monitoring Pathological Changes in Cone Outer Segment Structure Using Adaptive Optics Retinal Imaging <u>Kiyoko Gocho</u> , France	
12:10	Cataract and Diabetic Macular Edema: a Prospective Comparative Trial Investigating Phacoemulsification Associated with Intravitreal Micronized Triamcinolone Acetonide or Bevacizumab <u>Gianluca Besozzi</u> , Italy	
12:20	Intravitreal Bevacizumab for Choroidal Neovascularisation in Degenerative Myopia: a Retrospective Study in Real Life <u>Adonis Elsalloukh</u> , France	

Sunday, March 10, 2013

Morning Sessions - Hall B

08:00-09:00	Retina Free Papers Chair: <u>Ayala Pollock</u> , Israel	Hall B
08:00	Involvement of Arginase in Diabetic Retinal Vascular Dysfunction <u>R. William Caldwell</u> , USA	
08:10	The Effect of Intravitreal Triamcinolone on Macular Edema in Eyes with Retinal Vascular Disease Unresponsive to Intravitreal Bevacizumab <u>Ayala Pollack</u> , Israel	
08:20	Monosodium Urate Promotes Retinal Inflammation and Progression to Diabetic Retinopathy <u>Folami Lamoike</u> , USA	
08:30	Intravitreal Autologous Plasmin in Proliferative Diabetic Retinopathy <u>Ana Hervás Ontiveros</u> , Spain	
08:40	Lipoxygenase Pathway as a Therapeutic Target in Diabetic Retinopathy <u>Mohamed Al-Shabrawey</u> , USA	
08:50	Longterm Efficacy of Ciliary Muscle Gene Transfer of Three sFlt1 Variants in a Rat Model of Laser-Induced Choroidal Neovascularization <u>Mohamed El Sanharawi</u> , France	
09:00-09:45	Quantitative Imaging in Clinical Practice and Clinical Trials Chair: <u>David Garway-Heath</u> , United Kingdom	Hall B
09:00	Practical Application of GDx Imaging <u>Hans Lemij</u> , the Netherlands	
09:15	Practical Application of HRT Imaging <u>Michele Iester</u> , Italy	
09:30	OCT and Bringing Structure and Function Together <u>David Garway-Heath</u> , United Kingdom	
09:45-10:30	Glaucoma Free Papers Chairs: Alain Bron , France & Junguo Duan , China	Hall B
09:45	Evaluation of Oculohypotensive Activity of Resveratrol in Rat Glaucoma Model <u>Norhafiza Razali</u> , Malaysia	
09:54	Transforming Growth Factor beta (TGF-β) Inhibitors as Anti-Ocular Fibrotic Agent, an <i>in vitro</i> Evaluation <u>Khaled Nassar</u> , Germany	
10:03	The Experimental Study of Effects of Ginkgo Biloba Extract on L-Type Calcium Channel Currents in Rat Retinal Ganglion Cells <u>Junguo Duan</u> , China	
10:12	Adenosine A3 Receptor Agonist Prevents Retinal Ganglion Cell Degeneration <u>António Francisco Ambrósio</u> , Portugal	
10:21	Quantitative and Qualitative Label Free Imaging using Mass Spectrometry in the Context of an Ophthalmic Application <u>Gregory Hamm</u> , France	
10:30-11:00	Coffee Break	Exhibition Hall

Sunday, March 10, 2013

Morning Sessions - Hall B

11:00-12:30 Anterior Segment Free Papers		Hall B
Chair: Roger Beuerman, Singapore		
11:00	Autologous Serum Treatment for Ocular Surface Disease in Allergic Conjunctivitis <u>Sandra Johanna Garzón Parra</u> , Spain	
11:09	A Phase 3 Study (OPUS-1) Evaluating Lifitegrast Ophthalmic Solution, 5.0% versus Placebo for the Treatment of Dry Eye Disease <u>Charles Semba</u> , USA	
11:18	New Molecular Classes of Antibiotics effective against drug resistant Gram negative pathogens <u>Roger Beuerman</u> , Singapore	
11:27	Comparative Investigation of Chronic Blepharitis Combined Treatment Regimen Effectiveness <u>Ivan Pronkin</u> , Russia	
11:36	Anti-Inflammatory Effect of Eyelid Cleanser Based on <i>Melaleuca Alternifolia</i> in Non-Infectious Blepharitis <u>Sandra Johanna Garzón Parra</u> , Spain	
11:45	Matrix Therapy in Regenerative Medicine: from Basic Science to Cornea therapy <u>Denis Barritault</u> , France	
11:54	Topical Ayzthromycin Promotes Corneal Allograft Survival <u>Johannes Schwartzkopff</u> , Germany	
12:03	Evidence of epithelial remodelling in chronic ocular allergy by means of immunohistochemistry and <i>invitro</i> studies may suggest new treatment strategies. <u>Nikolaos Georgakarakos</u> , United Kingdom	
12:12	The Use of 0,05% Cyclosporine in Management of Herpes Viral Recurrent Erosions <u>Dmitry Maychuk</u> , Russia	
12:21	Posterior Capsule Opacification: Pharmacologic Prophylaxis with Kinase Inhibitors <u>Kirsten Eibl-Lindner</u> , Germany	

E- Posters

LentiVector®Platform: Clinical applications in ophthalmology

Nicola Adams, United Kingdom

Relationship Between the Metabolic Syndrome in Patients with Type 2 Diabetes and Diabetic Retinopathy in Deficiency of Vitamin D

Olena Antonenko, Ukraine

In Vivo Assessment of Pharmacologic Vitreolysis in Rabbits with the Digital Fluoroscopy System

Jeonghun Bae, South Korea

Topical Treatment with Cyclosporine 0,05% (CsA) for Subepithelial Infiltrates Secondary to Adenoviral Keratitis

Maria Bafa, Greece

Algorithm Approach for Severe Keratoconjunctivitis Sicca Diagnosis

Christophe Baudouin, France

The Relationship between the Cannabinoid CB Receptor System and Protection Against A2E Photo-Toxicity in Age Related Macular Degeneration (AMD)

Shimon Ben-Shabat, Israel

Macular Pigment Optical Density (MPOD) in Macular Health and Visual Function: Bridging the Gap between Clinical Research and Clinical Practice

Paul Bernstein, USA

Tolerance of a Sub-Conjunctival Injection of XG-102 in Ocular Inflammation

Talal Beydoun, France

Bioactivity in Retinal Cells of GDNF-Loaded Microspheres Intended for Intravitreal Administration

Irene Bravo-Osuna, Spain

Procoagulant and Anticoagulant Agents in Patients with Retinal Vein Occlusion Combined with Cardiovascular Disease

Maria Budzinskaya, Russia

Acute Angle-Closure Glaucoma After Bronchodilator Nebulization

Ana Cardoso, Portugal

Preventing Outbreaks of Herpetic Keratitis with L-Lysine

Maria Castroviejo, Sara Pose, Spain

Evaluation of Fast-Dissolving Matrices Containing Platelet-Lysate for Corneal Lesions Treatment

Patrizia Chetoni, Italy

Assessment of the Therapeutic Value of Phloroglucinol in Stargardt's Disease

David Cia, France

Impact of the Routes of Administration on the Effects of Cyclosporine in an Experimental Rat Model of Dry Eye

Nicolas Cimbolini, France

Role of Diagnostic Tests for Dry Eye in Patients with Blepharospasm

Biuk Dubravka, Croatia

Corticosteroids-Induced Toxicity and Cell Death Mechanisms in Vascular Endothelial Cells

Ikram El-Zaoui, France

Functional and Structural Retinal Abnormalities Associated with Didanosine-Induced Retinopathy

Céline Faure, France

The Role of RAGE in in vivo Angiogenesis and AMD

Josephine Glenn, United Kingdom

Efficacy Analysis of Preservative-Free Tafluprost and Timolol in Open-Angle Glaucoma and OHT Patients in a Phase-III Study

John Grunden, USA

Histologic Changes in the Retina and the Choroid After Atelocollagen Gel Injection into the Suprachoroidal Space of Rabbit Eyes

Atsushi Hayashi, Japan

The Change of Retinal Ganglion Cells and Expression of Vascular Endothelial Growth Factor in Diabetic Rat Model

Jie Hyun Kim, South Korea

Synaptic Plasticity of the Retinal Cells in Experimental Glaucoma Model

Jie Hyun Kim, South Korea

The Extract of Litsea japonica Ameliorates Blood-Retinal Barrier Breakdown in db/db Mice

Jin Sook Kim, South Korea

Long-term Outcomes of Intravitreal Triamcinolone Injection or Vitrectomy for Macular Edema Associated with Branch Retinal Vein Occlusion

Eriko Kirii, Japan

E- Posters

Comparison of Spectral Domain and Swept-Source Optical Coherence Tomography in Pathological Myopia

Laurence Lim, Singapore

Polymicrobial versus Monomicrobial Keratitis: a Retrospective Comparative Study

Nigel Lim, Singapore

A Novel Device for Depicting Metamorphopsia Pattern

Po-Kang Lin, Taiwan

Intravitreal Bevacizumab for Myopic Choroidal Neovascularization: Long Term Results

Maria Lopez, Spain

Assessment of the Efficacy of Topical Cyclosporine for Dry Eye Disease Induced by Mustard Gas using Tear Osmolarity Measurement

Mostafa Mafi, Iran

How to do the Microbial Characterization of a New Preservative Free Multi-Dose Devices for Ophthalmic Formulations?

Degenhard Marx, Germany

Ca Channel Blockers Effect on Visual Field in Normal and Hypertensive Primary Open Angle Glaucoma

Diana Melinte, France

Expression Pattern of Kinin-Dependent Genes in Peripheral Blood Mononuclear Cells after Age-Related Macular Degeneration Treatment with Ranibizumab

Katarzyna Michalska-Malecka, Poland

Two Patients with Optic Disc Granuloma due to Cat Scratch Disease

Nakhoul Nakhoul, Israel

Retinal and Peripapillary Nerve Fiber Layer Thickness in Eyes with Thyroid-Associated Ophthalmopathy

Meira Neudorfer, Israel

The Novel Antioxidant SkQ1 is an Effective Protector of Lacrimal Gland from Aging and Dry Eye Syndrome Development

Yulia Novikova, Russia

A New Method of Neural Retina Cultivation in vitro Efficient in Detection, Activation of Hidden Cell Sources for Retinal Regeneration

Yulia Novikova, Russia

Efficient Delivery of siRNA by Atelocollagen in a Murine Laser-induced Choroidal Neovascularization Model

Miho Nozaki, Japan

Comparison of Soluble Tear Muc-16 as a Clinical Endpoint for Dry Eye Studies in Mice and in Humans

George Ousler, USA

Focal/Grid Photocoagulation versus Bevacizumab Plus Laser for Diabetic Macular Edema (DME): a Randomized Trial

Alicia Pareja Ríos, Spain

Intravitreal Injection of Transferrin Preserves Photoreceptors from Light-Induced Degeneration

Emilie Picard, France

Giant Pituitary Adenoma – Mislead Diagnosis with Advanced Normal Tension Glaucoma

Alina Popa Cherecheanu, Romania

Outcomes of Combination Treatments in Refractory Neovascular Glaucoma. A retrospective Review in Patients with Advanced Proliferative Diabetic Retinopathy (PDR)

R Ramoa Osorio, Spain

Safety, Tolerability and Efficacy of Topical Delivery of a Recombinant Human Growth Hormone (rHGH) in a Corneal Debridement Model

MaryJane Rafii, USA

Ophthalmic Manifestations of Prothrombin G20210A Mutation

Riadh Rannen, Tunisia

Successful treatment of Recurrent Conjunctival Papillomatosis by using Topical Interferon Alfa-2b eye drop solution

Toda Ryotaro, Japan

Predictive Factors for Visual Outcomes after Intravitreal Bevacizumab for Diabetic Macular Edema: a Spectral Domain Optical Coherence Tomography Study

Valentina Sarao, Italy

Protective Effects of Agmatine on Lipopolysaccharide-Injured Microglia

Gong Je Seong, South Korea

Effects of Rho-Kinase Inhibitor (Y-27632) on Extraocular Muscle Surgery in Rabbits

Sun Young Shin, South Korea

Serum Vascular Endothelial Growth Factor and Ischemia Modified Albumin Levels after Unilateral and Bilateral Intravitreal Bevacizumab Injections

Uri Soiberman, Israel

E- Posters

Efficacy of Bevacizumab for Macular Edema following Branch Retinal Vein Occlusion Stratified by Baseline Visual Acuity
Min Sagong, South Korea

A Novel Presentation of Zoster Ophthalmicus, HHV 3 (VZV)
Shawkat Michel, Canada

Madarosis as Sinusitis Complication and the Medical Treatment
Mire Shoshi, Kosovo

Dexamethasone Intravitreal Implant for Persistent Diabetic Macular Edema in Vitrectomized Eyes
Maria Stefanidou, Greece

Pilot Study of Bromfenac 0.09% and Difluprednate 0.05% on Macular Volumes and Retinal Thickness after Uncomplicated Cataract Surgery
Melissa Toyos, USA

Clinical Characteristics of Choroidal Neovascularization of Younger Patients in Taiwan
Yu-Tang Tseng, Taiwan

Acuvue Oasys for Astigmatism Contact Lenses for the Correction of Residual Ametropia Following Intacs Implantation in Keratoconus
Ömür Uçakhan-Gündüz, Turkey

Corneal Collagen Crosslinking Following Intrastromal Corneal Ring Segment Implantation for Keratoconus: One Year Follow-Up Results
Ömür Uçakhan-Gündüz, Turkey

Three-Year Follow-Up of Intacs in Keratoconus
Ömür Uçakhan-Gündüz, Turkey

Pre-Operative Use of 0,05% Cyclosporine in Cases of Drug Induced Conjunctivitis in Glaucoma Patients
Olga Vasilyeva, Russia

Central Retinal Thickness Changes and Visual Outcome Following Uncomplicated Phacoemulsification Cataract Surgery in Diabetic Patients without Retinopathy and Normal Controls
Kai-Yun Wang, Taiwan

Functional and Structural Recovery after Intravitreal Anti-VEGF Antibody Treatment for Idiopathic Choroidal Neovascularization in Taiwan
Kai-Yun Wang, Taiwan

Evaluation of Topical SKQ1 in a Murine CAE™ Model of Dry Eye Disease
Andy Whitlock, USA

Expression of Efflux Transporters in Human Ocular Tissues
Xianggen Wu, China

Diquafosol Tetrasodium Increases the Concentration of Mucin-Like Substances in Tears of Normal Human Subjects
Masakazu Yamada, Japan

A Human Corneal Epithelium and Acellular Stroma Model Utilizing a Collagen Vitrigel Membrane and its Application to Drug Permeability Test
Hiroyuki Yamaguchi, Japan

The Effect of Cataract Surgery on Ocular Dominance the Effect of Cataract Surgery on Ocular Dominance
Yossi Yatziv, Israel

Twelve-Months Results from Clinical Practice of Epiretinal Strontium-90 Brachytherapy for the Treatment of Choroidal Neovascularization Secondary to Age-Related Macular Degeneration
Dinah Zur, Israel

ECTOINE: a New Strategy to Control Allergic Conjunctivitis Symptoms
Monica Zurria, Italy



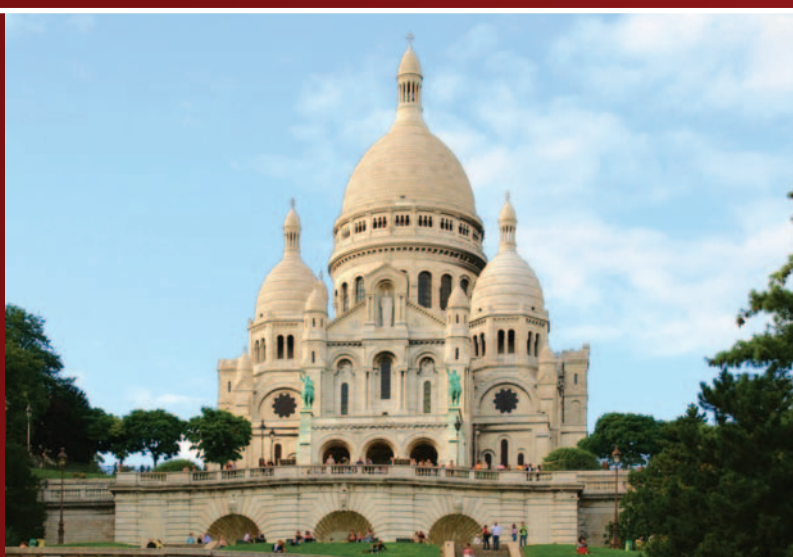
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Abstracts





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

Giorgio Dorin

Clinical Applications Development, IRIDEX, California, USA

Purpose: To define subthreshold micropulse laser therapy within the range of cellular and molecular changes inducible with laser exposures and to describe the therapeutic window for effective treatments without laser burns, once believed essential prerequisite for a useful therapy.

Methods: Analysis of concomitant photothermal interactions of laser photocoagulation, the current effective, but also destructive standard of care for diabetic retinopathy. Postulation of new hypotheses that explain the outcomes of numerous randomized clinical trials comparing the treatment of DME with *non-destructive* subthreshold micropulse versus *destructive* modified ETDRS focal/grid laser photocoagulation, which disprove the deeply rooted notion that a useful treatment must close microaneurysms and kill RPE cells that produce angiogenic mediators.

Results: Similar transactional biological activities, induced *directly* in subthreshold and *indirectly* in standard photocoagulation, elicit similar therapeutic paths and clinical benefits. Destructive laser burns are superfluous and the major cause of complications. Micropulse sublethal photothermal rises effectively alter and rebalance the retinal gene expression profile as an endogenous pharmacotherapy, which, avoiding iatrogenic damage and risks, ultimately result in superior clinical benefits. **Conclusions:** Subthreshold micropulse is an effective *non-destructive* treatment for DME, which has been shown to retain neural retina physiological functions on mf-ERG and to improve retinal sensitivity on microperimetry. The avoidance of laser lesions and enlarging scars discernable at any time postoperatively allows high density applications that lead to new levels of functional and anatomical benefits, enhanced by the possibility of re-treatments pro re nata, alone or in combination with pharmacological agents.

36 Month RISE and RIDE

David Boyer

Retina Vitreous Associates Medical Group, USC/Keck School of Medicine, California, USA

RISE and RIDE are identical, prospective, double-masked, phase III sham-controlled clinical trials. A total of 759 adults with DME (Best Corrected Visual Acuity [BCVA] 20/40-20/320 Snellen equivalent and central foveal thickness [CFT] $\geq 275\mu\text{m}$ on optical coherence tomography [OCT]) were randomized 1:1:1 to monthly 0.5 mg or 0.3 mg RBZ or sham injection. In the third year patients originally randomized to sham were eligible to cross over to monthly 0.5 mg RBZ. Macular laser was available to all, starting at month 3. BCVA was measured. CFT was measured using time-domain OCT. The primary efficacy outcome was the proportion of patients gaining ≥ 15 ETDRS letters in BCVA from baseline at month 24.

Visual acuity benefits of ranibizumab seen at Month 24 were generally maintained at Month 36. At Month 36, the proportions of subjects gaining ≥ 15 ETDRS letters from baseline were: sham/crossover 20.6%, RBZ 0.3 mg 44.0%, and RBZ 0.5 mg 40.9%. At 36 months, the BCVA score, on average, increased from baseline by 12.4 ETDRS letters in the 0.3-mg group and 11.2 ETDRS letters in the 0.5-mg group compared with 4.5 ETDRS letters in the sham/0.5mg group. Mean Month 24 CFT decreases were maintained through Month 36 in patients originally randomized to RBZ. Ocular and systemic AEs were generally consistent with other controlled Month 24 data. APTC events (deaths of unknown or vascular cause, non-fatal myocardial infarctions, and non-fatal strokes) occurred in 10.8% and 10.4% of 0.3 mg and 0.5 mg RBZ patients through Month 36.

Latest Outcomes of Aflibercept for DME Trials

Patricia Udaondo

Retina Department, Nuevo Hospital Universitario y Politécnico La Fe, Spain

Aflibercept (Eylea, formerly VEGF Trap-Eye, Regeneron Pharmaceuticals/Bayer HealthCare) is a fully human VEGF receptor fusion protein designed specifically to be a highly potent blocker of all forms of VEGF-A, as well as the related placental growth factor (PlGF); increase levels of VEGF in vitreous have been measured in patients with diabetic macular edema (DME) that is why its inhibition can play an important role in the management of this condition. We are going to analyze the different aflibercept trials for DME and the present situation of this new intravitreal therapy in the clinical practice.

Latest Outcomes of Steroid Implants for DME

Michaella Goldstein, Anat Loewenstein

Ophthalmology, Tel Aviv Medical Center, Israel

Background: Diabetic retinopathy is one of the leading causes of visual impairment in working-age adults. Corticosteroids have been shown to be efficacious in the treatment for diabetic macular edema (DME) due to its anti-inflammatory properties. New developments in sustained delivery devices of dexamethasone and fluocinolone acetonide show promising results.

Methods: Current literature and clinical trials were reviewed for steroid implant treatments for DME.

Results: Dexamethasone's Ozurdex® implant has promising results for DME. Ozurdex® is FDA approved for macular edema associated with retinal vein occlusion and uveitis. While it has been shown to be beneficial for vitrectomized eyes with DME, its use is still off-label. The fluocinolone-containing implant, Iluvien® demonstrated to be efficacious for DME for 3 years in the FAME trial and is now approved in Europe, but has yet to receive FDA approval. While steroids have raised safety concerns over increased intraocular pressure (IOP) and cataract development, the new slow-release devices have improved the safety profiles compared to intravitreal injections.

Conclusion: Slow-release steroid devices are advantageous and promising in the treatment of DME. Steroid treatment may be considered a good option for patients who have limited response to anti-VEGF injections or laser therapy.

Combination Therapy for Diabetic Macular Edema

Albert Augustin

Department of Ophthalmology, Klinikum 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.

Mechanisms of Action of Corticoid Hormones: Gluco and Mineralocorticoid Receptors

Nicolette Farman

Centre de Recherche des Cordeliers, Inserm U 872, France

Glucocorticoid hormones (GC) act through binding to the glucocorticoid receptor (GR) to exert pleiotropic functions on cell homeostasis and metabolism in almost all tissues. GC can also bind to the mineralocorticoid receptor (MR), possibly leading to distinct (and mostly unknown) effects. Both GR and MR are ligand-dependent transcription factors of the nuclear receptor superfamily. The MR has similar high affinity for aldosterone and for glucocorticoid hormones (that largely prevail in the plasma); permanent occupancy of the MR by circulating glucocorticoids is prevented to a large extent by the metabolizing enzyme 11- β hydroxysteroid dehydrogenase type II (HSD2) in classical mineralocorticoid-sensitive tissues that co-express MR and HSD2.

The MR is classically involved in the regulation of renal sodium reabsorption, contributing to body extra-cellular volume and blood pressure regulation. The aldosterone/MR pathway up-regulates the activity of the epithelial sodium channel, and also favors potassium excretion through regulation of K channels.

Non-classical mineralocorticoid targets include cardiomyocyte and vascular cells, neurons, adipocytes and keratinocytes. Pathological inappropriate MR activation has been evidenced in human cardiovascular diseases, and its antagonism by anti-mineralocorticoid drugs (spironolactone, eplerenone) has proven to be mostly beneficial to limit morbidity and mortality in heart failure and myocardial infarction. In diabetic nephropathy, reduction of renal injury has been observed following selective aldosterone blockade, in animal studies and human trials.

We now extend the concept of novel mineralocorticoid target to the retina, by identifying cell-specific MR and HSD2 expression and cellular targets, to elucidate the pathophysiological role of MR signaling in the neuroretina and choroid.

A Comprehensive Patient-Level Meta-Analysis Evaluating Systemic Safety Profiles of Marketed Formulations of Ranibizumab in AMD, RVO and DME

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Background: This meta-analysis compares safety profiles of sham, 0.3mg and 0.5mg ranibizumab using pooled safety data from a database of 22 Phase II, III and IIIb studies in age-related macular degeneration (AMD), retinal vein occlusion (RVO) and diabetic macular edema (DME).

Methods: The safety database comprises 22 studies and 10,300 patients (mean follow-up 15.9 months; maximum 64.2 months). The database contains patient-level data including dosing information, demographics, and key baseline ocular and systemic risk factors, and reported adverse events for patients from their first ranibizumab injection through their last evaluation. In this analysis, pairwise treatment comparisons (0.5mg versus control [sham/PDT], 0.3mg versus control, and 0.5mg versus 0.3mg) were performed, incorporating data from 14 studies that had both treatment arms being evaluated. Event rates for key prospectively defined endpoints were evaluated by indication.

Results: Pairwise comparisons showed, in DME, higher rates of death (1.6 vs 0.7, per 100 patient-years), stroke (1.1 vs 0.9, per 100 patient-years), and wound healing complications (1.6 vs 0, per 100 patient-years) for 0.5mg versus control, and higher rate of death for 0.3mg versus control (1.6 vs 0.7, per 100 patient-years). These imbalances were not observed in AMD or RVO. No imbalances in rates were observed for other key systemic events such as myocardial infarction, cardiovascular events, hemorrhage, gastrointestinal perforation, hypertension and proteinuria for all three patient populations.

Conclusions: This represents the largest comprehensive analysis of safety data for ranibizumab to date. These results are consistent with the established safety profile of ranibizumab.

Ocular Toxicity of Different Glucocorticoids

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Glucocorticoids are commonly used in the treatment of ocular pathologies associated with inflammation, vascular leakage, vessels abnormalities, and ocular neovascularization. Intravitreal injections of Triamcinolone Acetonide (TA) are used for the treatment of macular oedema, resulting in a dramatic macular thickness reduction, inconsistently correlated with long-term functional recovery. For the treatment of choroidal neovascularizations associated with Age-related Macular Degeneration (AMD), TA decreases the vascular leakage on the short-term, although its long-term effect on visual acuity gain remains controversial. We showed that glucocorticoids induce a specific and dose-dependent reduction in retinal cell viability, affecting essentially cells from the pigmented epithelium (RPE) and Müller glial cells (RMG). Caspase-dependent or independent apoptosis pathways were not detected in vivo or in vitro but cytoplasmic vacuolization was observed in both circumstances. Further analysis indicated that these cells die by an alternative cell death pathway called paraptosis.

We also show, that glucocorticoids exert direct toxic effect on endothelial cells through different cell death mechanisms, including caspase-independent mechanisms, depending on the type of glucocorticoid tested. When used in animal models of neovascularization TA induces endothelial cell death and decreases the amount of neovessels. However, this effect is also seen on endothelial cells of the general circulation challenging the mode of administration of these compounds.

These results have important implications on the therapeutic potential and safety use of glucocorticoids in human eyes. They also show the importance of considering cells death pathways other than caspases in the evaluation of these items.

Anti-Edematous Effects of Glucocorticoids: Mechanisms of Action

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Hydration of the retina depends on the activity of retinal Muller glial cells (RMG) that ensure functional connections between retinal neurons, blood vessels, vitreous and subretinal spaces. Potassium channel Kir4.1 and aquaporin-4 (AQP4) expressed in RMG are 2 main channels controlling retinal fluid movement. High doses of glucocorticoids are largely used in ophthalmology to treat retinal edema (which results from disturbance of fluid homeostasis), but could be accompanied by severe side effects. We used Kir4.1 and AQP4 as reporters of the action of dexamethasone (dex) and triamcinolone acetonide (TA) in the normal and endotoxin-induced uveitis (EIU) rat retinas. We showed distinct channel regulations 24 hours after intravitreal injection of 2 glucocorticoids.

Dex up-regulated Kir4.1 (not AQP4) in healthy and inflamed retinas, while TA induced AQP4 (not Kir4.1) down-regulation in normal retina and up-regulation in EIU. The differential gene regulations were evident at lower concentration (100 nM) than those used in clinics. We found, in EIU, down-regulation of glucocorticoid receptor transcripts, an effect prevented by 100 nM dex or TA intravitreal injections. EIU-induced reduction of Kir4.1 expression was prevented by dex, not TA, while TA (not dex) increased AQP4. Our results show that dex and TA are far from being equivalent to modulate RMG channels, a notion that should be taken into account to improve their clinical use. Furthermore, low doses of glucocorticoids could be efficient for therapeutic goals and may limit their toxicity.

The Theory of Cell Therapy for Uveitis

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Immunology, INSERM, France

It is now clearly established that CD4+CD25+Foxp3+ regulatory T cells (Tregs) play a critical role in preventing autoimmune diseases. In humans and mice, extreme Tregs deficiency is associated with a severe autoimmune syndrome leading to the death of children or pups. Regarding uveitis, Tregs have been shown to control the disease in mice and a Treg deficiency has been reported in patients. Thus, Treg cellular therapy is a promising in the treatment of chronic inflammatory diseases. At the moment, due technical limitations, only polyclonal Tregs can be used clinically. But when they were administered systemically, they did not control these diseases. A therapeutic alternative would consist in injecting pre-activated purified polyclonal Tregs directly into the site targeting by the autoimmune attack. The rationale for this approach is that in vitro pre-activation of polyclonal Tregs will trigger their suppressive function, which will take effect in the inflamed site after their injection. Indeed, Tregs may be capable of bystander suppression on all immune cells present in the inflamed eye. This approach can be evaluated in uveitis since cells can be injected directly into the vitreous. Furthermore, considering the small size of this organ, a therapeutic effect could be obtained with small cell numbers that are achievable without expansion in vitro. We first tested this cellular therapy strategy in a murine model. The pre-clinical data fully support this approach and lead us to propose a clinical trial in patients with severe bilateral uveitis and poor visual acuity who are refractory to other treatments.

Pragmatic Use of Diagnostic Procedures Before Treatment of CNV in AMD

Jonathan Dowler

The London Clinic, United Kingdom

The increasing incidence of neovascular AMD with age, the progressively increasing longevity of the population together with the need for ongoing surveillance and treatment, create an exponentially increasing demand for resources to manage acute manifestations of the disease. At the same time there is a need to ensure that diagnosis is secure, that disease variants such as RAP and IPCV are identified, that accurate prognostic information is gathered to manage patient expectations, and that baseline parameters sufficient to judge treatment efficacy and guide retreatment strategies are recorded. This presentation represents an evidence based approach to the development of a pragmatic algorithm for the evaluation of patients newly presenting with choroidal neovascularization which reconciles limitations of time and resources with the need to optimize management.

How Intravitreal Injections Change the Imaging Strategies for Diagnosis and Follow-Up of RVO

Michel Paques

CHNO des Quinze-Vingts & Institut de la Vision, France

The strong relationship between retinal structure and function in retinal vein occlusions shifted our practice toward image-based strategy. Optical coherence tomography (OCT) and the good long-term tolerance of anti-VEGF therapy profoundly changed the way we manage retinal vein occlusions. It is now possible to consider multiple injection at the very beginning of the disease. It is even possible to consider treating recurrences of edema before any visual loss, which is a frequent clinical situation. Not only the effect of the various intravitreal drugs can be objectively appreciated, but it also helps to understand the cause of residual visual loss when oedema has disappeared. Indeed, loss of the outer retinal structures in the fovea argues against aggressively pursuing treatment, although the resolution of perifoveal edema even in the presence of foveal atrophy may be well appreciated by patients. Also, the presence of surgically accessible vitreomacular traction and/or epiretinal membrane can be documented by OCT. These evolution progressively shrinks the place of fluorescein angiography. On the contrary, indocyanine green angiography may be useful to document the presence of macroaneurysms, a frequent cause of persistent macular edema.

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

Francesco Bandello, Maurizio Battaglia Parodi

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Diabetic macular edema (DME) is a major cause of vision loss in the diabetic patients, occurring in about 10% of all patients with diabetes. The Early Treatment Diabetic Retinopathy Study clinical trial defined the concept of clinically significant macular edema (CSME), and concluded that laser photocoagulation was able to improve the prognosis for eyes presenting with CSME. Focal/grid laser photocoagulation led to a 50% reduction in moderate visual loss at 3 years, with a best-corrected visual acuity worsening in the 12% and 24% of treated and untreated eyes respectively, over a three-year follow-up.

With the recent advent of other therapeutic options, new hopes can be offered to patients affected by DME. First step in the DME management is the appropriate classification. Combining the data of biomicroscopic examination and optical coherence tomography, DME can be classified in vasogenic, non-vasogenic, tractional, and mixed.

Vasogenic DME can be effectively treated by means of laser grid/focal photocoagulation.

Non-vasogenic DME, being generally poor responsive to laser, can be managed with anti-VEGF or steroids, whereas tractional DME should be addressed to surgery, possibly combined with anti-VEGF or steroids.

Overall, under the same definition of DME there are many clinical manifestations, and a specific approach should be chosen for each specific DME subtype.

Update on Clinical Trials

Bart Leroy

Dept of Ophthalmology & Ctr for Medical Genetics, Ghent University Hospital & Ghent University, East-Flanders, Belgium

Purpose: The talk will focus on an overview of gene therapy trials for inherited retinal disease, which are currently ongoing or have been finalized. In addition, successful trials in animal models will be mentioned.

Methods: Systematic review.

Results: Currently there are 6 trials around the World focusing on gene therapy for RPE65-related Leber congenital amaurosis, with good safety outcomes and considerable success in restoring some visual function. In addition, gene therapy trials are ongoing for Stargardt macular dystrophy (ABCA4), Usher type 1B (MYO7A), MERTK-related early-onset retinal dystrophy and choroideraemia (CHM1). So far, no safety issues have been encountered in these latter trials, whereas it is too early to evaluate restoration and/or stabilization of function.

Success in animal models has been obtained for X-linked retinoschisis, as well as models of CNGA3- and CNGB3-related achromatopsia.

Conclusions: Gene therapy trials for inherited retinal dystrophies are safe and somewhat successful in restoring and/or stabilizing retinal function.

Diabetic Retinopathy Experimental Treatments of Diabetic Retinopathy

David Boyer

Retina Vitreous Associates Medical Group, USC/Keck School of Medicine, California, USA

Treatments for Diabetic Macular Edema

New Lasers

1. Subthreshold
2. Navalis

PVD creation

1. Vitrase
2. Vitreosolve (Urea)
3. Integrin
4. Microplasmin

Anti-VEGF

- Ranibizumab FDA approved RIDE/RISE 0.3mg dose
READ 3 High dose 2mg and 0.5mg no difference in efficacy or safety
- Bevacizumab off label BOLT Study/DRCRnet showed superior to laser
- Pegaptanib Aptamer against VEGF165
- Aflibercept (Eylea) (VEGF Trap Eye) Soluble VEGF receptor fusion protein. Binds all forms of VEGF-A and binds placental growth factors

DRCR.Net Protocol T Compares Aflibercept/Bevacizumab/Ranibizumab in DME

Intraocular Steroids Pipeline

Ozurdex is a sustained-delivery system for long term delivery of dexamethasone.

Mediur implant (Iluvien)

Long acting delivery of fluocinolone (0.2µg/day) up to 3 years, non biodegradable ICo

- 2nd generation antisense
- Inhibits C-raf expression
- Blocks MAP kinase signal

Integrins (Allegro)

Integrins are receptors that mediate attachment between a cell and the tissues surrounding it, which may be other cells or the ECM.

AKB-9778 (Aeripo)

Works through inhibition of human protein tyrosine phosphatase beta (HPTPβ) and enhances Tie2 tyrosine kinase with immunoglobulin-like and EGF-like domains activation and signaling.

Quark ---QRK202 Matisse

Intravitreal injection

PF-04523655 (3mg,4.5mg,6mg) alone vs PF-04523655 in combination with ranibizumab vs ranibizumab alone

Mecamylamine

Antagonist of nicotinic acetylcholine receptors

Humanized anti-CCR2 monoclonal antibody (Takeda)

The MCP-1/CCR2 axis is believed to be important in ophthalmic diseases that are characterized by inflammation, fibroproliferation, and/or neovascularization.

The Choice of the Optimal Viral Vector for Severe Retinal dystrophies

Yvan Arsenijevic

Ophthalmology, University of lausanne, Jules-Gonin Eye Hospital, Switzerland

Gene therapy for severe retinal dystrophies directly affecting the photoreceptors is still a challenge for clinical application. One of the main hurdles is to generate high transgene expression specifically in rods and cones. So far, mainly ubiquitous promoters show the most efficient gene transfer, but such constructs raise safety concerns, knowing that vectors can be found in the peripheral blood after subretinal injection. In the present study, we investigate specific rod promoter sequences to drive rapid, precise and high transgene expression in rods.

Using AAV2/8 vectors, different sequences of the human Phosphodiesterase-6b gene (*hPDE6b*) were tested for their activity and efficiency in normal mice as well as in a severe form of *hPde6b* deficiency, the *Rd10* mouse. In our colony, photoreceptor death appeared at PN18 and rod loss was complete at PN28.

A short sequence of the *hPDE6b* promoter (-93 to +53) shows a more rapid expression than the CMV promoter in the adult normal retina and was used for a gene replacement strategy in the *Rd10* retina. In contrast with published works with CMV and Rhodopsin promoters, the injection of the AAV2/8-hPDE6bp-hPDE6b at PN9 not only rescued photoreceptors, but also restored rod function recorded at PN44. Retinal sensitivity was increased by around 300 fold. Rod function recovery correlates with the presence of outer segments expressing Pde6b.

The *hPDE6b* promoter (-93 to +53) sequence is the shortest rod-specific sequence allowing efficient gene transfer into rods and is thus of great interest for AAV vector design for gene transfer in these cells.

Corneal Imaging in Dry Eye

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The most recently developed in vivo confocal microscopy technology may now noninvasively provide excellent histologic-like patterns of the ocular surface tissues. Normal or metaplastic epithelial cells, inflammatory infiltrates, dendritic cells, rolling and extravasating cells, or new blood vessels can be easily identified without more invasive techniques. We used this technique in various inflammatory eye diseases to identify cell processes at a level allowing detection of live diapedesis, activated dendritic cells, or chromatin fragmentation, all of which were well correlated with cytological patterns. Animal models were also developed and they confirmed the usefulness of noninvasive confocal microscopy for inflammation or angiogenesis models. This technology has thus become a new routine method to explore ocular surface disorders and also has many promising applications in immunology, pharmacology, and angiogenesis research.

The Basis of Staining by Topical Dyes and its Relevance to Clinical Practice

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Water-soluble dyes are excluded from ocular surface epithelia by tight junctions and mature glycocalyxes. Shed cells can take up dye. Here, we review the debate as to the mechanism of staining. A proportion of normal corneas, show a time-dependent, punctate fluorescein uptake which we hypothesise is due to a graded loss of the glycocalyx barrier, permitting transcellular entry into pre-shed cells. In pathological staining, there is little evidence of 'micropooling' at sites of cells shedding; the term 'punctate erosion' may be a misnomer. It is more likely that the initial event involves transcellular dye entry and diffusion across defective tight junctions. Different dye staining characteristics probably reflect differences in molecular size and other physical properties, coupled with differences in visibility under the conditions of illumination. This is most relevant to the rapid epithelial spread of fluorescein from sites of punctate staining, compared to the apparent confinement of dyes such as lissamine green. We assume that fluorescein, with the lowest molecular weight, spreads initially by a paracellular route and secondarily by transcellular diffusion. Solution-Induced Corneal Staining (SICS) is related to the use of certain contact lens care solutions and has been attributed to the non-pathological uptake of cationic preservatives, such as the biguanides, into epithelial membranes and to secondary binding of the fluorescein anion. It is a transient phenomenon which usually does not imply corneal toxicity. The use of various systems of grading and the need to standardise the timing of grading will be discussed briefly.

OCT of Surface Eye Tumors

Rick Fraunfelder

Ophthalmology, Casey Eye Institute, USA

OCT imaging of surface eye tumors can be an adjunctive diagnostic tool in the management of multiple types of external eye malignancies. Malignant melanoma, Squamous cell carcinoma, lymphoma and pre-malignant processes are presented. OCT imaging alone is probably not indicated without excisional biopsy as the resolution is not accurate to the level needed to rule out cancer.

Fully Automated Quantification of Morphological Features of Different Epithelial Cell Layers in Human Corneas

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²Translational Centre of Regenerative Medicine, University of Leipzig, Germany

³Institute for Applied Computer Science and Automation, Karlsruhe Institute of Technology, Germany

Purpose: The purpose of this study was to introduce an effective methodology for an automatic quantitative analysis of different cell layers of the corneal epithelium.

Methods: In vivo confocal laser scanning microscopy was performed on the unilateral eyes of healthy volunteers. Stacks of 160 images (400 · 400 nm) with an interslice distance of 0.4 nm were used to generate full thickness volume data sets of the epithelium. Size and shape factors of basal (BC) and intermediate cell (IC) layers were quantified using appropriate image analysis algorithms. Evaluated parameters include mean area, compactness, solidity, major and minor diameter, and maximum boundary distance.

Results: Mean area of BC and IC demonstrated a linear increase from 80 to 160 nm². A similar trend was noted with major and minor diameter and maximum boundary distance. Major diameters of BC and IC measured between 13.2 and 17.0 nm, whereas minor diameter of these cells measured between 8.6 and 12.4 nm. The maximum boundary distance of BC and IC ranged from 7.0 to 9.1 nm. Compactness of epithelial cells clustered around 1.45 and 1.5, whereas cell solidity measured between 1.0 and 1.03.

Conclusion: Several characteristic morphologic quantities can be calculated using this methodology without manual intervention. Our study demonstrated promising results and suggests that this fully automated morphologic quantification can be successfully applied to assess microstructural changes of the epithelium in normal and various corneal disorders.

Scheimpflug Analysis in Corneal Ectasia

Ömür Uçakhan-Gündüz

Department of Ophthalmology, Ankara University Faculty of Medicine, Turkey

Scheimpflug imaging continues to be an important part of anterior segment evaluation and is particularly helpful in corneal ectasia. This technology enables clinicians to make early and accurate diagnosis of keratoconus or post-LASIK ectasia, follow progression of the disease, plan treatment/correction options and monitor post-treatment outcomes. This talk will describe the technology and give examples on the clinical uses of Scheimpflug imaging.

New Approaches to Screening for AMD

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Background: Age-related macular degeneration (AMD) is one of the leading causes of blindness in developed countries today. Early detection of choroidal neovascularization is essential for enabling treatment and halting the progression of vision loss. New developments in ophthalmology have improved the methods of screening for AMD.

Methods: Current literature and clinical trials were reviewed to evaluate new approaches in screening for AMD.

Results: Traditional methods of screening for visual changes include daily use of the Amsler grid and in office visual acuity tests, dilated eye exams, funduscopy or ophthalmoscopy, fundus photography, and fluorescein angiography. Modern devices such as optical coherence tomography (OCT), autofluorescence, and home perimetry have allowed for higher precision in the detection and progression of maculopathy. These tools can detect subretinal changes in new and intermediate AMD in great detail and high resolutions. Home preferential hyper acuity perimeter (PHP) allows patients to self-monitor their vision from their own homes with greater sensitivity and specificity than the Amsler grid.

Conclusion: The excellent contribution of new technology and devices such as spectral domain-OCT and PHP to the traditional methods of AMD screening have remarkably increased the ability to detect visual and anatomical changes to the retina.

The Role of Imaging in the Management of Dry AMD

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Precise identification and quantification of geographic atrophy (GA) is needed in order to evaluate the prognostic factors of progression rate spontaneously and after treatment. Fundus photography has been used in clinical trials to detect GA and in longitudinal studies to perform follow up. However, even graders at reading centers reported difficulty in measurement of atrophic patches. The contrast may be improved on the multicolor imaging system.

In fluorescein angiography, the hyperfluorescent areas show a high contrast levels for delineation. However, other changes may also lead to an increased fluorescence signal. In indocyanine green angiography (ICG-A), atrophic patches appear as hypofluorescent areas with loss of background fluorescence due to atrophy of the choriocapillaris.

Fundus Autofluorescence (FAF) identifies the junctional zone of GA between the very low FAF signals and the perilesional nonatrophic retina that has been shown to be of prognostic relevance. GA progression rate on FAF has been approved by the FDA as primary outcome measure in clinical trials on GA.

High-resolution spectral-domain OCT (SD-OCT) reveals morphological disturbances of the outer retinal layers and a hyporeflectivity in the choriocapillaris. The dynamic nature of development and progression of atrophy can be longitudinally analyzed. An "en face" fundus image may be helpful. Quantification of GA based on one imaging technique alone may be challenging. Simultaneous recording of cSLO and SD-OCT images with an exact topographic overlay in different imaging modalities allows to document the natural history of the disease, elucidate pathogenetic mechanisms and identify possible therapeutic effects.

AREDS2: The Rationale of Supplement Integration and the Role of Macular Pigment Measurement

Paul Bernstein

Moran Eye Center, University of Utah, Utah, USA

AREDS2 is a 5-year long, randomized, placebo controlled clinical study that has enrolled over 4000 subjects at nearly 100 centers which is dedicated to the determination of whether supplementation with lutein and zeaxanthin and/or omega-3 fatty acids can slow the progression of intermediate AMD to advanced AMD. The final results of the study due to be released in mid-2013 are certain to have major impact on clinical practice patterns just as the original AREDS study brought antioxidant supplementation into common use by retina specialists in their patients at high risk for visual loss due to AMD. In this talk, I will review the rationale for the selection of lutein/zeaxanthin (10 mg/2 mg) and EPA/DHA (650mg/350 mg) as the primary treatment arms of the study, and I will also report the initial results of the Moran Eye Center's ancillary study which measured our AREDS2 subjects' macular pigment optical density (MPOD) annually. The value of large scale clinical trials of nutritional interventions against AMD and the clinical importance of MPOD measurement in clinical practice will be discussed.

The Role of Genetic Testing in the Management of AMD

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Background: Age Related Macular Degeneration (AMD) is strongly associated with several single nucleotide polymorphisms (SNPs). While understanding the genetics of the disease has provided important insight into its pathogenesis, the role of genetic testing in the management of the disease is still evolving.

Methods: Review of the literature and evaluation of genetic markers for the diagnosis of AMD and for assessment of pharmacogenetic interactions among 255 neovascular AMD patients.

Results: Detection of risk alleles for AMD has been utilized by several groups to generate a risk assessment models for the development and progression of the disease. Several studies described an association between such risk alleles and response to therapy. Evaluating genetics for the diagnosis of AMD among 255 AMD patients yielded diagnostic accuracy that is lower than the standard accepted for clinical use.

Conclusions: While several genetic markers are strongly associated with AMD, detection of these markers for routine clinical purposes such as diagnosis of the disease, and prediction of progression and pharmacogenetic interactions provides limited value at the current time. Combining genetics with additional factors may be useful to develop appropriate tests for these purposes.

The TOGA Study: A Phase II/III Study Evaluating the Treatment with ORACEA doxycycline for Geographic Atrophy

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Multiple factors relate to the development of atrophic AMD, including chronic inflammation mediated via the complement pathway and by macrophage and microglia activation, oxidative stress, programmed cell death, and genetic and environmental risks. Tetracycline derivatives are potential therapeutic candidates for atrophic AMD given their ability to reduce reactive oxygen species, inhibit metalloproteinases, inhibit caspase activation thus preventing cell death, prevent complement activation, and inhibit cytokine production by their effects on microglia and T-cell activation. ORACEA (40 mg doxycycline; Galderma Laboratories, Fort Worth, Texas) is a tetracycline derivative that has an excellent long-term safety profile and at low doses (<40 mg/day) has anti-inflammatory properties. It is FDA approved for the treatment of rosacea. The TOGA Study is a 30-month, multicenter, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of 40 mg doxycycline in 286 study subjects with geographic atrophy. The primary endpoint is the change in the rate of enlargement in area of geographic atrophy over a 24-month treatment period as evaluated by color fundus photographs. Patient recruitment will commence in the spring of 2013.

Progress in the Development of Emixustat Hydrochloride for the Treatment of Dry AMD

Nathan Mata, John Chandler

Clinical Development, Acucela, Inc., Washington, USA

Light activation of rhodopsin is known to produce toxic retinoid by-products (e.g., A2E) which have been implicated in pathogenesis of geographic atrophy (GA). It is theorized that slowing activity of the visual cycle would be an effective means of reducing retinoid toxins and preserving the health of ocular tissues. Acucela is developing emixustat hydrochloride (HCL), an investigational oral drug for the treatment of GA associated with dry AMD. Emixustat HCL reduces visual cycle activity by interacting with the visual cycle isomerase, retinal pigment epithelium protein 65 (RPE65). Because RPE65 is uniquely expressed in ocular tissue, emixustat HCL has a highly specific effect within the eye. In preclinical studies, emixustat HCL has been shown to: 1) reduce rod photoreceptor activity; 2) protect photoreceptors from light-mediated damage; and 3) reduce the accumulation of A2E. In human subjects, emixustat HCL effectively modulated rod photoreceptor activity in a dose-dependent and reversible manner. Across 6 clinical studies which have been completed to date, emixustat HCL has shown a favorable safety profile with minimal systemic adverse events. Adverse events were typically ocular in nature with chromatopsia and delayed dark adaptation seen most frequently; these events are expected based upon the understood mechanism of emixustat HCL action. Experience gained in these clinical trials has provided the basis for continued development of emixustat HCL for the treatment of GA. A Phase 2b/3 study with approximately 440 GA patients is being initiated and enrollment is scheduled to begin in early 2013.

Alprostadiol for Dry Age Related Macular Degeneration (AMD)

Albert Augustin

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Purpose: The aim of this study was to assess efficacy and safety of intravenous alprostadiol infusion in patients with dry AMD.

Methods: This was a prospective, randomized, multi-center study. Patients were treated with intravenous infusion of either 60 µg alprostadiol 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 alprostadiol 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 alprostadiol 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 alprostadiol.

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

Vascular Risk Factors, Ethnicity and Glaucoma

Alon Harris

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The pathogenesis of glaucomatous optic neuropathy is not fully understood, and several pathogenic mechanisms are proposed to co-exist. Current treatment of glaucoma is limited to reduction of intraocular pressure (IOP) and many large clinical trials have demonstrated that many patients continue to experience glaucoma progression despite medically lowered IOP. The identification of ocular blood flow deficits in patients with glaucoma continue to be well documented. In large population based trails, reduced ocular perfusion pressure has been linked to the prevalence, incidence and progression of glaucoma. Although glaucoma has been associated with ocular blood flow deficits, there is a void of large longitudinal prospective clinical studies investigating ocular blood flow and glaucoma progression. In addition, different risk factors for specific ethnic and racial groups, especially vascular risk factors in persons of African Descent, have begun to be identified. An update on vascular risk factors, ethnicity and glaucoma will be presented with emphasis on what is currently known and what still needs to be investigated to reduce glaucoma pathology.

Optic Nerve Compartmentation in Normal Tension Glaucoma

Hanspeter E. Killer

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The spine, the brain and the optic nerve are surrounded by cerebrospinal fluid (CSF). It provides nutrition for neurons, axons and glial cells as well as a removal medium for toxic metabolites from the central nervous system (CNS). The importance of CSF is reflected in its proteome that contains more than 2000 different proteins. For a long time CSF was thought to be homogenous and continuous in composition and pressure throughout all CSF containing spaces, i.e. ventricles, subarachnoid spaces and cisterns. The concept of continuity was challenged when the concentration of beta-trace protein (L-PGDS) was simultaneously compared between the spinal CSF and the CSF in the subarachnoid space of the optic nerve SASON in patients with anterior ischemic optic neuropathy (AION), normal tension glaucoma (NTG) and papilledema. The reason for this concentration gradient is thought to be found in the dynamic anatomy of the SASON which resembles a cul de sac with an easy access for CSF but an impaired outflow capacity. The SASON is lined with meningotheelial cells that are highly reactive to pressure and biochemical stimuli. A second argument against a homogenous CSF comes from studies with computer assisted cisternography in patients with papilledema and normal tension glaucoma. These studies demonstrated large concentration gradients of contrast loaded CSF between the intracranial CSF spaces and the SASON, thus rendering evidence for reduced CSF circulation in the SASON.

The pathology of normal tension glaucoma is yet far from being understood. The possible pathophysiological mechanisms include intraocular pressure (IOP) and vascular dysregulation. Considering the recent cisternographic findings that demonstrate impaired CSF circulation in the SASON with a disturbed CSF composition, a third component, toxicity of local CSF stasis seems very likely.

Cerebrospinal Fluid Pressure and Glaucoma: Ocular Perfusion Aspects

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Intraocular pressure (IOP) is the most important risk factor for glaucoma and treatment of the disease is directed towards lowering IOP. The disease is, however, not closely linked to the level of IOP and many subjects with increased IOP never develop glaucoma. It is nowadays assumed that several factors, including biomechanical properties of ocular tissues, cerebrospinal fluid pressure and blood flow to the ocular tissues. The relation between these factors is complex and not fully elucidated. Undoubtedly IOP is an important regulator of ocular perfusion, because it is closely linked to venous pressure in the eye. In addition, there is evidence that the ocular circulation shows less regulatory capacity when venous pressure is modified than when arterial pressure is modified. The biomechanical properties of tissue may also determine the level of ocular perfusion, because mechanical deformation of the lamina cribrosa may affect blood flow through the posterior ciliary arteries. Finally, cerebrospinal fluid pressure may be related to ocular perfusion, because it affects pressure distribution and fluid exchange. An overview of the potential interaction of these factors in the pathogenesis of glaucoma is given.

Cerebrospinal Fluid Pressure and Glaucoma: Anatomical Facts and Theoretical Myths

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Features of normal-pressure glaucoma such as loss of neuroretinal rim, a deepening of the optic cup, and an enlargement of parapapillary atrophy are not found in vascular optic neuropathy, with the exception of an enlargement and deepening of the optic cup in arteritic anterior ischemic optic neuropathy. One may additionally take into account (1) that it is the trans lamina cribrosa pressure difference (and not the transcorneal pressure difference, i.e. the so called "intraocular pressure") which is of importance for the physiology and pathophysiology of the optic nerve head; (2) that studies have shown that the anatomy of the optic nerve head including the intraocular pressure, the anatomy and biomechanics of the lamina cribrosa and peripapillary sclera, retrobulbar orbital cerebrospinal fluid pressure and the retrobulbar optic nerve tissue pressure may be of importance for the pathogenesis of the highly myopic type of chronic open-angle glaucoma; (3) that studies have suggested a physiologic association between the pressure in all three fluid filled compartments, i.e. the systemic arterial blood pressure, the cerebrospinal fluid pressure and the intraocular pressure; (4) that an experimental investigation suggested that a low cerebrospinal fluid pressure may play a role in the pathogenesis of normal (intraocular-) pressure glaucoma; and (5) that recent clinical studies reported that patients with normal (intraocular-) pressure glaucoma had significantly lower cerebrospinal fluid pressure and a higher trans lamina cribrosa pressure difference when compared to normal subjects. One may, therefore, postulate that a low cerebrospinal fluid pressure may be associated with normal (intraocular-) pressure glaucoma.

Adverse Ocular Drug Reactions Recently Identified by the National Registry of Drug-Induced Ocular Side Effects

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Purpose: To report recent signals identified by the National Registry of Drug-Induced Ocular Side Effects.

Methods: Case reports from the National Registry, World Health Organization, and Food and Drug Administration were collected and adverse drug reactions categorized as follows: certain, probable/likely, possible, unlikely, conditional/unclassifiable.

Results: Pamidronate, hydroxychloroquine, fluoroquinolones, and Isotretinoin have been associated with previously unreported visual side effects. These adverse events are presented.

Conclusion: Recent reports to the National Registry have led to identification of adverse drug reaction/medication combinations of which ophthalmologists should be aware.

Intramural Deposition of Alexidine into Heated Bausch & Lomb ReNu Plastic Bottles and the Worldwide *Fusarium* Keratitis Epidemic of 2004-2006

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Purpose: Our previous studies indicated that heating ReNu containers ($>42^{\circ}\text{C} \leq 56^{\circ}\text{C}$) resulted in pan-antimicrobial inadequacy of the disinfectant, alexidine. The present study was undertaken to determine the exact mechanism of this pharmaceutical failure.

Methods: To determine if an alexidine-inhibiting compound might be leaching from heated ReNu bottles, phosphate buffered saline (PBS) was incubated at room temperature and 56°C in ReNu bottles and tested for its ability to inhibit alexidine's anti-*Fusarium* capability. Similar PBS samples were analyzed for potential leachates by Raman spectroscopy, with and without colloidal silver nanoparticles. To determine if the alexidine concentration decreases in heated vs. unheated ReNu bottles, alexidine levels were measured by Liquid Chromatography-Mass Spectroscopy. To determine if alexidine migrates and deposits into heated ReNu plastic containers, bottles were methanol extracted and analyzed for alexidine by Fourier Transform Infrared Spectroscopy.

Results: Alexidine's anti-*Fusarium* capability was not neutralized with a PBS solution that had been heated in ReNu containers, and no leachates were identified. The alexidine concentration in ReNu bottles was 2.8 times greater in the unheated (vs. heated) solution. Alexidine deposited into the ReNu bottle wall at an amount 3.0-3.6 times greater in the heated (vs. unheated) container.

Conclusions: Alexidine preferentially deposits into the walls of heated ReNu plastic bottles, thereby diminishing its concentration within the solution and allowing *Fusarium* and other antimicrobial growth. This phenomenon appears to be an unusual mechanism of pharmaceutical failure which may have resulted in the worldwide ReNu-related *Fusarium* keratitis epidemic of 2004-2006.

Safety and Efficacy of Anti VEGF Therapy in Retinal Diseases

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VEGF has been implicated in a variety of retinal vascular conditions and treatment with anti-VEGF agents has emerged as the standard of care in the management of these diseases. Bevacizumab, Ranimizumab and Aflibercept are currently approved for use in a variety of retinal diseases.

However, VEGF has also been described as a neuroprotectant [22-25], particularly against oxidative stress in the central nervous system [26-30] and the retina [31-32]. Thus, total VEGF blockade with anti-VEGF agents may have unintended negative effects.[33]. We summarize the role of VEGF in neuroprotection, and describe the potential consequences of anti-VEGF therapy on retinal ganglion cells. In addition we will also describe the effect of escalating doses of anti vegf agents on a variety of ocular structures including corneal epithelial cells, corneal endothelial cells, trabecular meshwork cells, retinal pigment epithelial cells, retinal ganglion cells and choroidal endothelial cells

Effects of Preservatives to the Ocular Surface

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There is now large evidence from experimental and clinical studies that the long-term use of topical drugs may induce ocular surface changes, causing ocular discomfort upon instillation, tear film instability, conjunctival inflammation, subconjunctival fibrosis, conjunctival epithelium apoptosis, corneal surface impairment, and potential risk for failure of further glaucoma surgery. Subclinical inflammation has also been described with significant infiltration of conjunctival epithelium and *substantia propria* by inflammatory cells, in patients receiving antiglaucoma treatments for long periods of time. However, the mechanisms involved, *i.e.* allergic, toxic or inflammatory, as well as the respective roles of the active compound and the preservative in inducing toxic and/or proinflammatory effects of ophthalmic solutions is still being debated. The most frequently used preservative benzalkonium chloride has widely and consistently demonstrated its toxic effects in laboratory, experimental and clinical studies. As a quaternary ammonium, this compound has been shown to cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and even blood-aqueous barrier disruption in the early phase of pseudophakia, leading to the concept of pseudophakic preservative maculopathy. Drug-induced adverse effects are therefore far from being restricted to only allergic reactions. Care should thus be taken to avoid preservatives in a long-term use as much as possible and to limit their concentration, as their toxicity is dose- and time-dependent, in order to reduce inflammatory reactions and improve ocular surface tolerance over the long term.

The Role of Innate Immunity on dry Eye Pathogenesis

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The Ocular Surface is a functional unit intended to protect the eye from the external environment and provide for an optimal refractive surface of the cornea through the production of an efficient tear film. Among its defense mechanisms, innate immunity provides a controlled immunological reaction against antigenic challenges deriving from the external environment. Therefore, also healthy subjects, without any ocular surface disease, present an immunological activity supporting the role of the ocular surface in providing an "immune tone".

The malfunctioning of one or more of the ocular surface structures determines compensatory changes of the others belonging to the functional unit, in order to maintain an efficient tear film production. When a chronic alteration develops, the production of an efficient tear film will be impaired, configuring a dysfunctional tear syndrome. This is an inflammatory condition, derived by tear hyperosmolarity and the consequent epithelial damage.

The innate immune system defends the host from external aggressions in a non-specific manner.

Several mechanisms were indicated as promoters for innate immunity. Among these were described the altered production of molecules such as lactoferrin, lysozyme, lipocalin (TLC), secretory immunoglobulin A (sIgA), AMCase, PLA2, TG, together with the activation of TLRs.

Irritating stimuli, such as hyperosmolar tears, determine in the epithelial cells the interaction with receptors that activate response pathways, such as MAPKs, leading to the production of pro-inflammatory molecules. These events, occurring on both epithelial and dendritic cells, are responsible for the onset and maintaining of inflammation on the ocular surface.

sPLA2-IIa and Innate Immunity of the Ocular Surface

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Inflammation is a common pathologic change associated with external disease and has been specifically associated with dry eye disease. What triggers the inflammatory response is not clear, but recent work with sPLA2-IIa has shown that it can "turn on" epithelial surface cells (conjunctiva and cornea) and cause them to become immune cells that manufacture inflammatory cytokines. This research suggests that innate immunity can play a significant role in the immune response of the ocular surface and may provide a target to control inflammation and reduce associated ocular surface disease.

Immune Mechanisms in Dry Eye Pathogenesis

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The immunopathogenic mechanisms of dry eye disease (DED) involve multiple steps: change in ocular surface homeostasis that promotes a pro-inflammatory microenvironment, activation and mobilization of ocular surface antigen-presenting cells which permit their trafficking to lymphoid tissues, priming and expansion of autoreactive CD4+ T helper-1 (Th1) and Th17 cells, and the homing of these pathogenic T cells to the ocular surface through expression of specific chemokine receptor-ligand pairs. Several of these molecular mechanisms can be targeted effectively, thereby suppressing the initiation and maintenance phases of DED. This short presentation will provide an overview of these important immune mechanisms and identify potential therapeutic targets.

Different Underlying Inflammatory Mechanisms in Dry Eye Disease – Heterogeneity at Molecular Level

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To dissect the underlying mechanisms of inflammation as they pertain to dry eye disease (DED) pathophysiology and to characterize patient heterogeneity at molecular level, we profiled a large number of immune mediators and other protein factors of potential immunopathological relevance in tears from 85 DED patients who had dry eye symptoms as measured with Ocular surface Disease Index and different level of corneal fluorescein staining. In this study, we identified in the tear film the presence of cytokine signatures for Th17 immunity (IL-17, IL-23 and IL-1b) and IL-8/neutrophil, among other immune activation markers. Furthermore, the expression profiles of the tear cytokine and protein markers revealed considerable patient heterogeneity and could divide dry eye patients into at least 2 - 3 but otherwise undistinguishable subsets. One subset of patients had significantly elevated levels of proinflammatory cytokines including IL-17, IL-23 and IL-1b ($P < 0.05$), indicating involvement of Th17 immunity in these patients; while another subset of patients had significantly higher level of IL-8 but low levels of IL-17, IL-23 and IL-1b ($P < 0.05$), indicating the absence of Th17 immunity but rather, involvement of IL-8/neutrophils in these patients. We showed, for the first time, subsets of DED patients having distinct molecular and cellular components of immune activation, thus contributing to DED heterogeneity at molecular level. Further analysis of the tear marker profiles and associated inflammatory mechanisms in DED will be discussed.

Oral Medications to Control Dry Eye Pain - Our Experience with Lyrica (Pregablin) and LDN (Low Dose Naltrexone)

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We have a subset of patients that we have been able to treat their Severe Dry Eye due to Meibomian Gland Dysfunction with Intense Pulse Light. So we initially see these patients and their pain can be easily categorized by their poor tear film, decrease Tear Break Up Time, increased osmolarity and lid pathology. But once these signs and symptoms are improved why do some patients still report pain. Some of these patients have had a prior cornea procedure like lasik which has been shown to disrupt the normal corneal nerve architecture. We know that Dry Eye Disease is an inflammatory problem so we first tried oral NSAIDs that had no effect, granted, in the small group of patients that we tried it on. We then turned to Oral Pregablin (Lyrica) a chronic pain medication that is used for Fibromyalgia and Low Dose Naltrexone a drug that has gained popularity for many ailments without many efficacy studies to back it up. We will look at the science behind these medications and dissect the clinical experience with patients in our clinic who have taken these medications for chronic eye pain due to Dry Eye Disease.

Nanotechnology and Posterior Segment Diseases

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The earliest impact of nanomedicine in ophthalmology is likely to involve the areas of biopharmaceuticals, implantable materials (e.g., tissue regeneration scaffolds, bioresorbable materials), implantable devices (e.g., glaucoma drainage valves), and diagnostic tools (e.g., intraocular pressure (IOP) monitors). Nanotechnology will bring about the development of regenerative medicine (i.e., replacement and improvement of cells, tissues, and organs) and artificial vision. In this presentation, we review some ophthalmic applications of nanotechnology in the following areas: drug and trophic factor therapy for glaucoma, retinal degenerative, and retinal vascular disease; gene therapy for retinal degenerative disease; regenerative medicine, including optogenetics and optic nerve regeneration; and diagnostics (minimally invasive IOP monitoring). Nanotechnology will play an important role in both early- and late-stage intervention in the management of blinding diseases.

New Therapeutic Targets in CNV

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Purpose: MyD88 is an adaptor protein that transduces Toll-like, IL-1 and IL-18 receptors signaling to downstream IL-1R associated kinases (IRAKs). We recently showed that MyD88 is a critical checkpoint in the pathogenesis of atrophic age-related macular degeneration (AMD). We sought to determine whether MyD88 also regulates choroidal neovascularization (CNV) in AMD.

Methods: A mouse model of laser injury-induced CNV was used. MyD88 was targeted by gene ablation, RNA interference, or peptide inhibition. The IRAK1/4 downstream kinases were targeted by a small molecule inhibitor. TLRs-2/3/4/7/9 were targeted by multi-gene deletion. IL-1 and IL-18 were targeted by neutralizing antibodies. Phosphorylated IRAK4 abundance was assayed in mouse CNV and in human CNV tissue specimens.

Results: Increased levels of IRAK4 phosphorylation were also found in the RPE/choroid of mice with laser-induced CNV and phospho-IRAK4 was immunolocalized in human CNV specimens. Both the small molecule inhibitor and the siRNA targeting MyD88, as well as a small molecule inhibitor of IRAK1/4 suppressed CNV in wild-type mice. MyD88-deficient mice had reduced CNV compared to wild-type mice. However, there was no difference in CNV volumes between wild-type mice and multi-TLR-deficient mice. Also, IL-1 or IL-18 inhibition did not reduce CNV in wild-type mice.

Conclusions: MyD88 inhibition, which prevents cell death in atrophic AMD, also could be beneficial in neovascular AMD.

Intravitreal Injections: an Healthcare Failure Modes and Effects Analysis

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The present abstract is submitted on behalf of the Intravitreal Expert Group (IVEG).

Purpose: To identify and assess the risks associated with intravitreal injections and suggest improvements to current practice using the Healthcare Failure Modes and Effects Analysis (HFMEA) method.

Methods: A pan-European, multidisciplinary team of vitreoretinal surgeons, a statistician, an epidemiologist and an expert on public health, conducted an HFMEA analysis of intravitreal injection technique. Possible failures at each stage in the procedure were identified and their potential causes and effects considered. A risk priority number (RPN) was then calculated and used to identify the risk associated with each of the potential failures. Agreement between scores has been analysed.

Results: The intravitreal injection process was divided into the following main stages: patient evaluation and preparation; staff selection and preparation; room features and preparation; materials preparation; intravitreal injection procedure; and patient discharge. Sub-processes and possible failures were identified for each step. Specific steps that require particular caution are equipment preparation, needle sterility, technique of administering intravitreal injections and patient discharge information.

Conclusion: The HFMEA methodology systemically identified the procedural elements of intravitreal injections associated with the highest degree of adverse event risk. This analysis, has allowed generation of targeted recommendations to improve the failure modes associated with intravitreal injections.

Ocriplasmin for Pharmacologic Treatment of Vitreomacular Traction (VMT): Results of the MIVI-TRUST Program

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Background: The ocriplasmin MIVI-TRUST program included two phase 3, multicenter, randomized, double-masked trials to determine efficacy and safety for treatment of VMT.

Methods: Patients with OCT-confirmed VMA were randomized to receive a single intravitreal injection of 125 µg ocriplasmin (n=464) or placebo (n=188). The primary end point was VMA resolution at 28 days post-injection. Selected secondary end points included total posterior vitreous detachment (PVD) at 28 days post-injection, pharmacologic closure of full-thickness macular hole (FTMH, equivalent to stage II), and visual acuity (VA) improvement of ≥3 lines.

Results: Pharmacologic VMA resolution at day 28 was observed in a significantly larger proportion of patients in the ocriplasmin group (26.5%) compared to placebo (10.1%; $P<0.001$). Total PVD at day 28 was observed in a significantly larger proportion of patients in the ocriplasmin group (13.4%) versus placebo (3.7%; $P<0.001$). Pharmacologic FTMH closure at day 28 was observed in a greater proportion of patients in the ocriplasmin group (40.6%) compared to placebo (10.6%; $P<0.001$). VA improvement of ≥3 lines at 6 months occurred in 12.3% of the ocriplasmin group compared to 6.4% of the placebo group ($P=0.024$). Most suspected treatment-related adverse events were mild, non-serious, and occurred within 7 days post-injection. No cases of endophthalmitis were reported.

Conclusion: A single intravitreal injection of ocriplasmin was superior to placebo in the resolution of VMA, inducement of total PVD, and closure of FTMH in a phase 3 clinical trial program. It represents a new paradigm in the treatment of VMT and FTMH.

AAV Gene Transfer Following Intravitreal Injection – Mice are Different from Monkeys (Man?)

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VEGF antagonists are useful for treating AMD but require frequent if not monthly intravitreal injections for maximal benefit. An improvement for patients would be sustained benefit from a single injection of a gene therapy vector vs. repeated intraocular injections. An improvement for patients and retinal specialists alike would be the ability to employ the more straightforward and safer intravitreal route of gene therapy vector administration vs the subretinal route of delivery. Our approach to AMD gene therapy is to combine the proven mechanism of anti-VEGF therapy with the attractive features of intravitreal AAV gene therapy vector administration. To prepare for AAV AMD clinical trials, an extensive series of efficacy and safety testing in animals was completed in rodents and in non-human primates. Key findings non human primates were the demonstration of expression of the sFLT01 anti-VEGF protein for more than a year and efficacy in the challenging laser CNV model. This clinical trial is still ongoing. In parallel, we have been investigating in greater detail the AAV vector gene transfer patterns in both mice and monkey eyes following intravitreal administration. Important differences exist between the rodent and non-human primate eye and there are important differences in the gene transfer patterns as well with implications for vector choice in clinical applications. Details of AAV gene transfer to the retina and other structures within the eye will be presented.

Ongoing Trials and Requirements on Usher Syndrome

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Usher syndrome (USH) is the most frequent cause of combined deaf-blindness in humans. Among the three clinically distinguished types of USH (USH1, USH2, USH3) caused by different gene defects, USH1 is the most severe form in terms of both the extent of the sensorineural hearing impairment and the precocity of retinitis pigmentosa (RP) onset. At present, no treatment can prevent or reverse the hearing and vision loss in this disease. Despite the progress in understanding the pathogenetical mechanisms underlying the hearing deficit, the pathogenesis of the RP observed in USH1 remains highly elusive. Since mouse and human retinal phenotypes differ significantly and in the absence of animal models for the USH1 visual defect, development of gene therapy strategies is particularly difficult. Recent study revealed that auditory and visual sensory cells harbor microvilli or microvillus-cilium structures interconnected by the USH1 protein network, highlighting some crucial aspects of the disease pathogenesis and understanding of the defective cell functions and molecular mechanisms that need to be restored. The first ever clinical study of UshStat (the investigational drug of Oxford BioMedica) in patients with RP associated with USH1B is currently underway (NCT01505062, Phase I/II). UshStat is a gene-based therapy to deliver a corrected version of the MYO7A gene. A single administration of the product is expected to provide long-term or potentially permanent correction.

ODISSEY - The European Consensus on Severe Dry Eye

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Keratoconjunctivitis sicca (KCS), also called dry eye syndrome, is a multifactorial disease of the tears and ocular surface that has a social and economic impact. It is the result of a vicious circle of events, due to the continuous self-sustained process of inflammation, hyperosmolarity and poor tear film. The diagnosis of the disease and its severity classification represent real challenges for ophthalmologists, not only in patient management but also in KCS study design, due to the current lack of standardised diagnostic methods and the lack of correlation between signs and symptoms. To do so, the ODISSEY European Consensus Group experts have established a simple but comprehensive diagnostic tool, the **Severe KCS diagnostic algorithm**.

In this symposium, Prof. Baudouin will first report why the dissociation between signs and symptoms represents a key challenge in severe KCS.

Then, Prof. Van Setten will detail what to do in order to establish the diagnosis of KCS, reviewing the different clinical practice.

Subsequently, Prof. Bonini will address the need to review and simplify the current state of scientific research and knowledge on the diagnostic approach and the diagnostic criteria for severe KCS, explaining the consensus reached with the ODISSEY algorithm.

And finally, Prof. Aragona will highlight the role of inflammation in KCS and its origin as well as the perspectives for research and therapy.

Microaneurysm Turnover and Phenotypes of Nonproliferative Diabetic Retinopathy Progression to Clinically Significant Macular Edema

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The evolution and progression of diabetic retinopathy vary between different individuals and does not necessarily progress in every patient to vision loss. It is however difficult in clinical practice to predict the clinical course and to identify which eyes will develop vision-threatening complications: clinically significant macular edema or proliferative retinopathy. There is a clear need to identify biomarkers of disease progression.

Microaneurysm turnover computed automatically in digital color fundus photography images using the RetmarkerDR is a good biomarker for retinopathy worsening with development of clinically significant macular edema. For long-term prediction, ten years, a microaneurysm formation rate higher than 2 per year predicts the development of clinically significant macular edema. For short-term prediction, two years, a microaneurysm turnover lower than 9 indicates that development of clinically significant macular edema is highly unlikely. Short-term prediction of progression to an outcome such as clinically significant macular edema will help in identifying patients to be included in clinical trials.

Subclinical Macular Edema as a predictor of progression to CSME

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Objective: To examine the relationship between subclinical diabetic macular edema (DME), as defined by Stratus central point thickness (CPT) and development of clinically significant macular edema (CSME) in nonproliferative diabetic retinopathy (NPDR).

Research Design and Methods: A prospective, monocenter, observational study was designed to follow eyes/patients with diabetes type 2 and NPDR (ETDRS levels 20 and 35) with no prior laser treatment for two years or until development of CSME. 410 patients, one eye per patient, fulfilled the inclusion/exclusion criteria and were included in the study. Ophthalmologic examinations including BCVA, fundus photography and optical coherence tomography (OCT) were performed at baseline, six-month and at the last study visit (24-month or before laser treatment).

Results: 348 eyes/patients performed the 24-month visit or developed CSME. Of these 348 eyes/patients 26 developed CSME. Presence of subclinical DME was defined as a CPT at baseline between 225 and 299 μ m. Thirty two eyes/patients presented with subclinical DME at baseline. Six of these 32 eyes/patients developed CSME.

Eyes/patients with subclinical DME present a risk for DME progression 3.123 times higher than eyes/patients without subclinical DME (95%CI=1.221; 7.988). The presence of subclinical DME at baseline showed a positive predictive value for CSME development of 18.7% and a negative predictive value of 93.7%.

Conclusions: Subclinical DME identified by Stratus CPT predicts development of CSME in eyes with NPDR. The absence of subclinical DME indicates that these eyes are less likely to develop CSME in a two-year period.

Responder Analysis of the Effect of 9-cis Beta-Carotene on ERG and Visual Field in Patients with Retinitis Pigmentosa

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Purpose: To compare the efficacy of oral treatment with 9-cis β -carotene on visual functions of "responders" and "non-responders" with retinitis pigmentosa (RP).

Methods: Randomized, double-masked, placebo-controlled, crossover trial of 29 RP patients. Patients were treated daily for 90-days with capsules containing 300mg of 9-cis β -carotene-rich alga *Dunaliella bardawil* (β -carotene ~20 mg) or placebo (starch). Following a 90-day washout period, they were treated for 90-days with the other capsules. Primary outcome- changes in dark-adapted maximal b-wave response. Secondary outcomes- changes in light-adapted maximal b-wave response, dark- and light-adapted maximal a-wave response, dark- and light-adapted visual-field (VF) and best corrected visual acuity (BCVA).

Results: Ten participants demonstrated an increase of more than 10microV for both eyes (range of 11-42microV) in dark-adapted b-wave following 9-cis β -carotene treatment vs. none following placebo. These 10 "responders" demonstrated significantly improved dark- and light-adapted b-wave and a-wave responses following 9-cis β -carotene treatment compared to placebo. The group of patients receiving treatment first demonstrated better correlation between improved dark-adapted VF following 9-cis β -carotene treatment vs. placebo, than the group receiving placebo first.

Conclusions: 9-cis β -carotene treatment increased a-wave and b-wave responses in 34% of RP patients. The optimal therapeutic regimen is being determined in a larger clinical trial. 9-cis β -carotene may represent a new therapeutic approach for some patients with RP.

Oral Docosahexaenoic Acid in Prevention of Exudative Age-Related Macular Degeneration: the NAT2 Study

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Objective: The NAT2 (Nutritional AMD treatment-2) study was a randomized, placebo-controlled, double-blind, parallel, comparative study. Our purpose was to evaluate the efficacy of docosahexaenoic acid (DHA) enriched oral supplementation in preventing exudative age-related macular degeneration (AMD). Here we correlate

Patients and Methods: 263 patients with early lesions of age-related maculopathy and visual acuity better than 0.4 LogMAR units in the study eye and neovascular AMD in the fellow-eye. Patients were randomly assigned to receive either 840 mg/day DHA and 270 mg/day eicosapentaenoic acid (EPA) from fish oil capsules or the placebo (olive oil capsules) for 3 years.

Results: Time to occurrence and incidence of CNV in the study eye were not significantly different between the DHA (19.5 \pm 10.9 months, 28.4%, respectively) and placebo groups (18.7 \pm 10.6 months, 25.6%, respectively). EPA+DHA level significantly increased in RBCM in the DHA group (+70%; p<0.001), suggesting that DHA easily penetrated cells, but unexpectedly also in the placebo group (+9%; p=0.007). We observed a wide range of EPA+EPA levels at month 6 and year 3 in both placebo and DHA groups. In the DHA-allocated group, patients steadily achieving the highest tertile of EPA+DHA levels in RBCM had significantly lower risk (-68%; p=0.047; HR=0.32 (0.10-0.99) of developing CNV over 3 years).

Conclusions: The RBCM measurements revealed that CNV incidence was significantly reduced in highly DHA-supplemented patients showing steadily high EPA+DHA index over 3 years.

Testing Therapy in a Mouse Model of Geographic Atrophy

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We are testing the hypothesis that oxidative stress in the retinal pigment epithelium (RPE) is a contributing factor to the development of age related macular degeneration. To examine the role of mitochondria in this process, we reduced the level of the protective enzyme manganese superoxide dismutase (MnSOD) in mice, either by RPE-specific deletion of the *Sod2* gene or by delivering an *Sod2*-specific ribozyme using adeno-associated virus (AAV). For periods up to one year, mice were examined regularly by fundus microscopy, spectral domain-optical coherence tomography (SD-OCT) and electroretinography (ERG). Finally, mice were euthanized and their retinas studied microscopically. Depletion of MnSOD led to RPE atrophy, damage to the underlying Bruch's membrane and death of photoreceptors. While we observed subretinal deposits resembling reticular pseudodrusen, sub-RPE drusen-like deposits were rare and choroidal neovascularization did not occur. We are using this model to study pharmacologic and gene transfer based therapy for geographic atrophy. In one set of experiments we tested systemic administration of 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH DPAT) an agonist of the 5-hydroxytryptamine 5-HT_{1A} receptor. This drug reduced oxidative stress and lipofuscin accumulation and improved the ERG response in the MnSOD-knockdown mice. Another approach to therapy in these mice was the consequence of high-throughput screening of synthetic molecules for those that elevated cytoprotection via the anti-oxidant response element. Among these compounds we have identified one that selectively induces the antioxidant response in the retina following systemic delivery, and we are preparing to test this in our mouse model of geographic atrophy.

Biomarkers in External Disease- HLA and Cytokines

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Though dry eye disease is likely multifactorial, most agree that inflammation of the ocular surface is nearly universally present. Minimally invasive objective metrics are needed to better assess new treatments for dry eye and at the same time improve our understanding of the immune mechanisms at work in dry eye disease and other external diseases. We have established standard operating procedures (Biomarker Laboratory) for sampling and analyzing in a masked fashion both percent surface cells expressing HLA-DR (associated with upgrade of inflammation), and tear cytokines. Having reliable biomarkers that can be incorporated into clinical trials will enhance our ability to determine efficacy of new treatments and at the same time improve our understanding of the immune mechanisms involved and so lead to new treatments for ocular surface inflammation.

Macular Carotenoids in Infant Ocular Health and Development

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Introduction: Lutein and zeaxanthin are dietary carotenoids specifically concentrated in the human macula that may be important in infant macular and visual development. We evaluated the correlation of carotenoid levels between mothers and their infants at birth.

Methods: We conducted a prospective, controlled, clinical study comparing carotenoids in 40 mother/infant pairs. Skin carotenoids were measured with resonance Raman skin devices. Blood and breast milk carotenoids were examined via HPLC. Macular pigment optical density (MPOD) was assessed on a subgroup of 14 infants using RetCam imaging.

Results: Mother skin carotenoids correlate with infant skin carotenoids ($R=0.48$, $P<0.01$). Mother serum carotenoids correlate with infant levels ($R=0.42$, $P=0.02$). MPOD was measurable in all term infants (mean = 0.108). Infant serum zeaxanthin correlates with MPOD ($R=0.68$, $P<0.01$). Mother serum zeaxanthin correlates with infant MPOD ($R=0.59$, $P=0.03$). Infant and maternal serum lutein did not significantly correlate with infant MPOD ($P>0.05$).

Conclusions: MPOD was measurable in term infants, contrasting with our previously reported lack of detectable MPOD in preterm infants. Infant MPOD correlates with infant and mother serum zeaxanthin, but not lutein, suggesting an important role for zeaxanthin in macular development. Finally, infant carotenoid status is dependent on maternal dietary intake, and serum zeaxanthin may be important for infant macular development in utero.

The Tears as a Diagnostic Substrate for Understanding Ocular Surface Disease

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The tears are a complex extra-cellular fluid integrating and reflecting the health of the epithelial cells covering the ocular surface. Cellular contributions to the aqueous layer include electrolytes, proteins/peptides, growth factors, cytokines and small molecule metabolites, such as amino acids, urea, glucose, and lactate. The tears as a resource can be used to understand eye disease and to develop clinically useful biomarkers. In these studies tears were collected by a Schirmer's Type I procedure, protein content measured and after LC are analyzed with a mass spectrometer such as the ABSCIEX 5600, Triple TOF. Often a semi-quantitative method such as iTRAQ is used with an appropriate control group. In the human tear proteome specific proteins such as lipocalin-1, and lacritin from the lacrimal gland are present but in about 1500 proteins can be identified of which 10% are extracellular. Abundant proteins including lysozyme (LYZ), lactoferrin (LTF), lipocalin (LCN-1), slgA, lacritin (LACRT), and proline-rich proteins (PRRL4, PROL1, etc.) comprise more than 90% of the total amount of tear proteins. In inflammatory conditions such as dry eye and pterygium the S100 calcium binding proteins A8/9, often released by neutrophils, as well as orsomucoid, an acute phase protein. In a recent study on keratoconus LCN-1 was found to be related to the severity of the disease. Thus, the tears have excellent clinical potential to offer quantitative biomarkers with relevance to the disease process as well as correlating to disease severity.

Potential Biomarkers of Disease Activity in Ocular Surface Inflammation

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Biomarkers are essential in the discovery and development of new drugs and for the establishment of personalized medicine. Biomarkers help monitoring health status, as they are key indicators detecting risk of disease, disease progression, disease activity, prediction of response to therapies or adverse events, and drug interactions.

Several studies have proposed different molecules and/or cellular parameters as potential biomarkers for ocular surface inflammation, mainly for dry eye disease (DED) and ocular allergy. New significant correlations with clinical symptoms and signs have been described for some tear proteins, cytokines, metalloproteinases, and mucins. Correlation with disease severity has also been shown for some of them. For instance, MUC-1 mRNA conjunctival expression levels had been shown to have great sensitivity and specificity for DED diagnosis, whereas some tear molecules or conjunctival cell viability and proliferative capacity are showing promise as DED activity markers.

This study will present new data, ours and from other colleagues, about molecules whose expression in tears and/or conjunctival/corneal tissues is significantly different between patients and control subjects and/or correlates with clinical parameters in DED and ocular allergy, and that have been proposed or suggested as potential biomarkers.

Clinical Markers of Inflammation and Exudation in ME due to RVO

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Inflammation is a major factor in the development of ME, as inflammatory biological changes occur early and before fluid accumulation. An increase of inflammatory mediators is associated with vascular permeability increase, leukocyte infiltration, endothelium malfunction which will lead to macular edema development. Microglia and tissue macrophages are very important in the inflammatory processes. Their activation is one of the earliest features.

To detect possible clinical signs associated with inflammation, clinical evaluation should always include FA (leakage and ischemia) and SD-OCT to quantify changes in thickness and some peculiar characteristics as vascular hyperpermeability, retinal thickening (intra and sub-retinal fluid) and specific patterns such as outer retinal changes and hyperreflective dots.

One of the most important signs of inflammation are the hyper reflective dots (HRD). These "bright dots" seem to be associated with inflammation, adjacent to cystoid spaces but frequently disseminated as far as the inner layers. They may represent microglia cells accumulation. HRD seem to be present in all active or recurrent cases. They will rapidly resolve in response to steroid treatment.

In ischemic RVO, SD-OCT has allowed to visualize interruption of the ELM and IS/OS interface (Ellipsoid portion of inner segment: EPIS). Inflammation may also favour the development of epiretinal membranes.

Inflammation is pivotal in the pathogenetic cascade leading to ME and a correlation between cytokine levels and degree of hyperpermeability and ME has been shown. Therefore, FA and OCT are the gold standard imaging tools for the diagnosis, management and monitoring of macular edema.

Ranibizumab for RVO: BRAVO, CRUISE, HORIZON

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The management of retinal vein occlusion (RVO) has greatly improved over the past few years. Many multicentre, randomized clinical trials have proven the efficacy and the safety profiles of a number of treatments. More specifically, the intravitreal administration of anti-VEGF agents, such as ranibizumab, bevacizumab, and aflibercept, is able to increase the chances of macular edema (ME) resolution, and visual acuity improvement. In particular the most important body of evidence is related to the intravitreal administration of ranibizumab. Both the BRAVO, and CRUISE trials, for branch RVO and central RVO, respectively, have demonstrated the efficacy of this approach at 6 months, and that the VA gain could be sustained up to a 12-months follow-up. Moreover the further extension of the trials, defined HORIZON, has shown good outcomes for branch RVO, and limited results for central RVO, probably owing to the study design.

The same studies have also suggested that an earlier treatment for ME allows a better functional prognosis, so that the previous concept of a 3-month wait prior to initiation of treatment should be modified. It has also been shown that the ranibizumab-based approach may be beneficial even in some long-standing RVO cases presenting with chronic ME. The side-effects related to the treatment turned out to be limited, especially bearing in mind that the subset of patients with BRVO are already generally affected by cardiovascular disorders. However, many problems are still open, including the necessity of frequent retreatment, the management of ischemic or neovascular RVO forms, and the best treatment algorithm for each patient. Future efforts will be addressed in an attempt to tailor the best therapeutic solution for the specific condition of each patient.

Aflibercept for Central Retinal Vein Occlusion

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Introduction: Aflibercept is a blocker of vascular endothelial growth factor (VEGF) and placental growth factor. It is thought that VEGF inhibition may help decrease vascular permeability and macular edema in patients with central retinal vein occlusion (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.

Results: In the COPERNICUS study, after twelve months, 55% of patients receiving aflibercept 2 mg gained at least 15 letters of BCVA from baseline. Visual acuity improved, on average, by 16.2 letters. In the GALILEO study, after twelve months, 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.

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

Dexamethasone Implant: GENEVA Trial's Everyday Clinical Practice

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The GENEVA trial was the big trial that demonstrated the efficacy and safety of the sustained release dexamethasone intravitreal implant (Ozurdex®) in the treatment of macular edema secondary to vein occlusion. The favorable effects of the dexamethasone implant on visual acuity and macular thickness are sustained for up to 6 months; but how applicable are these results to clinical practice? We analyze our experience of 30 months with the dexamethasone implant in management of macular edema in vein occlusion including more than 40 patients. We can conclude that the implant is both safe and effective.

Prolonged Intravitreal Release of the Endothelin_A-Receptor Antagonist BQ123 from an Injectable Polymer System Aiming at a Retinal Vasodilator Response

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The endothelin_A-receptor antagonist BQ123 is a potent vasodilator, which could be envisaged as therapeutic agent for treatment of retinal vein occlusions. Limitation of a single intravitreal BQ123 injection is its short half-life. This work investigates a novel formulation for intravitreal administration, in which BQ123 is incorporated in a biodegradable, liquid polymer¹ by simple mixing, aiming at a sustained BQ123 release over 7 days. *In vitro* release profiles of BQ123 from the polymer depot were obtained in porcine vitreous humor during 7 days (n=6). The *ex vivo* biocompatibility was investigated by placing the polymer in contact with porcine retinal tissues and performing histology. *In vivo*, the change in retinal vessel diameter of mini pigs was followed over 3 hours after intravitreal injection (n=2). The *in vivo* release of BQ123 from the polymer up to 7 days (n=6) was quantified by HPLC. *In vitro*, a zero order release profile was obtained, with 91% of BQ123 being released at $t_{7\text{days}}$. Good *ex vivo* biocompatibility was observed. *In vivo*, a vasodilative response was maintained over the duration of the study; the retinal vessel diameter increased 39%. The BQ123 concentration in the vitreous humor at 3 hours was $0.7 \pm 0.2 \mu\text{g/ml}$, followed by $1.5 \pm 1.0 \mu\text{g/ml}$ and $1.1 \pm 0.8 \mu\text{g/ml}$ after 3 and 7 days. The drug depot stayed clearly visible during the study and was well tolerated. This initial investigation shows promising results, demonstrating the therapeutic potential of this novel drug delivery system in the management of retinal vein occlusions.

¹Asmus et al, *EJPB* 2012;81(3):591-599

Intravitreal Concentrations of a Near-Infrared Fluorescence – Labeled Biotherapeutic Determined In Situ Using Confocal Scanning Laser Ophthalmoscopy

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The pharmacokinetics of ophthalmic biotherapeutics are difficult to determine in human vitreous humor. Because of the high transparency of living tissue to near-infrared (NIR) light, the temporal changes in vitreous concentrations of a biomolecule labeled with an NIR fluorescent probe can be monitored in situ with a scanning laser ophthalmoscope (SLO).

A humanized IgG was labeled with the NIR probe IRDye800CW (CVX-4164). Rabbits were given CVX-4164 intravitreally, and NIR fluorescence intensity was measured in the central plane of the vitreous humor with an SLO. Fluorescence intensities were converted to concentrations by using standard curves.

Little background fluorescence was detected, and the minimum detectable concentration of CVX-4164 was 10 nM. Vitreal concentrations of CVX-4164 determined in situ declined with time, with $C_{\text{max}} \approx 1 \mu\text{M}$ and $t_{1/2} \approx 145$ hours (112- μg dose). The $t_{1/2}$ of CVX-4164 was three times greater than that of IRDye800CW alone, whereas the vitreal clearance and volume of distribution of the native dye were 2000- and 550-fold greater than the conjugate. CVX-4164 concentrations determined in situ were 2.6 to 4.4 times higher than those determined by *ex vivo* NIR fluorescence or ELISA in homogenized vitreous humor, reflecting the greater spatial resolution of in situ imaging. Moreover, vitreal concentrations determined in situ were ≈ 3 orders of magnitude greater than plasma concentrations of CVX-4164, as determined by ELISA, with a different kinetic profile.

In conclusion, determining the pharmacokinetics of intraocular biotherapeutics labeled with NIR fluorescent probes by in situ monitoring is feasible.

Novel Micelle Carriers for Topical Ocular Delivery: a Novel Approach for Treating Dry Eye Disease

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Purpose: The aim of the present study was the *in vitro* and *in vivo* evaluation of a novel aqueous formulation based on polymeric micelles for the topical delivery of cyclosporin A (CsA) for dry eye treatment.

Methods: *In vitro* experiments were carried out on primary rabbit corneal cells, which were characterized by immunocytochemistry using fluorescein-labelled lectin I/isolectin B4 for the endothelial cells and mouse monoclonal antibody to cytokeratin 3+12 for the epithelial ones. Living cells were incubated for 1 hour or 24 hours with a fluorescently labelled micelle formulation and analysed by fluorescence microscopy. *In vivo* evaluations were done by Schirmer test, osmolarity measurement, CsA kinetics in tears and CsA ocular distribution after topical instillation. A 0.05% CsA micelle formulation was compared to a marketed emulsion (Restasis®).

Results: The *in vitro* experiments showed the internalisation of micelles in the living cells. The Schirmer test and osmolarity measurements demonstrated that micelles did not alter the ocular surface properties. The evaluation of the tear fluid gave similar CsA kinetics values: $\text{AUC} = 2339 \pm 1032 \text{ min} \cdot \mu\text{g/mL}$ and 2321 ± 881.63 ; $C_{\text{max}} = 478 \pm 111 \mu\text{g/mL}$ and 451 ± 74 ; half-life = $36 \pm 9 \text{ min}$ and 28 ± 9 for the micelle formulation and Restasis®, respectively. The ocular distribution investigation revealed that the novel formulation delivered $1540 \pm 400 \text{ ng CsA/g}$ tissue to the cornea.

Conclusions: The micelle formulation delivers active CsA into the cornea without evident negative influence on the ocular surface properties. This formulation could be applied for immune-related ocular surface diseases.

Biodegradable Microspheres as Drug Delivery Systems in the Treatment of Retinal Diseases

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Treatment of chronic pathologies affecting the posterior segment of the eye often need repeated injections. However, the efficacy of treatment is limited due to the side effects of the injections. Intraocular drug delivery systems have been developed to avoid successive intraocular administrations. Depending on their size, the devices can be implanted through a relatively large surgical incision or administered through a smaller tissue perforation. Among the intraocular sustained release systems, biodegradable microspheres (1-1000 μm size) are currently under investigation due to their ability to release the active substance for weeks or months. Furthermore, the formulation can be dispersed in different vehicles and easily administered as a conventional suspension without surgical procedures. Since the microspheres are biodegradable they will disappear from the site of injection after delivering the drug.

Biodegradable microspheres present certain advantages. Depending on the target site, they could be injected by different routes (either intraocular or periocular). Moreover, biodegradable microspheres can be loaded with one or more active substances. This fact results of special interest in the treatment of multifactorial diseases (i.e. combination of neurotrophic factors and antioxidants in the case of pathologies affecting the optic nerve). These new microsystems can be considered as emerging therapeutic tools for the treatment of retinal diseases.

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Ocular Allergy: Magnitude of 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.

Mouse Model of Corneal Involvement in Ocular Allergy

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Severe and chronic ocular allergy, such as in vernal and atopic keratoconjunctivitis, is a vision threatening condition. Unfortunately, there are no animal models that mimic this area of unmet medical need. Development of a relevant model would therefore be a significant advancement that could permit for laboratory experimentation and possible drug testing. To this end, our group has modified an established mouse model of ocular allergy in a manner that leads to corneal manifestations as well as periorbital sequelae often accompanied with chronic ocular allergy. This system is based on a systemic allergen sensitization and subsequent once daily instillations of allergen onto the ocular surface for one week. Mice mount acute hypersensitivity, e.g. chemosis, tearing, hyperemia, and lid swelling, within 20 min following instillation. Strikingly, clinical manifestations also seen in these mice include corneal erosions, meibomian gland dysfunction, and periorbital dermatitis. This may therefore be a useful model as such manifestations are consistent with what is seen clinically in patients with chronic allergy.

Allergic Conjunctivitis: Overview of Current Classification

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Allergic ocular disorders can be classified under a number of categories. The most common forms are seasonal and perennial allergic conjunctivitis (SAC and PAC). The most important feature of both is itching. Other important features of include a personal or family history of atopic disease including allergic rhinitis (hay-fever), asthma, and/or atopic dermatitis. SAC is associated with seasonal exposure to airborne allergens such as ragweed and other grass and tree pollens, and is generally most prevalent in the Spring and Fall. PAC usually involves sensitization to antigens that are present year-round, such as dust mites, animal dander, mold, and air pollutants.

More severe forms include Vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC). The latter is not a true form of allergic conjunctivitis, as it is a non-IgE mediated inflammation caused by mechanical trauma from contact lenses or ocular prostheses.

VKC is a severe disease occurring predominately in male children living in warmer climates and it usually resolves spontaneously with puberty. It is characterized by sticky mucous discharge, giant tarsal papillae and it frequently involves the cornea. It is associated with asthma or eczema in over 70% of patients.

AKC is a severe allergic inflammation of the conjunctiva, eyelids, and cornea, affecting individuals with a history of atopic dermatitis. It occurs predominantly in adults 20 to 50 years old. Patients present with a ropy mucoid discharge, tearing, burning, photophobia, chemosis, papillary reaction of inferior tarsal conjunctiva, and intense bilateral itching of the eyelids, periorbital area, and conjunctiva.

Diagnosis and Management of Vernal Keratoconjunctivitis

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Vernal keratoconjunctivitis (VKC) is an important disease in children that has the potential to cause vision loss from corneal scarring, induced irregular astigmatism or steroid-induced glaucoma. Presenting signs of VKC vary in different parts of the world. Treatment is multi-factorial. Topical medications including mast cell stabilizers, steroids and calcineurin inhibitors are effective in controlling VKC. Treatment of associated systemic allergic disease and modification of the home environment are essential elements of disease management. Prompt diagnosis of VKC and initiation of appropriate therapy will reduce the visual morbidity of this condition in children.

Atopic Keratoconjunctivitis (AKC) in Pediatric Age

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Allergic ocular diseases represent a broad spectrum of prevalent ocular problems, some of them holding a potential for visual impairment. There are four major types of ocular allergic involvement: allergic conjunctivitis (acute or chronic), giant papillary conjunctivitis, vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC). AKC is a multifactorial and chronic ocular surface problem in the context of atopic dermatitis (AD). Main symptoms include itching, burning, photophobia, and abundant mucoid discharge. It may include eyelid eczema, chronic blepharitis, cicatrizing conjunctivitis and compromised vision from corneal opacity. It is the most severe atopy-related ocular disorder, and the least frequent, although this is changing due to the increasing prevalence of AD. Although it is typically found in adults, it can also occur in children. Since the most frequent chronic and severe atopy-related disorder in pediatric age is VKC, ophthalmologists are permanently confronted with the dilemma of differentiating VKC from pediatric AKC. Although some findings could be more characteristic of one or the other, it is not always possible to differentiate both disorders. To have an exact differential diagnosis may not be crucial in terms of therapeutic management but it has an important prognostic value, since pediatric AKC is likely to continue into adulthood whereas VKC will most likely vanish or diminish its severity after puberty. In our opinion, a child with a probable diagnosis of VKC and concomitant AD (active or inactive) should be diagnosed of AKC over VKC and parents then informed about the potential of the disease to extend beyond puberty.

Urge to Rub: Is there a Link Between Eye Rubbing, Atopy and Keratoconus

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While keratoconus patients have been observed & stereotyped as eye rubbers and eye rubbing and atopy have been historically linked to keratoconus, there is little controlled scientific evidence that directly links these conditions. The etiology of keratoconus is multifactorial with variable pathways that probably share a final common pathway.

While it is believed to have a genetic component, the details have been elusive. It is presumed autosomal dominant with variable penetrance. Keratoconus is reported in from 8.8 to 54.4 per 100,000 and varies significantly between ethnicities and geographies. Atopy has been found at a significantly higher rate in Caucasian keratoconus patients. There has been, however, a strong association between atopy, eye rubbing and keratoconus.

Whether Atopy and/or eye rubbing is partially causative or an attempt by the patient to improve their vision is not known.

One of the current theories is that atopy and eye rubbing are inciting events in a cornea already genetically predisposed to ectatic change due to a weakened collagen matrix. It is thought that there is a genetic disposition where eye rubbing or inflammatory mediators from atopy stimulate keratocyte apoptosis and finally ectatic change. The etiology of keratoconus is probably multi-factorial with a final common pathway for a variety of different genetic mutations.

Complement Inhibition Using Gene Therapy for AMD

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Age-related macular degeneration (AMD) is strongly linked to variations in the complement cascade. Formation of membrane attack complex (MAC) is the terminal step of all three arms of the complement cascade. Individuals with AMD who harbor complement variations display over-activity of complement and increased deposition of MAC in the choroid and retinal pigment epithelium. Human studies confirm that decreased MAC activity significantly reduces the incidence of wet AMD. CD59 (protectin) is a naturally occurring membrane-bound blocker of MAC. Hemera Biosciences (Boston, MA, USA) has developed and licensed an adeno-associated viral vector that expresses a novel soluble form of CD59 (AAV2-sCD59). Intravitreal injection of AAV2-sCD59 in a murine model of laser induced CNV reduces deposition of MAC and inhibits CNV growth. Hemera has raised Class A funding to proceed with manufacturing of GMP grade drug and initiate animal toxicity studies with plans to file for an IND in 2014.

Stem Cells in Dry AMD

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Transplanted cells can secrete numerous molecules that may exert a beneficial effect on the host retina and/or choroid even if they do not cure the underlying disease. Ideally, with a single transplant operation, many different pathways can be modified, which may reduce the chance of "escape" associated with typical pharmacotherapy as well as the need for repeated drug administration. In addition, transplanted cells can replace dead cells (e.g., photoreceptors). Stem cells seem to be a logical choice for starting material because they can be produced en masse safely, and they can be induced to differentiate into ocular cells with potential for replacement and rescue therapy. Although preclinical studies demonstrate the feasibility of using stem cells for treating retinal diseases associated with abnormalities in the retinal pigment epithelium and/or photoreceptors, the immunogenicity of the cells, stability of cell phenotype (both inherent and environment-induced), the propensity to form tumors in situ, the abnormal microenvironment that can accompany degenerative disease, and the synaptic rewiring that accompanies retinal degeneration may pose challenges to clinical implementation. Cell transplants might prevent progression of geographic atrophy (through replacement of dysfunctional or dead RPE) and might even bring about some visual improvement in selected cases (through rescue of photoreceptors that are dying but not dead). Cell-based therapy may one day be sight-restoring for patients who are blind due to retinal degeneration of various etiologies. RPE transplantation is an attractive starting point for this sort of therapy since these cells can integrate with the host retina easily.

Toward Personalized Medicine in AMD

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The role of genetic factors in the occurrence of AMD is commonly admitted. The next steps to elucidate the role of genetics in AMD attempt to establish genotype-phenotype correlations, to investigate the genes involved in the natural course and severity of AMD and to analyze the genes potentially involved in therapeutic responses.

Early age of onset, higher rates of progression and bilateralism of the CNV have been observed with carriers of at-risk alleles. 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-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. 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.

Multimodal Functional and Morphological Aspects of Reticular Pseudodrusen

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Purpose: To analyze the integrated imaging of reticular pseudodrusen using confocal scanning laser ophthalmoscopy (cSLO) and high-resolution spectral domain optical coherence tomography (SD-OCT) and to investigate the impact of reticular pseudodrusen on macular function in a prospective observational cases series.

Methods: Eighteen consecutive patients (18 eyes) with reticular pseudodrusen (group 1), and without medium/large drusen, underwent cSLO multimodal imaging, SD-OCT, and microperimetry. Eighteen age- and sex-matched subjects (18 eyes) with typical drusen and without pseudodrusen (group 2) also underwent microperimetry.

Results: cSLO revealed a "target" aspect for the center of reticular pseudodrusen: an area of increased autofluorescence/reflectance surrounded by halos of reduced autofluorescence/reflectance. SD-OCT showed a well-defined round or triangular hyper-reflective deposit localized between, externally, the retinal pigment epithelium (RPE) layer, and, internally, the external limiting membrane (ELM) or the outer plexiform layer (OPL). Moreover, SD-OCT showed the loss of both outer segment (OS)/RPE interface, and inner segment (IS)/OS interface over the hyper-reflective lesions, as well as an abrupt interruption of both these 2 interfaces at the border of the hyper-reflective lesions. Microperimetry revealed a significant difference in overall mean macular sensitivity ("square 7x7"; 49 points) between group 1 and group 2 (5.9 ± 1.7 dB vs 8.8 ± 2.4 dB, $p < 0.001$).

Conclusions: The peculiar "target" aspect of reticular pseudodrusen, suggests the presence of central lipofuscin-like retinal deposits localized above the RPE. We showed that eyes with reticular pseudodrusen present a greater extent of reduced sensitivity than eyes with typical drusen.

Treatment for Acute Central Retinal Artery Occlusion by the Intravenous Drip of Prostaglandin E1

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Purpose: To evaluate the effect of systemic prostaglandin E1 (PGE1) monotherapy for acute central retinal artery occlusion (CRAO).

Methods: The best-corrected visual acuity (BCVA) and side effects were evaluated retrospectively in 10 consecutive eyes with acute CRAO treated with PGE1 monotherapy. In four eyes, the retinal vessel diameters were assessed on serial fundus photographs.

Results: The mean of best-corrected visual acuity was recovered from hand motion to 0.3 after 1 month. The time-to-treatment influenced the BCVA, however, gender or age did not affect BCVA. Compared to baseline, the mean changes in the vessel diameters in four cases were remarkably dilated in the artery and the vein. Angialgia during injection was the only side effect.

Conclusions: Intravenous drip of PGE1 for acute CRAO rapidly restores retinal blood flow by its vasodilatory effects, improves VA, is well tolerated with few side effects.

Protective Effect of TGF- β 1 in RPE Cells Upon Oxidative Stress as a Model for Oxidative Damage During Dry AMD

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Purpose: The aim of the study was to investigate the role of the TGF- β 1 (transforming growth factor β 1) on the survival and proliferation of human RPE (retinal pigment epithelium) cell culture as a model for the dry form of AMD. Upon TGF- β 1 stimulation multiple signaling cascades are activated, including: Smads, TAK1 (transforming growth factor β -activated kinase 1), stress kinases such as p38 MAPK and phosphatases such as PTEN. The goal of the present study was to delineate TGF- β 1 involvement in the RPE cells fate upon oxidative stress for better understanding of diseases associated with RPE atrophy.

Methods: To investigate the effect of TGF- β 1 on oxidative stress-induced by H_2O_2 , we have used, RPE cells FACS and XTT analysis and specific inhibitor of TGF- β 1 substrates.

Results: Treatment of H_2O_2 with or without the addition of TGF- β 1, enhanced the number of cells demonstrating oxidative damage and apoptosis (from 0.2% to 1.66% of the cells). However, inhibition of the TGF- β 1 substrate TAK1 or the receptor increases cell apoptosis to 6% and 7.8%, respectively. Moreover, TGF- β 1 stimulation did not affect cell proliferation, although inhibition of the TAK1 reduces cells propagation.

Conclusions: This study demonstrates that TGF- β 1 may protect RPE cells via TAK1 activation. The progressive oxidative damage of macromolecules resulting from exposure of cellular components to oxidative stress has long been implicated in aging and AMD diseases. The present study suggests a novel approach to reduce RPE cell death upon oxidative stress by activating TAK1, aiming at halting the progression of dry AMD.

Aqueous Cyclosporine A Prodrug Topical Formulation to Treat Ocular Diseases

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Cyclosporine A (CyA) is an immunosuppressive peptide frequently used in ophthalmology. Nevertheless, its poor water-solubility makes its formulation challenging. The development of a water soluble prodrug [Lallemant 2005, Hamel 2005] converted the "practically insoluble" CyA into a "freely soluble" prodrug, making possible topical ophthalmic formulations within aqueous vehicles.

The behavior of the aqueous prodrug formulation was compared *in vivo* and *ex vivo* to conventional CyA oily formulations [Rodriguez-Aller 2012, Rodriguez-Aller submitted]. Experimental results showed that the prodrug formulation displayed a 10 times lower CyA precorneal loss than CyA formulation (elimination rate of 0.02 min⁻¹ for the prodrug vs. 0.22 min⁻¹ for CyA formulation). In addition, the prodrug formulation was able to create large corneal and conjunctival deposits, between 5 and 70 times higher than those obtained with CyA formulations. Additionally, investigations highlighted the preference of the prodrug formulation to enter the eye through the conjunctival route, involving important advantages: i) conjunctival area is 20 times greater than the cornea [Watsky 1988] and ii) conjunctival route allows direct access to the posterior chamber [Jarvinen 1995]. Finally, the prodrug water-based eye drops avoid issues linked to oily vehicles, such as tolerance [LeBourlais 1997] and availability [Diaz-Llopis 1989].

The prodrug formulation allowed the delivery of active levels of CyA to the eye. Furthermore, it presents the advantage of being patient-friendly due to: i) local administration, ii) absence of secondary effects linked to oily vehicles (irritation, blurred vision or burning) and iii) lower risk of systemic complications compared with CyA oral treatment.

Rationale for the Use of Cationic Emulsions in Ophthalmology: From Bench to Bedside

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Topical delivery has always been an issue in term of drug penetration. In the early 2000, emulsions have gained interest in ophthalmology with the launch of the first emulsion dedicated to the treatment of an eye condition. In the continuing effort of improving ocular bioavailability of drugs, cationic emulsions were then developed with new features. This positively charged dosage form has the property to interact with the negatively charged ocular surface providing a longer retention time and an enhanced tissue penetration. This original and patented concept was applied to the delivery of several actives of which cyclosporine A (CsA).

CsA is a very lipophilic molecule which is very difficult to formulate as an eye drop. Cationic emulsions are adequate formulations to administer this molecule to the eye. However, cationic agents were often considered as deleterious to ocular surface and emulsions are unstable systems. A wide formulation development led to the choice of a safer cationic agent, cetalkonium chloride and to very stable nanoemulsions designated as Novasorb® technology. Safety and ocular pharmacokinetics were evaluated in rabbits with a two-fold increased penetration in cornea and conjunctiva compared to anionic emulsions and an improved healing of ocular surface lesions. Clinical trials revealed good tolerability and safety in patients and significant clinical efficacy in the treatment of severe dry eye with a once-a-day dosing regimen. This cationic cyclosporine A emulsion is now in the late stage of development.

In Vitro Sustained-Release and Stability of Single-Chain VEGF Antibody Fragments

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The therapy and market success of the VEGF-antibody Lucentis® (ranibizumab) in the treatment of age related macular degeneration (AMD) rapidly increased the interest in ophthalmic protein formulations. However, the intraocular injection adds new challenges to the anyway sophisticated preparation of protein formulations. Next to protein formulation and stability issues, the intraocular injection itself is unpleasant for the patient. Thus, a reduction of the injection frequency to several months is envisioned, requiring the use of sustained-release formulations. A potentially interesting approach is to use biodegradable excipients to formulate intraocular sustained-release formulations, as is hexylsubstituted poly(lactic acid) (hexPLA).

Formulations with hexPLA were prepared containing a lyophilisate of ESBA903, a single-chain anti-VEGF-A antibody fragment. The compatibility and stability of the antibody fragment with the polymer matrix was investigated and the proteins showed good stability at 4°C. The release from formulations containing different drug loadings and polymer molecular weights was investigated to adapt the duration and drug release to the need in clinics. Release periods of up to 14 weeks were achieved, possibly prolonging the treatment period after a single injection. Size exclusion chromatography, SDS-PAGE and surface plasmon resonance analysis showed that the protein was predominantly released in its monomeric state and that it maintained its biological activity after release from the hexPLA matrix. Therefore, hexPLA showed its feasibility to be used as an excipient for ophthalmic sustained-release formulations of proteins.

New Approaches to Wound Healing

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Dry eye disease in its severe form presents with keratitis and clear signs of ocular surface disease and like other wound healing problems continues to be a vexing clinical problem that is often difficult to improve. One approach is the use of autologous serum that has been shown in small case series to help with surface healing; recent research suggests components of serum, including serum albumin enhances mucin production by conjunctival epithelium and may provide expanded opportunities for treating ocular disease. Additional innovative approaches to wound healing will be reviewed, including the use of histatin and its effect on epithelial healing in a rabbit model.

Ocular Sensitivity. Update

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Purpose: To review the methods to measure ocular sensitivity and present results in healthy and ocular surface disease.

Methods: Literature review and clinical experience Belmonte's gas esthesiometer.

Results: The different methods of measure corneal sensitivity are reviewed with special focus on Belmonte's gas esthesiometer. Values in healthy individuals and ocular surface disease are presented.

Conclusions: Mechanical, chemical, and thermal corneal sensitivity in the central cornea were measured in healthy and ocular surface diseases. Ocular sensitivity measurement could be a parameter to characterize ocular surface diseases and the response to medical and surgical intervention.

Innervations of the Ocular Surface. Experimental Models and Clinical Applications

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Purpose: To present the modification of corneal innervation in healthy and nerve-genetic manipulated mice with age and with response to corneal surgery.

Methods: Clinical and histopathological studies in an experimental model of corneal wound healing in normal and genetic manipulated mice to express corneal innervation.

Results: There were changes in nerve density and in nerve subtypes related with age and related with corneal wound healing with special role of cold-fibers and dry eye.

Conclusions: There are clinical, anatomical and functional changes in corneal innervation related with age and corneal surgery that could be correlated with ocular surface disease like dry eye.

Collagen Crosslinking in Keratoconus

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Keratoconus is a bilateral, non-inflammatory, progressive, ectatic disorder of the cornea characterized by progressive corneal thinning and protrusion. Corneal collagen crosslinking (CXL) using the photosensitizer riboflavin (vitamin B2) and ultraviolet A (UVA) irradiation at 370 nm increases corneal tissue strength and rigidity by inducing production of covalent bonds between stromal collagen. Today, CXL is recognized as a new treatment which stops the progression of the disease in keratoconus. This talk will describe our experience with CXL in keratoconus, and the morphologic, topographic and visual outcomes of the treatment in long-term follow-up.

Photodynamic Therapy (PDT) in Infectious Keratitis

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Background and Purpose: Today, infectious keratitis tends to be therapy resistant. To discuss the potential role of photodynamic therapy (PDT) as an adjunct modality in therapy resistant infectious keratitis.

Methods: PDT on the cornea can be performed as Riboflavin-UV-A Crosslinking (wavelength 370 nm) or using Chlorine e6 (wavelength 670 nm). Experimental and clinical results will be presented.

Results: PDT is a potential treatment alternative, especially in therapy resistant keratitis. PDT may kill virus, bacteria, fungi and acanthamoeba. However, PDT triggers apoptosis and decreases viability of human keratocytes and endothelial cells in vitro.

Conclusion: Advantages, disadvantages and the limitations of PDT for keratitis should be analysed in experimental and clinical studies. Organ culture experiments are now in progress using Chlorine e6 and red light. Prospective clinical studies should analyse the short **and** long-term success and side effects of "corneal PDT" in the future.

The Steroids for Corneal Ulcer Trial - 5 years of SCUT

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Introduction: The use of adjunctive topical corticosteroids in bacterial keratitis has been debated for more than 50 years. Some fear the potential to enhance infection, others note the possibility to decrease scarring and improve visual outcomes. Previous experimental, animal, observational, and randomized studies have found indeterminate results. In order to provide conclusive evidence to guide treatment practices, the Steroids for Corneal Ulcers Trial (SCUT) assessed the effect of adjunctive corticosteroids on clinical outcomes in bacterial corneal ulcers.

Methods: 500 patients with culture-positive bacterial ulcers received at least 48 hours of topical moxifloxacin before being randomized to either topical prednisolone phosphate or topical placebo. Three-month best spectacle-corrected acuity was the primary outcome.

Results: 3-month acuity was not significantly different between the two arms. Beyond a possible delay in healing, no harm was found to result from the use of corticosteroids. Sub-group analyses suggested that patients with more severe ulcers may have benefited from the addition of corticosteroids, and that corticosteroids may be associated with worse clinical outcomes in patients with ulcers caused by *Nocardia species* compared with patients with ulcers caused by other bacterial organisms. By 12-months, there was a modest, statistically significant improvement in acuity in the steroid-treatment cases.

Conclusion: The primary outcome of SCUT revealed no benefit of adjunctive corticosteroids at 3 months from enrollment. Secondary analysis suggests a modest benefit of steroids in the worst ulcers, and in all ulcers by 12 months, and harm with steroids in *Nocardia* cases.

Targeting GAPDH Nuclear Translocation as a Potential Novel Therapy against Hyperglycemia-Induced Retinal Injury

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Background: The translocation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) to the nucleus has closely been associated with cell death induction. Previously, we have demonstrated that elevated glucose levels induce GAPDH nuclear accumulation in retinal Müller cells in vitro and in vivo. The E3 ubiquitin ligase seven in absentia homolog-1 (sia-1) has recently been identified as a potential shuttle protein to transport GAPDH from the cytosol to the nucleus. Therefore, this study investigated the role of sia-1 in high glucose-induced GAPDH nuclear translocation and subsequent cell death in retinal Müller cells.

Methods: Müller cells were incubated with normal (5mmol/l) or high (25mmol/l) glucose medium for 24 hours in the presence or absence of siRNA against sia-1 or drugs targeting the sia-1/GAPDH binding. Following treatment cellular and nuclear GAPDH amounts were assessed using immunohistochemistry. Cell death was assessed using trypan blue exclusion assays.

Results: Under hyperglycemic conditions, sia-1 formed a complex with GAPDH and was predominantly localized in the nucleus of Müller cells. Sia-1 knock-down using 50nM sia-1 siRNA significantly decreased high glucose-induced GAPDH nuclear accumulation at 24 hours by 43.8±4.0%. Further, knock-down of sia-1 prevented high glucose-induced cell death of Müller cells potentially by inhibiting p53 phosphorylation. Drugs targeting the sia-1/GAPDH binding also prevented hyperglycemia-induced nuclear accumulation of GAPDH and cell death in Müller cells.

Conclusions: Therefore, targeting GAPDH nuclear translocation might represent a novel therapeutic strategy to prevent hyperglycemia-induced retinal cell injury.

Brief Low Intensity Far-Red Light Inhibits Early Lesions that Contribute to Diabetic Retinopathy

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Treatment with light in the far-red to near-infrared region of the spectrum has beneficial effects in a number of tissue injuries. We investigated if brief (4 min per day) daily photobiomodulation (PBM) with far-red light could inhibit parameters relevant to the development of diabetic retinopathy. Studies were conducted in vivo (streptozotocin diabetes in Lewis rats; 10 weeks duration) and in vitro (RGC5 cell line). Daily exposure to 4 min far-red light PBM throughout the study resulted in significant inhibition in the diabetes-induced death of retinal ganglion cells, as well as a partial improvement in ERG amplitude (photopic b wave responses) (both P<0.01). In an effort to explore the mechanism for these beneficial effects, we examined physiologic and molecular changes related cell survival, oxidative stress and inflammation. Neither diabetes nor PBM altered cytochrome oxidase expression or activity in retina, so this protein seems unlikely to account for the effects observed. PBM did significantly inhibit diabetes-induced production of superoxide and corrected MnSOD expression in vivo. Diabetes also significantly increased both leukostasis and expression of ICAM-1, and PBM essentially prevented both of these abnormalities. In RGC-5 cells, high (30mM) glucose significantly induced molecular changes related to cell survival, oxidative stress and inflammation, and PBM inhibited all these effects. Since PBM has been associated with minimal risk, and is noninvasive, inexpensive, and easy to administer, it may be a simple adjunct therapy to help inhibit diabetic retinopathy.

Approaches Using Inhibition of Mitochondrial Damage

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Mitochondrial dysfunction is considered to play a crucial role in the apoptosis of capillary cells, a phenomenon that precedes the development of retinal histopathology characteristic of diabetic retinopathy. In diabetes, mitochondrial superoxide levels are elevated in the retina and their membranes leak out cytochrome c into the cytosol. In addition, DNA of the mitochondria (mtDNA) is damaged and its biogenesis is impaired, and the electron transport system (ETC) is compromised initiating a ferocious cycle of superoxide production. Matrix metalloproteinases (MMPs), especially MMP-9, are important in regulating a variety of cellular functions, including apoptosis, proliferation, differentiation and angiogenesis. Diabetes activates MMP-9 in the retina and its capillary cells, and activated MMP-9 functions as a pro-apoptotic factor. Furthermore, due to increased binding with the chaperon proteins, MMP-9 levels are elevated in the mitochondria. We have shown that MMP-9 knockout mice are protected from the development of diabetic retinopathy, and their retinal mitochondria are intact with tightly packed cristae and mtDNA biogenesis. Thus, the inhibition of MMP-9 by pharmacological inhibitors has potential therapeutic value in protecting the integrity of the mitochondria and its ETC system. This would help retard the development/progression of diabetic retinopathy.

Future perspectives of retinal OCT

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Optical coherence tomography (OCT) is a rapidly emerging non-invasive, optical diagnostic imaging modality enabling in vivo cross-sectional tomographic visualization of internal microstructure in biological systems at resolution levels of a few micrometers. Novel high speed detection techniques as well as development of ultrabroad bandwidth and tunable light sources have recently revolutionized imaging performance and clinical feasibility of OCT. In this view OCT can now be considered as an optical analogue to computed tomography and magnetic resonance imaging, not enabling full body imaging, but non-invasive optical biopsy, i.e. micron/cellular resolution three-dimensional visualization of tissue morphology.

Extensions of OCT have been developed that enable non-invasive contrast-enhanced, depth resolved functional imaging of the retina, providing spectroscopic, blood flow or physiologic tissue information. These extensions of OCT should not only improve image contrast, but should also enable the differentiation of retinal pathologies via localized metabolic properties or functional state.

Ophthalmic and especially retinal imaging has so far not only been the first, but also the most successful clinical application for OCT. Objectively this is evidenced by the fact that nearly 50% of all OCT publications so far have been published in ophthalmic journals. In addition, more than half a dozen companies offer this technology in its fourth generation as three-dimensional retinal OCT. Consequently retinal OCT represents the fastest adopted imaging technology in the history of ophthalmology.

Fatty Acid Elongases as Therapeutic Targets in Retinal Diseases

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Retina has a unique fatty acid profile with the highest levels of n3 polyunsaturated fatty acids (PUFA), especially docosahexaenoic acid (DHA) and very long chain (VLC) PUFA in the body. This unique profile would suggest high level of retinal-specific fatty acid metabolism. Indeed, we demonstrated that retina has very high expression level of fatty acid elongases. Among retinal elongases Elovl4 shows the greatest expression level, followed by Elovl2, Elovl1 and Elovl6. Elovl4 synthesizes \geq C26 saturated and PUFA. Diabetes induced dramatic down regulation of EloVL4. Decreased EloVL4 expression or function has been associated with multiple retinal disorders, including blood-retinal barrier breakdown, in animal and human studies. This led us to hypothesize that EloVL4 modulates diabetes-induced retinal vascular degeneration. Using an adenovirus and capsid-modified AAV2 to overexpress EloVL4 in human RPE and retinal endothelial cell culture models of the blood-retinal barrier, we found that EloVL4 did not affect glycerophospholipid VLCPUFA content, but rather increased levels of C26 fatty acids incorporated into ceramide while decreasing shorter chain ceramides. Altered sphingolipid content by EloVL4 decreased cell activation in response to stimulation by IL-1 β . Intravitreal delivery of EloVL4-AAV2 to retinas of STZ diabetic rats increased retina VLC ceramides, reduced retinal vascular activation, blunted diabetes-induced retinal vascular permeability, and increased endothelial expression of blood-retinal barrier components. Taken together these data indicate that EloVL4 overexpression prevents early stage vascular degeneration in diabetic retina through modulation of sphingolipid metabolism. Retinal delivery of EloVL4 by AAV2 vectors may represent an effective intervention to prevent early vascular lesions of diabetic retinopathy.

Vitamine E Tocopherols and Glaucoma

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Oxidative stress is strongly implicated in glaucoma in different tissues including trabecular meshwork, human Tenon's fibroblasts, and retinal ganglion cells and their axons. An established, naturally occurring anti-oxidant is Vitamin E. Vitamin E is found in phospholipid cell membranes where it prevents lipid peroxidation and membrane damage by acting as a peroxyl radical scavenger. Alpha tocopherol is perhaps the best known form of Vitamin E, although d- tocopheryl polyethylene glycol 1000 succinate (TPGS), a water soluble form of vitamin E, is also well-described being used as a drug delivery vehicle. Vitamin E has recently been shown to have other roles including regulating signal transduction, gene expression, and acting as redox sensor and is being investigated in neurodegeneration. This talk will discuss the various applications of Vitamin E in glaucoma.

Glaucoma and Lipids: Cholesterol and Glaucoma

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The links between cholesterol and glaucoma are still under debate, based especially on the unresolved mechanisms behind the effects of statins in the progression of glaucoma. Cholesterol must not be restricted only to its circulating levels. Indeed, cholesterol is a prominent component of the central nervous system, including the retina. As such, cholesterol homeostasis must tightly be regulated. Cholesterol-24S-hydroxylase (CYP46A1) catalyzes the formation of 24S-hydroxycholesterol from cholesterol. In the brain, CYP46A1 is specific to neurons where it accounts for the elimination of the major part of cholesterol. CYP46A1 expression has been localized in the retina and especially in retinal ganglion cells, while low or even no expression was found in photoreceptors and pigmentary cells. It was thus clearly understandable that CYP46A1 would be associated with glaucoma but not with Age-related Macular Degeneration (AMD). The analysis of single nucleotide polymorphism in CYP46A1 gene in populations suffering from retinal pathologies validated this assumption since an association, although of unknown origin, was found with glaucoma but not with AMD. Experimental glaucoma was induced in the rat. On the contrary to our expectations, CYP46A1 expression and 24S-hydroxycholesterol levels were maintained at steady states in the retina, despite the loss of retinal ganglion cells.

These findings highlight not only the importance of CYP46A1 in the retina but also its neuron-specificity. CYP46A1 deserves further interest in connection with the process of retinal ganglion cell death and glaucoma.

Vascular Structure of the Choroid in Health and Ocular Pathology of the Posterior Eye Examined with 3D-1060nm-OCT

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Purpose: To examine vascular structure of Haller's and Sattler's layer in healthy subjects and in a range of ocular maculopathies (age-related-macular degeneration (AMD), and central serous chorioretinopathy (CSC) using a 3D-1060nm-Widefield-OCT.

Methods: Three-dimensional choroidal tomograms and vascular segmentations of Hallers and Sattlers layer from 40 healthy subjects, 20 wet (pre- and post-treatment) and dry AMD and 2 CSC were automatically segmented and examined qualitatively and statistically. Visual acuity, axial eye length, and indocyanin green angiography (only in pathology) were taken. Images taken with a 3D 1060nm OCT (512x512 A-scans at ~7 µm axial resolution over 36° angle) were used to generate maps automatically.

Results: Haller's layer was 118±70µm and Sattler's was 128±98µm (range 0-357µm) in healthy eyes. Vascular segmentation was confirmed by angiography and areas of watershed and blood vessel alteration were observed over a wide field of view relating to the type of maculopathy and in comparison with healthy subjects (p<0.05).

Conclusions: Enhanced depth penetration of 1060 nm OCT enabled the in vivo investigation of choroidal blood vessels and choroidal thickness. Although retinal changes in AMD and CSC are well documented with OCT, choroidal thickness and vascular structure has the potential to become an important new biomarker in posterior eye pathology.

Glaucoma and Lipids: Fatty Acids and Glaucoma

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Neuronal tissues such as the retina are known to contain high amounts of particular phospholipids named as "plasmalogens". One particularity of plasmalogens is to concentrate polyunsaturated fatty acids (PUFA) before releasing them under specific conditions. Several data from our team suggest that plasmalogens might be involved in the pathophysiology of primary open angle glaucoma (POAG), the second leading cause of blindness worldwide. Different experiments were carried out on human patients with POAG as well as on rodent models of ocular hypertony. They concerned either the identification of specific alterations of plasmalogen metabolism, or the efficacy of PUFAs to prevent retinal damage. The results have shown a loss of several circulating plasmalogens in POAG patients. This was stage-dependent and may have started years prior to first clinical diagnosis. In animals, several combinations of dietary PUFAs were efficient in preventing retinal glaucomatous damage. The biophysical and biochemical properties of plasmalogens are very consistent with a protective role in the pathogenesis of glaucoma.

Central Retinal Thickness Measurement and Observance of Macular Reaction using intraoperative OCT in Cataract Surgery before and after Phacoemulsification

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Purpose: To demonstrate feasibility of intraoperative central retinal thickness (CRT) measurement with a novel combination of a Carl Zeiss Meditec™ Cirrus HD-OCT™ system adapted to the optical pathway of a Zeiss OPMI VISU 200™ surgical microscope (Intra-OP-OCT) during uneventful small incision cataract surgery.

Methods/Design: 512x128 high resolution macular cube scans were performed in 50 subjects during surgery, pre- and immediately after intraocular lens (IOL) implantation. Inter-observer variability was calculated from measurements of two observers. In four subgroups of healthy, diabetic, hypertensive and diabetic and hypertensive (both) subjects, measurement reliability and reproducibility is demonstrated.

Results: Scans of 41 eyes (diabetes n=11; hypertension n=15 or both n=26 and healthy n=15) with sufficient quality for CRT measurement by both observers. Intraobserver precision was 1 µm, mean interobserver difference was -0.9 µm, with limits of agreement from +15.1 to -12.4 µm. Preoperative CRT (mean± SD, µm) of 210 ± 30 (121 – 286) increased significantly by 8.2 ± 11.7 to 218 ± 27 (154 – 296) (P<0.001). No significant difference was observed between subgroups (P>0.05).

Conclusion: CRT measurement using Intraop OCT is feasible. A significant increase of CRT of 8µm immediately after surgery was detected but no difference between the subgroups. Intra-OP-OCT offers novel, highly reproducible information, about structural behaviour of the retina during small incision cataract surgery. IntraOP-OCT can contribute with precise measurements to better understanding of macular changes following cataract surgery. These findings might become even more relevant in patients with macular diseases needing cataract surgery.

Primary Endpoint Results of the SAVE Study - Sirolimus As Therapeutic Approach To Uveitis

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Purpose: To evaluate the safety and bioactivity of sirolimus as an immunomodulatory therapeutic (IMT) agent, delivered subconjunctivally (SCJ) or intravitreally (IVT), in patients with non-infectious posterior, intermediate, or panuveitis.

Methods: 30 patients were stratified at baseline (BL) into 3 categories/groups: (1) active disease receiving no treatment; (2) active disease receiving prednisone ≥ 10 mg/day and/or at least 1 other IMT; (3) inactive disease receiving prednisone < 10 mg/day and/or at least 1 other IMT. Patients in each category were randomized into SCJ or IVT arm (1:1). Study eyes received SCJ (1320 μ g) or IVT (352 μ g) injections at days 0, 60, and 120, with primary endpoint at day-180. Study subjects may be followed and treated until M12. Beyond safety, study parameters include change in visual acuity (VA), vitreous cells/haze, and reduction in dosage of systemic corticosteroid (CS) compared to BL. Visual Function Questionnaire (VFQ) was also performed at BL, M6, and M12.

Results: 28 subjects completed the 6-month primary endpoints; 2 subjects discontinued. Both SCJ and IVT sirolimus injections were well tolerated. None of the adverse events (AE) were deemed to be related to sirolimus. At M6, VA improved in 39% (SCJ=43%; IVT=36%) and stabilized in 39% of all patients. Vitreous haze improved in 82% of patients (SCJ=79%; IVT=86%). 20 patients were on systemic CS therapy at BL; all had their doses of CS reduced at M6. 7/20 were, in addition to CS, on systemic IMT, which was discontinued prior to screening. 1/7 patients required re-initiation of IMT, albeit for systemic disease reactivation. In group 2, CS dose was successfully reduced to < 10 mg/day in 85% of subjects, (median dose: BL=20 mg/day; M6=8 mg/day). In group 3, median CS dose was reduced from 9 (BL) to 3 mg/day (M6). VFQ scores increased for both SCJ and IVT groups at M6 compared to BL.

Conclusions: Locally administered (subconjunctival or intravitreal) sirolimus

appears to be safe in patients with noninfectious uveitis. Sirolimus has demonstrated bioactivity by reducing vitreous haze and cells, improving VA, and in decreasing need for systemic CS. Additional clinical trials are indicated to confirm the role of locally-delivered sirolimus and to determine its appropriate dosage and frequency of administration.

Evolution of our Treatment Paradigms

Manfred Zierhut

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In the last years some uveitis paradigms have changed, and a few of them will be presented here.

1. In previous years Juvenile idiopathic arthritis associated Uveitis (JIAU) has shown a bad long term prognosis, induced by the high rate of complications, like macular edema (ME). Nowadays OCT allows the detection of even mild fluid in the macula, therefore we suggest today to treat ME, even when the vision is 20/20.

2. Also a bad prognosis is reported for Behçet's Disease (BD), due to occlusive vessels in retina and optic nerve. Multiple reports from the last ten years have shown that vasculitis in BD is successfully treated by interferon-alpha, with quick response and long term improvement, even after stop of treatment. No prophylactic treatment is necessary anymore.

3. In acute anterior uveitis, the unilateral, probably side-changing disorder is still grouped into HLA-B27 positive and negative disease. We do not use this criterion anymore, strictly following the clinical appearance. Treatment will be the same, outcome also.

4. Another highly critical disease is serpiginous chorioretinitis. The last years have brought some evidence that tuberculosis may induce this disorder, at least in some patients. Therefore in quantiferon positive patients we always include anti-TB treatment in the management of these patients.

Local vs Systemic Therapy in Uveitis

Carlos Pavesio

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The options for the treatment of non-infective posterior uveitis have widened in recent times with the development of new modalities both at local and systemic level. Local therapy remains a very attractive alternative for unilateral or asymmetric cases, but is usually confronted with the problem of duration of effect and local side effects. The use of intraocular injections and the development of slow-release devices have introduced a treatment modality, which allows high levels of the pharmacological agent where it is most wanted. Apart from steroids, with the well-known problems of cataract and high intraocular pressure, other alternatives, such as anti-VEGF agents, have become an option, and another (Sirolimus) is under investigation. Retisert, Ozurdex and Iluvien have made it possible to extend the duration of the beneficial effects, but also increased the risk of glaucoma and cataract. Systemic therapy is the alternative of choice in ocular inflammation associated with systemic diseases and in bilateral or resistant cases. After many years of counting only on a few alternatives, including systemic steroids, antimetabolites, alkylating agents and one calcineurin inhibitor, we are witnessing trials for several new options, including a new calcineurin inhibitor and especially monoclonal antibodies such as anti-TNF alpha agents. These options are bringing hope for the control of diseases for which until now we had limited efficacy. There is certainly hope in the horizon.

Scleritis-Differences and Similarities in Therapeutic Approach to Uveitis

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Scleritis is usually a chronic, painful, progressive, potentially blinding condition involving both the episclera and the sclera. It is often associated with ocular complications (anterior uveitis, peripheral keratitis, glaucoma) potentially causing decrease of vision, and also with systemic connective tissue or vasculitic diseases, some of them potentially lethal. Patients with idiopathic diffuse or nodular scleritis with low degree of scleral inflammation or without ocular complications may respond to non steroidal anti-inflammatory agents (NSAIDs). Patients with idiopathic diffuse or nodular scleritis with high degree of scleral inflammation may respond to steroidal anti-inflammatory agents (SAIDs). Patients with diffuse or nodular scleritis with associated systemic disease, may respond to immunosuppressive therapy (IMT) or biologic response modifiers (BRM). Patients with necrotizing scleritis may respond to IMT, mainly alkylating agents.

Uveitis is usually an acute or chronic potentially blinding condition. It may be associated with ocular complications (keratitis, scleritis, glaucoma, macular edema, retinal neovascularization) potentially causing decrease of vision, and also with local or systemic diseases, some of them potentially lethal. Patients with anterior uveitis may respond to topical or regional SAIDs, patients with intermediate uveitis may respond to regional SAIDs, IMT or pars plana vitrectomy, and patients with posterior uveitis may respond to IMT or BRM +/- SAIDs.

The Relevance of Objective Followup Criteria (Endpoints) to Patient Well Being

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Objective, reproducible and pre-defined clinical endpoint measures (or outcomes) are an essential part of a well-designed clinical study. Although pre-defined outcomes are always used in prospective studies, they also may be employed in retrospective studies—making these studies more robust and generalizable. Given the rarity of some forms of uveitis, retrospective data are often utilized to describe clinical and treatment outcomes. Therefore the purpose of this talk is to describe the use of objective endpoints in clinical studies in uveitis, with a focus on studies from the Johns Hopkins Cohort and the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study. Specific endpoints will be described and examples given as to how those endpoints have impacted clinical care in uveitis.

From Cohort Studies to Individual Case Management

Michal Kramer

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Non- specific down-regulation of the over-active immune system is the core of treatment for all types of non-infectious uveitis (NIU). Treatment had shifted from corticosteroids, which possess a broad down-regulating effect, knocking down additional endocrine and metabolic pathways, to immunosuppressive agent that target merely the immune system. The new era of biologics further shifted towards targeting specific immune mediators. Still, most treatment paradigms assume that various types of intra-ocular inflammation would similarly respond to “non specific” immune suppressive drugs. This is based on an assumption of similar cellular and humoral components involved in all types of noninfectious immune uveitis. Up till recently the pharmaceutical industry did not consider NIU a target for drug development. One of the reasons might be the scarcity of patients when breaking down NIU to specific etiologies. Thus, individual patients therapy based on cohort NIU studies poses a major challenge: Does one drug fit all? Is a study in Bechet's patients applicable for all NIU patients? These questions interlace with a broader dilemma of applying clinical cohort study data to the individual patient. The current presentation dissects the limited data known to us on this issue based on known immunologic mechanisms acting in various uveitis entities, such as HLA-B27 related uveitis, Juvenile idiopathic arthritis and behcet's disease. Questions related to the possible application of this knowledge to treatment of specific diseases, as reflected in individual case history will be presented and discussed.

New Challenges for Clinical Research in Europe – EVICR.net as a Disease-Oriented Clinical Research Network

Maria Cecília Martinho

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Background:European Vision Institute Clinical Research Network – EVICR.net, is a network of European ophthalmological clinical research sites, dedicated to perform clinical research in ophthalmology with the highest standards of quality, following the European and International Directives for Clinical Research according to harmonized SOPs. This platform for Ophthalmology clinical research in Europe is a useful Academia and Industry resource in the process of development of new drugs and medical devices.

Methods:The main aims of EVICR.net are:

- Guarantee a high level of quality and excellence in ophthalmology clinical research performed by its members according to ICH GCP Guidelines.
- Promote multicentre clinical research within the EU.
- Coordinate training activities for its members.
- Serve as a resource for Industry in performing clinical research in Ophthalmology.

Since 204 the EVICR.net has actively reinforced its role as a support in the development of Investigator-Driven Clinical Trials (IDCTs) and Epidemiological Studies across Europe. New study proposals may be submitted by EVICR.net Members to be evaluated by a subspecialty Expert Committee. Once approved, the Coordinating Centre takes the leadership of coordination and management of these IDCTs. EVICR.net has at the moment 8 ongoing multicentre clinical trials of which 3 are EU funded projects and 5 are IDCTs.

Conclusions/Discussion:Disease-Oriented Clinical Research Networks such as EVICR.net are being called to perform a central role in the support of the recent emphasis on clinical research assessment by the EU Research Framework Programme. The Network has at the moment 78 Centres members from 16 countries with growing perspectives.

Increasing the Rigor of Preclinical Studies: Academia vs. Industry

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Preclinical research is the basis for the proper identification of pathophysiologic pathways and therapeutic or preventive compounds that might develop into clinically efficacious drugs. Currently, the success rate is estimated to be about 1% for a compound identified in preclinical experiments as a promising drug to succeed as therapeutic agent in a clinical trial. The reasons for this rather disappointing translational success rate are manifold. Among these, one aspect has recently gained public recognition, namely the lack of reproducibility of preclinical research. According to analyses performed by industry, one can assume that about 80% of preclinical research cannot be reproduced, meaning that many clinical trials are based on wrong assumptions. This presentation will summarize the current data on reproducibility rates and will give recommendations for measures to improve the quality and rigor of preclinical research.

Decision Analysis and Proof of Concept Studies

Leonard Levin

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One of the most critical roadblocks in translational research is the pathway from preclinical studies to clinical trials. In most cases, there is value in performing a "proof of concept" trial before embarking on large, pivotal phase 3 studies that will be both costly and risky. The proof of concept trial has specific design issues that are necessary to resolve in advance, in order for it to provide value in deciding whether to proceed to larger studies. These include choosing the power of the study, which is primarily a function of the number of subjects, the effect size that is desired to be detected, and the alpha level. In addition, there has to be an estimate of how well the preclinical data is likely to correlate with the results of the proof of concept study, the net present value of the revenue stream if the drug/device were to be approved, and the cost of the studies as a function of their power and alpha levels.

In this talk, a decision-analytic framework will be presented to help in the design of proof of concept studies, based on preclinical data sets and the economic value of future phase 3 study results.

Regulatory Issues: From Bedside to Bench

M Francesca Cordeiro

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One of the biggest hurdles in glaucoma in recent years has been the successful translation of laboratory advances to the clinic. This is not unique to glaucoma - such a problem has been well-described in different spheres of medicine. In fact, a search in PubMed on this subject reveals over 1000 references. Various grant-giving bodies have recently focussed on the need for improving translatable research. A major identifiable bottleneck is the adherence to regulatory requirements. Regulatory issues and common problems will be provided, using examples that are well-documented in the field of glaucoma.

Essential Fatty Acids (EFA) and Dry Eye Disease

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The DEWS definition of dry eye disease states that it is a "multifactorial disease of the tears and ocular surface.... Accompanied by inflammation of the ocular surface." Numerous clinical trials and case reports suggest that EFA, especially omega 3, are beneficial (rheumatoid arthritis, cardiac disease, AMD etc.) The clinical research on dry eye disease is actually minimally - generally small clinical trials at single centers and using varying amounts of EFA with variable endpoints and significant findings. The data suggests EFA can be helpful in DED, but a well-designed RCT is needed to determine efficacy. Current information on EFA will be reviewed.

Updating the Role of MGD in Dry Eye

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Meibomian gland dysfunction (MGD) is a global, symptomatic disease whose prevalence rises steadily from middle age. A key feature is terminal duct obstruction, causing reduced meibum delivery, tear film lipid layer (TFLL) changes and the release of inflammatory mediators into the tears. The symptoms of MGD may be due to lid disease alone, to its effects on the ocular surface or, with severe MGD, to evaporative dry eye (EDE). Each of these states may contribute to the symptoms of MGD-EDE. Meibomian lipid, delivered by secretion and blinking, spreads onto the tear film with each blink, creating a lipid layer that retards evaporation. In MGD-EDE, abnormalities in quality and/or thickness of the TFLL remove this protection and promote desiccation. Diagnosis depends on assessment of the TFLL, lid margin inspection and gland expression. Gland expression, meibometry, non-invasive meibography and interferometry can all be standardised. Detection of tear hyperosmolarity marks the transition from MGD alone into MGD-EDE. Apart from the direct measurement of tear evaporation to diagnose EDE, dynamic tests of lipid layer function have recently become available which can assist in the diagnosis of TFLL abnormalities. The stability of the lipid layer interference pattern is altered in MGD and its disturbance can be observed and quantified. The relationship between TFLL performance and dry eye is complex. Tear film lipid layer spread is slowed in MGD and the spread time can be used in diagnosis. But spread time is also dependent on tear volume and may be reduced in aqueous-deficient dry eye.

Characterization of Clinical Tests Currently Used in Dry Eye Clinical Trials

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Dry eye disease (DED) is a highly prevalent ocular condition in many regions of the world. However, currently safe and effective treatments available to DED patients are limited. It is thought that limited understanding of the underlying disease mechanism, poor correlation between DED clinical signs and subjective symptoms, large variability and poor reliability associated with current clinical tests are some of the major challenges in the development of new therapeutics for DED. Variability observed in a clinical test between visits embodies both measurement error and real subject variation. The lack of precision or standardization of a test could lead to a large measurement error; certain disease characteristics, such as being unstable or hypersensitive to environment or other factors, could also cause patient variation from time to time. Thus, it is important to understand the relative contribution of the variance, whether it is due to lack of precision and/or standardization or due to disease characteristics giving rise to significant variance. To examine and compare clinical test performance in different DED patient groups, and compare performance and association of different DED tests within the same study, we conducted a prospective, multicenter, non-interventional clinical study in asymptomatic controls and 3 groups of DED patients with different severity (based on corneal staining), and we assessed, over three visits, three DED symptom questionnaires and a collection of clinical tests. We will discuss the characterization and comparisons of the clinical tests from this study.

Artificial Tear Based on Liposomes and Hyaluronic Acid. Translational Research

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Ophthalmic unpreserved formulations containing components similar to the ones present in the precorneal tear film (PTF) are emerging therapeutic tools in the management of dry eye disease. These formulations must include lipids and aqueous components. Pharmaceutical nanosystems (liposomes) can resemble the lipid layer. Lipid vesicles are dispersed in a solution of a bioadhesive polymer with similar characteristics to the aqueous layer.

The novel artificial tear developed in this work is composed by liposomes (186.3 \pm 12.2 nm size) which have as main components phosphatidylcholine, cholesterol and α -tocopherol (antioxidant). The nanosystems were dispersed in a hypotonic solution (200 mOsm/L) including hyaluronic acid (0.2%) and trehalose (1.6%). The formulation resulted in viability values higher than 80% after short (15 min) and long (1 h and 4 h) exposure times (human corneal and conjunctival cell lines).

After instillation of the novel liposomal drop, there was a significant improvement in tear film stability. TBUT measurements were performed before (9.25 \pm 2.3 seconds) and 2 minutes (11.25 \pm 2.1 seconds) and 30 minutes (12.7 \pm 2.4 seconds) after administration in healthy subjects.

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Outcome Analysis in Ocular Rosacea

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Aims: To evaluate the efficacy of topically applied PRGF-Endoret®, plasma rich in growth factors, as supplementary treatment in severe dry eye due to ocular rosacea.

Methods: This retrospective, nonrandomized, observational case-series study, included 41 eyes of 22 consecutive patients, with severe dry eye due to ocular rosacea. Patients were treated with 6-week cycles of autologous PRGF-Endoret® eye drops in addition to the standard treatment. Staging and clinical response of dry eye were determined before and after treatment with a combination of clinical examination, dry eye subjective scales (OSDI, VAS) and best corrected visual acuity, when applicable. Positive response to combined treatment was defined as improvement in clinical signs concurrent with improvement in subjective scales. Secondary effects of treatment were documented.

Results: Average combined treatment time was 4.6 \pm 2.5 months. Positive response to treatment was seen in 65.9% of eyes, 29.3% showed no change and 4.9% worsened. Subjective scales showed an improvement in symptoms of 21.39, 12.28 and 25.57% respectively after treatment. BSCVA improved marginally. ($p < 0.01$)

Conclusion: The combination of PRGF-Endoret® and standard treatment seems to be safe and effective in dry eye due to rosacea.

Dry Eye Syndrome after Refractive Surgery

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Background: Refractive surgery is a common procedure for correction of myopia, hyperopia and astigmatism. Dry eye syndrome is the most common complication of refractive surgery.

Purpose: To assess the incidence, risk factors and treatment options for dry eye syndrome after refractive surgery.

Methods: A thorough search in Pubmed, Cochrane and Medline for randomized control trials (level I) and prospective cohort studies (level II) investigating dry eye syndrome after refractive surgery was performed. The search resulted in 203 articles only 40 original articles were qualified for the review. Each article was reviewed by the authors and assessed for post surgical dry eye syndrome incidence and characteristics such as: lacrimal gland function, tear osmolality, tear film stability, goblet cell density, corneal sensitivity, corneal barrier function, corneal nerve fibers and ocular surface changes. Besides, each article was reviewed for post surgical dry eye syndrome risk factors such as: preoperative dry eye syndrome, predisposing medical conditions, surgical method, mechanical or laser assisted flap creation, hinge location, hinge angle, flap thickness, ablation depths and diameter of the wound. Treatment options were also assessed.

Conclusions: Dry eye syndrome may be caused by different preoperative and intraoperative factors but mostly it is transient and curable. Patients should be warned about this distressing complication.

Effects of Long Term Use of Topical NSAIDs in Dry Eye Patients

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Inflammation and Inflammatory mediators play an important role in the signs and symptoms of dry eye. Many physicians use steroid drops to control dry eye. But as we know steroid drops can not be used on a long term basis. NSAID drops could be used to control the inflammation of dry eye but are not commonly used by physicians due to a past history of corneal melts. We did a retrospective study of 73 patients who had been on NSAID Qday for at least a 3 month and looked at efficacy and adverse events. NSAIDs proved to be effective in controlling pain associated with dry eye and improved tear break up time. No corneal melts were seen with few adverse events.

Tear Film Imaging Using OCT

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Dry eye syndrome (DES) is a highly prevalent ocular condition with severe consequences for the patients reaching from ocular discomfort in its simplest form up to visual impairment and corneal ulceration in severe cases. Despite all efforts to develop standard clinical tests for the diagnosis of DES, all methods currently available do only poorly reflect patients' complains and are therefore only of limited use to monitor therapy success or to evaluate the efficacy of therapy approaches.

The recent development of new high-resolution optical coherence tomography (OCT) systems allow now for the direct visualization of the tear film. Based on these OCT systems both tear film thickness and tear film stability can be assessed non-invasively in patients with DES. Furthermore, a high resolution visualization of the tear film will also allow for the determination of the residence time of topical applied drugs. In this talk, the current developments in tear film imaging with OCT will be summarized and the potential clinical applications will be covered.

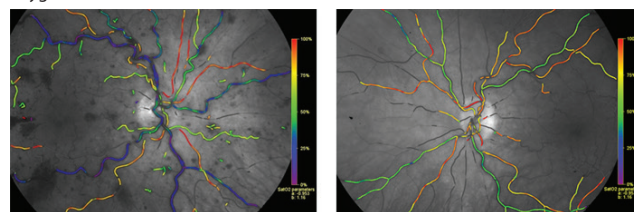
Non-Invasive Retinal Oximetry

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There are indications of disturbed blood flow and / or oxygenation in major eye diseases, such as retinal vessel occlusions, diabetic retinopathy, glaucoma, age-related macular degeneration and retinopathy of prematurity. Several research groups have developed technology to measure retinal oxygenation with non-invasive imaging.

Dual wavelength, fundus camera based oximetry has been shown to be sensitive to changes in retinal vessel oxygen saturation and to give repeatable results. Low saturation has been confirmed in retinal venules in central retinal vein occlusion (CRVO). The image below shows a map of oxygen saturation in an eye with CRVO and the fellow eye in the same patient. In contrast, retinal venous oxygen saturation appears to be higher than normal in diabetic retinopathy, glaucoma and possibly in age-related macular degeneration. The possible explanations include poor distribution of oxygen (diabetic retinopathy) and decreased oxygen consumption due to atrophy of tissue (glaucoma, age-related macular degeneration and possibly diabetic retinopathy).

Non-invasive retinal oximetry provides the opportunity to study retinal oxygenation in various diseases and the effect of various treatments. This will complement studies on ocular blood flow as well as animal studies on retinal oxygenation.



Doppler OCT

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Morphological and functional changes of retinal vessels do not only reflect ocular vascular pathologies, but are also associated with systemic disease. Changes of the retinal vascular system may serve indicators for systemic disorders such as diabetes and hypertension. As such, much emphasis has been put into the development of new and sophisticated methods to assess retinal blood flow in vivo. One approach is based on Doppler optical coherence tomography (OCT), yielding in principle information on both, velocity and diameter. We developed a technique based on diameter measurements with a fundus-camera based system and bi-directional Fourier Domain Doppler OCT. Using this technique it is possible to measure total blood flow in both arteries and veins. Comparison of velocity data as obtained with bi-directional Fourier Domain Doppler OCT showed good correlation with laser Doppler velocimetry data during both normoxic and hyperopic conditions. In addition, data measured at retinal bifurcations indicate the validity of the technique. Finally, measurements at retinal arterial and venous vessels show that absolute retinal blood flow can be extracted with high precision.

Epimacular Brachytherapy (EMBT) for Age Related Macular Degeneration Patients

Pravin Dugel

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Purpose: To present safety and efficacy outcomes from two multi-center studies of epimacular brachytherapy (EMBT) in neovascular age-related macular degeneration (nAMD) patients.

Methods: Patients underwent pars plana vitrectomy and 24-Gray beta irradiation, using a device to deliver Strontium-90 brachytherapy (NeoVista, Newark, CA). Anti-VEGF injections were administered on an as needed basis following the one-time surgical intervention.

Results: Various data outcomes will be presented.

Conclusions: The CABERNET study did not meet its primary endpoint. However, EMBT has been shown to not only reduce the treatment burden, but also improve vision in select patients.

Different Drugs and Regimens in the Treatment of Wet-AMD: What to Choose?

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Purpose: Ranibizumab and aflibercept are inhibitors of human VEGF, approved for the treatment of CNV due to AMD. Large, multi-center, randomized clinical trials have been conducted exploring the safety and efficacy of the drugs. Relevant data provide guidances to assist ophthalmologists in clinical practice to enhance treatment outcomes.

Methods: Evidence available from prospective, multi-center clinical studies evaluating different treatment schedules with the use of ranibizumab and aflibercept is utilized to generate evidence-based recommendations.

Results: Ranibizumab and aflibercept are indicated for CNV with active disease. Pivotal trials that explored the efficacy of ranibizumab showed that treatment initiation with three consecutive monthly injections, followed by continued monthly injections, has provided the best VA outcomes. If continued monthly injections are not feasible after initiation, a flexible strategy appears viable, with monthly monitoring of lesion activity recommended.

Aflibercept, administered every 2 months after 3 initial monthly doses, has been shown to be non inferior to monthly ranibizumab during the first year of therapy in the VIEW trials. The use of a mixed prn/fixed regimen in the second year of the studies produced a slight decrease of the visual acuity improvement obtained after 1 year in both the ranibizumab arm (-0.8 ETDRS letters) and in the aflibercept arm (-0.8 ETDRS letters).

Conclusion: With the advent of anti-VEGF therapy the prognosis of CNV has changed dramatically. Data from well-conducted clinical trials suggest that ranibizumab and aflibercept are effective and well tolerated in patients. Evidence-based guidelines will help to optimize treatment outcomes with anti-VEGF compounds in neovascular AMD.

Effects of VEGF Inhibition on Vascularized Pigment Epithelium Detachment due to Occult Choroidal Neovascularization

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Purpose: To report the results of vascular endothelial growth factor (VEGF) inhibition for vascularized pigment epithelium detachment (PED) associated to choroidal neovascularization (CNV) due to age-related macular degeneration.

Methods: A retrospective analysis of patients affected by vascularized PED treated with intravitreal anti-VEGF (0.5 mg ranibizumab or 1 mg bevacizumab) and a follow-up of 12 months was performed. Retinal angiomatous proliferations were excluded from analysis. Treatment was conducted with an initial loading phase followed by a pro re nata phase. Fluorescein angiography and indocyanine green angiography were performed at baseline and every three months.

Results: Forty eyes were included in this study. After a follow-up of 12 months and 5.5 treatments on average, BCVA did not change significantly. Central retinal thickness and PED height significantly reduced while the CNV area remained constant.

Conclusions: In vascularized PED, anti-VEGF therapy shows visual stabilization but not BCVA gain. However, it is associated with significant morphological improvements and it may offer a benefit over the natural course of the disease.

Implications of the EVEREST Study on Current Paradigms in Diagnosis and Treatment of Polypoidal Choroidal Vasculopathy

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Polypoidal choroidal vasculopathy (PCV) is an important cause of serosanguineous maculopathy, especially among Asians. Recent observations have improved our ability to recognise, diagnose and classify PCV. There is also increasing data on natural history, prognostic factors and response to various modalities of treatment. There are now consensus guidelines on the diagnosis and treatment of this disease. Extrafoveal PCV can still be adequately treated with laser photocoagulation. Verteporfin photodynamic therapy (PDT) has been shown to be effective in ablative closure of subfoveal or juxtafoveal lesions, although vision improvement may be limited and inconsistent. The recent availability of anti-vascular endothelial growth factor (VEGF) agents such as ranibizumab (Lucentis) has resulted in improved visual outcomes. However, anti-VEGF monotherapy does not effect closure or angiographic obliteration of the PCV lesions in 9 out of 10 cases. Hence, verteporfin PDT in combination with anti-VEGF may be a reasonable alternative treatment. The results of the EVEREST study on combination therapy for PCV and their impact on current standard of treatment will be discussed.

Dealing with Heterogeneity in Clinical Studies for Uveitis

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Introduction: Uveitis encompasses a spectrum of rare diseases with heterogeneous presentations and different etiologies. To demonstrate the efficacy of new treatment methods, clinical trials require the inclusion of a sufficient number of cases. Hence, patients with different types of uveitis are usually pooled into single studies, which need to be designed with appropriate outcome measures to deal with this heterogeneity.

Methods: Review of the methodology used in selected clinical trials in the field of uveitis.

Results: Among the different causes of uveitis, some entities have been the object of specific trials focused on a single diagnosis, such as ocular toxoplasmosis, B27-associated uveitis and Behçet's disease. Otherwise, the majority of recent trials have pooled cases of intermediate and posterior uveitis of various non-infectious etiologies. The main outcome measures have been vitreous haze in the dexamethasone intravitreal implant studies and rates of recurrence in the Intravitreal fluocinolone acetonide implant studies. Other outcome measures have been the control of inflammation, steroid-sparing effect and visual acuity. Because macular edema is judged to be a consequence of uveitis rather than one of its primary features, OCT-based studies focused on the effect of treatment on uveitic macular edema are lacking. Some ongoing studies, such as the Visual trial (ClinicalTrials.gov Identifier: NCT01148225), use a combination of outcome measures to assess a time to treatment failure.

Conclusions: Adequate design of clinical trials in the field of uveitis are needed to deal with its variable presentations.

Extracellular Matrix (ECM) – Choroidal Neovascular (CNV) Interaction as a Potential Therapeutic Target for Wet AMD

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Purpose: ECM-Endothelial cell signaling has shown be important in endothelial cell survival. Volociximab, is an $\alpha 5\beta 1$ integrin antagonist, and interruption of such signals is evaluated in wet AMD patients in combination with ranibizumab. Alpha5 Beta1 ($\alpha 5\beta 1$) integrins are transmembrane receptors which bind to fibronectin in the extracellular matrix. This leads to intracellular signal transduction controlling critical events involved in angiogenesis such as cell proliferation, survival and migration. These $\alpha 5\beta 1$ integrin mediated activities are downstream to VEGF and other activators of angiogenesis. Alpha5 Beta1 integrin antagonism has demonstrated potent anti-angiogenic effects in preclinical oncologic and ophthalmic models.

Methods: Phase 1/2a, open label, multicenter, dose escalation study in eyes with choroidal neovascularization secondary to AMD. Patients received three monthly intravitreal injections of the combination of volociximab, an anti- $\alpha 5\beta 1$ integrin monoclonal antibody (0.2, 0.5, 1.25 or 2.5 mg) and ranibizumab (0.5 mg). Both anti-VEGF treatment-naïve eyes (n=52) and anti-VEGF experienced eyes (n=11) were treated. Treatment-experienced eyes were investigator determined to be unresponsive to previous anti-VEGF monotherapy (lack of visual and anatomic response).

Results: Fifty-two (52) patients received three administrations of volociximab in combination with ranibizumab for a treatment-naïve wet AMD lesion in one eye. Baseline visual acuity was 52.4 letters and OCT central subfield thickness was 348.0 μm . After three doses of combination therapy (week 12) the mean change in VA was +11.0 ETDRS letters. Thirty-five percent of patients gained ≥ 3 lines (15 letters) of vision. The mean change in OCT central subfield thickness was -119.7 μm .

Eleven (11) patients received three administrations of volociximab in combination with ranibizumab in previously treated eyes with monotherapy anti-VEGF agent ("treatment-experienced"). Baseline visual acuity was 56.5 letters and OCT central subfield thickness was 313.8 μm . After three doses of combination therapy (week 12) the mean change in VA was +7.5 letters. Thirty percent of patients gained ≥ 3 lines (15 letters) of vision. The mean change in OCT central subfield thickness was -86.6 μm . Dose escalation was completed without evidence of dose-limiting toxicity.

Conclusions: Results of this phase 1 study of volociximab combined with ranibizumab suggest a favorable safety profile.

Ocular Surface Disease Induced by Preservatives

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Preservatives are used in ocular preparations to extend their shelf life and prevent contamination from repeated use and currently BAK is the most commonly used preservative worldwide. However, extensive data has shown that preservatives, especially BAK, can have deleterious effects on the ocular surface. These effects have been demonstrated in tissue culture models, animals and humans. Not only is BAK associated with ocular surface disease that can be observed by slit lamp examination, but also these ocular changes are associated with symptoms of pain and irritation and likely inter with compliance with use of topical agents and may adversely effect treatment goals.

Effects of BAK on Corneal Nerves

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Purpose: To determine and characterize the effect of topical application of benzalkonium chloride (BAK) on corneal nerves *in vivo* and *in vitro*.

Methods: *Thy1-YFP+* neurofluorescent mice eyes were treated topically with vehicle or BAK (0.01% or 0.1%). Wide-field stereofluorescence microscopy was performed to sequentially image the treated corneas *in vivo* every week for 4 weeks, and changes in stromal nerve fiber density (NFD) and aqueous tear production were determined. Western immunoblot analyses were performed on trigeminal ganglion and corneal lysates to determine abundance of proteins associated with neurotoxicity and regeneration. Compartmental culture of trigeminal ganglion neurons was performed in Campenot devices to determine whether BAK affects neurite outgrowth.

Results: BAK-treated corneas exhibited significantly reduced NFD and aqueous tear production, and increased inflammatory cell infiltration and fluorescein staining at 1 week ($p < 0.05$). These changes were most significant after 0.1% BAK treatment. The extent of inflammatory cell infiltration in the cornea showed a significant negative correlation with nerve fiber density. Sequential *in vivo* imaging of corneas showed two forms of BAK-induced neurotoxicity: reversible neurotoxicity characterized by axonopathy and recovery, and irreversible neurotoxicity characterized by nerve degeneration and regeneration. Although both BAK doses (0.0001% and 0.001%) reduced nerve fiber length, the reduction was significantly more with the higher dose ($p < 0.001$). **Conclusion:** Topical application of BAK to the eye causes corneal neurotoxicity, inflammation, and reduced aqueous tear production.

Could Trabecular Meshwork be Damaged by Preservatives?

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Purpose: Long-term exposure to BAK-containing eye drops has been shown in a large variety of reports to cause chronic ocular inflammation over the ocular surface, causing irritancy symptoms, treatment discontinuation, and dry eye disease. We raised the hypothesis that antiglaucomatous medications administered over the long term may also adversely affect deeper ocular tissues, including the trabecular meshwork (TM).

Methods: Trabecular specimens were examined using immunohistology and RT-PCR. A trabecular cell line was stimulated by BAK and examined for apoptosis, oxidative stress, fractalkine and SDF-1 expression, and modulation of their receptors. An experimental model was developed with BAK subconjunctival injections to induce TM degeneration. Mass spectrometry imaging (MSI) assessed BAK penetration after repeated instillations in rabbit eyes.

Results: Trabecular specimens showed extremely low densities of trabecular cells and presence of cells expressing fractalkine and fractalkine receptor and their respective mRNAs. Benzalkonium *in vitro* induced apoptosis, oxidative stress, and fractalkine expression and inhibited the protective chemokine SDF-1 and Bcl2, also inducing a sustained IOP increase, with dramatic apoptosis of trabecular cells and reduction of aqueous outflow. MSI showed that BAK could access the TM at measurable levels after repeated instillations.

Conclusion: BAK enhances all characteristics of TM degeneration typical of glaucoma and causes degeneration in acute experimental conditions, potentially mimicking long-term accumulation after repeated use of preservative-containing eyedrops over decades. This supports the hypothesis that antiglaucoma medications, through the toxicity of their preservative, may cause further long-term trabecular degeneration and therefore enhance outflow resistance, thus reducing the impact of IOP-lowering agents.

Benzalkonium Chloride Effects on Deep Ocular Structures

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Background: Benzalkonium chloride (BAK) is the most commonly used preservative in eye drops and its side effects on the ocular surface in long-term treated glaucoma patients have been greatly demonstrated. But no study has confirmed its possible effects on deep ocular tissues. We investigated in a rabbit model, the eye distribution of topically instilled BAK using mass spectrometry imaging (MSI).

Methods: The eyes of New Zealand rabbits receiving 0.01%BAK twice-a-day for 5 months or 0.2%BAK one drop-a-day for 1 month were compared to non-instilled control eyes. Cryosections were performed on glass slides for histological and immunohistological controls (hematoxylin-eosin staining, CD45, RLA-DR for inflammatory cells and vimentin for Müller cell activation) and ITO or stainless steel plates for MSI experiments using Matrix-assisted laser desorption ionization time-of-flight.

Results: Using MSI techniques, BAK was detected in cornea and conjunctiva and also in sensitive areas involved in glaucoma: iridocorneal angle and optic nerve areas. This presence of BAK was confirmed with histological studies showing an increase of the number of CD45-, RLA-DR-positive cells in treated eyes. Moreover, vimentin staining increased in all retinal layers in treated eye confirming an activation response to a cell stress.

Conclusions: This toxicological study confirms the presence of BAK not only in ocular surface structures but also in deeper structures involved in glaucoma. The inflammatory cell infiltration and Müller cell activation confirmed the deleterious effect of BAK. Although obtained in animals, these results highlight the importance of the safety-first principle for the glaucoma treatment.

Pseudophakic Preservative Maculopathy: Updates

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Many anti-glaucoma eyedrops are reported to induce cystoid macular edema (CME) in relatively early postoperative aphakic or pseudophakic eyes. We have carried out several clinical studies to compare the incidence of CME and magnitude of blood-aqueous barrier disruption among the early postoperative pseudophakic eyes with preserved, non-preserved anti-glaucoma eyedrops and their vehicles. To confirm the above clinical results, we have, then, investigated the effects of latanoprost, timolol and benzalkonium chloride (BAK) on cell morphological damage and expression of inflammatory chemical mediators including prostaglandin E in human lens epithelial cell line in culture. These studies suggest that addition of BAK contributes considerably to CME produced by anti-glaucoma eyedrops, rather than main agents does in early postoperative pseudophakic eyes. We have also found the concomitant use of topical NSAIDs with anti-glaucoma eyedrops prevent CME in early postoperative pseudophakias. We have proposed the above phenomenon as "pseudophakic preservative maculopathy". This talk will describe and update this pathological situation.

Inhibition of VEGF During Choroidal Neovascularization and Retinal Stresses by Gene Transfer Strategy

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Background: In this study, we investigated animal models of choroidal neovascularization as well as mice subjected to retinal stress induced by high light exposure in order to evaluate the effect of an anti-VEGF therapeutic approach, knowing that VEGF has a dual role in the retina as angiogenic and neurotrophic factor.

Method: MA lentiviral vector (LV) coding for a single chain antibody anti-VEGFA isoforms (V65) was cloned and used to inhibit VEGF action in mice subjected to argon laser injury or high light exposure.

Results: LV-V65 had a potent action to diminish neovascularization induced by argon laser impacts. The number of GFAP positive cells was also decreased and the photoreceptor layer was well preserved in the LV-V65 treated group, but not in the LV-GFP control.

After high light exposure a peak of VEGF was detected in the neuroretina, followed by an immediate breakdown of the outer blood retinal barrier. To evaluate whether VEGF, in retina stress condition, is present as a neuroprotective factor or has a role on RPE permeabilization, animals were treated with LV-V65. Blocking VEGF inhibits outer blood retinal barrier breakdown and retinal degeneration.

Conclusions: The present data show that anti-VEGF gene transfer therapy can be efficient to prevent both neovascularization and side effects generated by VEGF release during retinal stresses, such as those encountered during ageing and metabolism dysfunction. Nonetheless, "intelligent" vectors are to be generated to avoid constitutive ablation of VEGF which may be deleterious for choroidal vessels and, in consequence, for the retina.

Targeting Complement Factor 5 in Neovascular AMD

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Purpose: Genetic linkage and pathobiological studies have implicated activation of the complement system in AMD. Preclinical studies confirm a role for complement effector molecules in the induction and severity of choroidal neovascularization. This study assessed the safety of intravitreal injections of the aptamer ARC1905, which inhibits activation of complement factor 5, in combination with ranibizumab for the treatment of neovascular AMD.

Methods: Forty-three treatment-naïve patients were enrolled in a phase 1, prospective, noncontrolled multicenter, dose escalating study of all subtypes of subfoveal neovascular AMD. These patients received six monthly intravitreal injections of the combination of ARC1905 (0.3 mg, 1 mg, 2 mg) and ranibizumab (0.5 mg). Secondary endpoints included change in visual acuity and OCT. Complement-associated SNP analysis was conducted in a cohort of patients.

Results: Dose escalation was completed without evidence of dose-limiting toxicity. Two patients had non-ocular serious adverse events that were unrelated to study drug. Preliminary analysis revealed 51% of patients gained ≥ 3 lines (≥ 15 ETDRS letters) of VA (46%, 47%, 60% for the 0.3 mg, 1 mg, and 2 mg dose groups, respectively) from baseline to Week 24. The mean change in OCT center point thickness was -153 μm (-143 μm , -175 μm , -137 μm for the 0.3 mg, 1 mg, and 2 mg dose groups, respectively) at Week 24. Baseline OCT center point thickness did not influence the response to therapy.

Conclusions: The combination of C5 and VEGF inhibition in neovascular AMD is well tolerated without evidence of acute toxicity.

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

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Background: The pivotal MARINA and ANCHOR trials established monthly ranibizumab as standard-of-care for wet age-related macular degeneration (AMD). Aflibercept was recently approved by U.S. FDA for treatment of AMD and bevacizumab is used off label. The varied clinical presentation and response to anti-VEGF therapy has prompted the study of individualized dosing regimens that adjust treatment frequency based on patient's response.

Methods: We compared published trial data from the MARINA, ANCHOR, HARBOR, CATT, IVAN and VIEW studies in search for evidence that may guide the choice of VEGF-inhibitor and treatment regimen. Of particular interest was the relationship between treatment schedules, clinical outcomes and the molecular characteristics and pharmacokinetics of different VEGF inhibitors.

Results: With the inherent limitations of cross trial comparisons, comparing results from major clinical studies is confounded by differences in primary outcomes, control arms and treatment schedules. Nevertheless, our review suggests that monthly treatment continues to provide consistently optimal results as indicated by visual acuity and anatomic outcomes. When the decision to treat is guided by specific functional and anatomic criteria, significant visual improvement and number of administered injections tends to equilibrate between the 3 VEGF inhibitors. This suggests that claimed differences in affinity and potency are not supported by differences in clinical efficacy or injection frequency.

Conclusions: AMD is an aggressive disease and sub-optimal treatment can lead to irreversible vision loss. Current clinical data reaffirms the efficacy of monthly and less than monthly treatment and emphasizes the need for careful follow-up when less than monthly treatment is used.

An Update on Adenoviral Antivirals

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Adenovirus ocular infections (epidemic keratoconjunctivitis [EKC], follicular conjunctivitis, and pharyngeal conjunctival fever) are the most common ocular viral infections worldwide, including more than 1,000,000 cases annually in Japan. To date, there is no US FDA or European Medicines Agency approved antiviral therapy for these infections. However, several agents are currently in clinical trials for the treatment of these infections. Industry, academic, and investigator sponsored clinical trials have been initiated with several agents: NVC-422 (0.33%, NovaBay), ganciclovir (0.15%, Bausch + Lomb; 0.15% Adapt Produtos Oftalmológicos Ltda.; 0.15% Laboratoires Thea; 0.3% Adapt Produtos Oftalmológicos Ltda.), povidone-iodine (2%, Mahidol University; 5% Betadine for EKC Internet Study), and 0.4% povidone-iodine/0.1% dexamethasone (FST-100, Foresight Biotherapeutics; University of Campinas, Brazil). This presentation will examine the characteristics of these agents and rate their chances for approval. The first antiviral to treat adenovirus ocular infections will hopefully be available in the not too distant future.

The Treatment of Conjunctivitis in Pediatric Population

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Infectious conjunctivitis affects all ages but is particularly common in children. Ocular surface bacterial infections affect subjects of all ages with a high frequency in newborns and children. Bacterial etiology represents one of the most common ocular diseases in childhood, occurring in approximately one in eight children each year. In infant, children and teenagers, the most common ocular pathogens are *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and also *Moraxella* species and could lead to ulcers and sight-threatening complications. The objective is to review the update on topical antibiotics and current options available in Europe. Publications data on efficacy and safety can lead to recommendation for the use of eyedrops in children. Over the past years new development in topical antibiotics essentially focused in diversification of fluoroquinolones. Several recent publications identified effective topical ocular antibacterials requiring a reduced dose regimen and a short treatment course, easily used in children. Additional literature reviewed, included data on novel perioperative prophylaxis, indications for topical fortified antibiotics and innovative research including the risk of resistance. Safe and effective antibiotic eyedrops for the treatment and prevention of ocular infections must be adapted to the type of bacteria suspected. The use of highly effective fluoroquinolones should be reserved for the most severe cases to avoid resistance. Advantages of topical anti-microbial treatments are to provide symptomatic relief, hasten microbial eradication, shorten disease duration, reduce risk of developing sight-threatening and improve quality of life of children and their parents.

An Update on Treatment for Bacterial Keratitis

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Purpose: To discuss challenges in management of bacterial keratitis in India

Methods: Review of experience at a tertiary eye care centre in India

Summary: Infectious diseases of cornea are important causes of ocular morbidity and blindness. It is estimated that 1.5 to 7 million corneal ulcer cases occur each year in the developing world. Further, the proportion of bacterial and fungal infections reaches almost 50% in India and other developing nations.

The management of bacterial corneal infections seems relatively straight forward as most antibacterial drugs are bactericidal and administration of drugs directly to the site of infection is likely to result in cure in most cases. However, several factors are complicating the situation. A vast majority of cases of corneal ulcer are treated empirically because of both because of the lack of access to microbiology laboratory facilities and desire among ophthalmologists. This results in delay in institution of appropriate treatment or drug toxicity. Most bacterial isolates of corneal ulcer are showing increasing resistance to fluoroquinolones including the more recently introduced drugs such as moxifloxacin and gatifloxacin. There is increase in rate of oxacillin resistance among gram positive isolates. *Pseudomonas* isolates are showing resistance to multiple antibacterial drugs. Due to lack of awareness diagnosis and management of *Nocardia* and atypical mycobacterial keratitis is often delayed.

Conclusion: Despite availability of bactericidal drugs management of bacterial corneal ulcer is complicated by several emerging challenges.

The Assessment of Anti-Acanthamoeba Solutions Using a Complete-Kill Assay

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Background: Acanthamoeba keratitis requires effective topical drug therapy to eradicate the pathogenic agent.

Methods: An assay was created to determine whether 0.02% poly(hexamethylene biguanide) hydrochloride (PHMB), 0.02% chlorhexidinedigluconate (CHL), 0.1% c-desomedine (DESO), and 1.0% c-voriconazole (VOR) were effective in completely killing 15 different isolates of acanthamoeba at time points 24, 48, and 72 hours in comparison to a saline control. Each 0.5 ml volume of solution was inoculated with 0.1 ml of acanthamoeba cysts at a concentration of $1-5 \times 10^6/\text{ml}$ and allowed to incubate at 30°C. Aliquots from each treatment group were inoculated onto non-nutrient agar overlaid with *Enterobacter aerogenes*. The plates were microscopically examined for growth at time points 1 and 2 weeks. At 2 weeks, all plates were sub-cultured onto fresh medium. At 7 days, growth in sub-culture at each time point was graded 1 for growth and zero for no growth. The time points were combined for each drug with a possible grade from 0 to 3. The grades were non-parametrically (Mann Whitney) compared to determine any significance in positive growth between the drugs.

Results: Complete-kill was determined more frequently with PHMB and DESO ($p=1.0$) than CHL ($p=0.04$). PHMB, DESO, and CHL demonstrated more complete-kill than VOR ($p=0.01$) which was more effective than the saline control ($p=0.0003$).

Conclusion: The complete-kill assay appears to provide separation in the effectiveness of different anti-amoebic drug solutions. This assay may provide an alternative evaluation of possible new anti-infectives in the treatment of acanthamoeba keratitis.

Graft-to-Host Transmission of Herpes Simplex Virus after PKP – Myth or Reality?

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Background and Purpose: Repeatedly there have been speculations about “new-onset” herpetic eye disease after corneal surgery. The purpose of this study was to assess whether keratitis or primary graft failure after penetrating keratoplasty (PKP) may be attributed to donor contamination or latent viral load of the host.

Methods: In 176 cases of PKP, a piece of the excised host tissue and of the corneoscleral rim of the donor were examined for herpes simplex virus (HSV-1) DNA by polymerase chain reaction. Postoperative complications such as epithelial keratitis, primary graft failure were recorded during the first 4 weeks after PKP. In all but two patients with HSV positive donor or recipient corneas acyclovir was administered as recommended.

Results: We identified six of 176 HSV-1 positive donor corneas (3.4%). Two of these grafts transplanted to HSV free keratoconus patients developed primary graft failure and persistent epithelial defects on the graft even after repeat transplantation. Eighteen primarily excised corneas were HSV-positive (10.2%). In ten of these 18 eyes, herpetic eye disease had not been expected clinically. On the other hand, 16 patient corneas with clinically expected herpetic eye disease were HSV negative using PCR (9.1%).

Conclusions: Graft-to-host transmission of HSV seems to be a real phenomenon with potential impact on the graft survival after PKP. To enables an appropriate prophylactic acyclovir treatment in distinct cases after PKP, we advocate the screening of donor and patient corneas for HSV-1 by use of PCR.

Antibiotic Resistance - A Global Problem

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Emerging resistance to antimicrobial drugs has been a global issue for years for systemic treatment. Now, recent surveillance studies have demonstrated a similar problem associated with ocular isolates and topical agents used in ophthalmology. The development of resistance has several causes including overuse of systemic antibiotics; improper dosing regimens, extended duration of treatment, patient non-compliance and environmental pressures. Topical fluoroquinolones have been the mainstay of broad-spectrum treatment for years. However the TRUST study (Tracking Resistance in the US Today) clearly demonstrated that resistance is not an isolated phenomenon with only a few organisms and only selected antibiotics. Methicillin-resistant Staph aureus (MRSA) are by definition resistant to penicillins and other beta Lactam antimicrobial agents; TRUST and ARMOR (Antibiotic Resistance Monitoring of Ocular Microorganisms) have both demonstrated the rise in MRSA ocular isolates and multi-drug resistance is common among the fluoroquinolones. Surveillance studies will be helpful in deterring trends in drug resistance and can be used to guide drug selection for clinical practice.

Methods to Evaluate Neuroprotection in the Retina

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Because retinal injuries may induce functional and morphological alterations in different retinal layers, to evaluate neuroprotection it is crucial to know the numbers and distribution of retinal neurons in control and injured retinas. We have recently developed automated routines to quantify and represent the spatial distribution of the total population of retinal ganglion cells (RGCs), cells in the ganglion cell layer (GCL) and cones. RGCs were identified by retrograde tracing of Fluorogold (FG) or Brn3a immunodetection, and cells in the GCL were identified with nuclear staining. L- or S-opsin immunodetection was used to identify L- or S- cones, respectively. These populations were analyzed using customized macros developed to count automatically the total numbers of the labeled cells and to generate isodensity maps depicting neuronal densities and retinal distribution. In control albino rat retinas, there are 83,449 Brn3a⁺RGCs or 80,251 FG⁺RGCs. Cells in the GCL approximate 210,000. The whole population of S-cones is 41,098 and of L-cones is 231,736. Retinal distribution of RGCs, cells in the GCL and L-cones is parallel, with higher densities in the central retina that decrease towards the periphery, where their densities reach their lowest. In conclusion, we have developed reliable tools to identify, quantify and visualize the distribution of the total population of RGCs, cells in the GCL and cones in naïve, injured or treated rat retina. It is anticipated that these tools will allow precise and objective studies of neuroprotection in the retina.

Microsporidial Stromal Keratitis - a Therapeutic Challenge

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Purpose: The aim of this presentation is to share our experience with Microsporidial stromal keratitis. Methods: Review of experience at a tertiary eye care centre in India as well as the literature published from other parts of the world. Summary: Although keratoconjunctivitis is the most common form of ocular infection caused by the parasite the stromal keratitis is an ill-defined disease and there is paucity of literature on this form of infection. We collected data on 30 eyes of 29 cases and analyzed various aspect of this disease. The disease is characterized by a slowly progressive course with a significantly prolonged duration of symptoms. 11 subjects in our series had symptoms of more than 1 year duration. The corneal picture resembles that of herpes simplex virus (HSV) stromal keratitis or fungal keratitis cases. 14 patients were referred to us as HSV keratitis. Further, even at our center 16 (55.1%) subjects were clinically diagnosed as HSV stromal keratitis and 12 (40.0%) received treatment with topical corticosteroid and acyclovir. The diagnosis of Microsporidia infection is usually made by microscopic examination of smears in patients with ulcerative keratitis or on histopathology examination of corneal tissues. In the absence of definitive medical treatment nearly all the patients require surgical treatment. Conclusion: The confusion about the parasite Microsporidia is not just limited to its classification but also extends to various aspects of the corneal disease produced by it.

Use of High Content Screening to Identify Novel Neuroprotective Agents

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To identify neuroprotective agents that could complement intraocular pressure-lowering therapies for glaucoma, we developed a high-throughput phenotypic screen using primary mouse RGCs. A screen of over 15,000 small molecules identified the protein kinase inhibitor (PKI) sunitinib as being highly neuroprotective both in vitro and in vivo. Although sunitinib is a well-characterized PKI, the mechanism by which it promotes RGC survival was not immediately obvious as it can inhibit over 100 kinases.

To identify biologically relevant kinase(s) whose inhibition promotes RGC survival, we developed an siRNA-based high-throughput, high-efficiency system for knockdown of specific PKIs in cultured RGCs. We screened the Sigma Mission kinome library (1869 siRNAs covering 623 genes) for oligonucleotides that increased RGC survival. The top two survival-promoting hits were dual-leucine kinase (DLK) and its substrate, mitogen activated protein kinase kinase 7 (MKK7). Simultaneous knockdown of both kinases was as neuroprotective as sunitinib, and survival was sustained for over two weeks. Consistent with these results, DLK is a known target of sunitinib. Moreover, sunitinib loses its neuroprotective properties in the setting of knockdown of the DLK pathway (as might be expected if DLK were a relevant target). Injured RGCs demonstrate a marked post-transcriptional increase in DLK expression at the protein level. And conditional knockout of DLK in vivo promotes RGC survival following mouse optic nerve crush.

Identification of specific small molecule DLK inhibitors could aid in the development of novel neuroprotective drugs for the treatment of glaucoma and other forms of optic neuropathy.

Controversies in Glaucoma Neuroprotection

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For at least four decades there has been interest in using therapies other than intraocular pressure (IOP) lowering to prevent the progression of glaucomatous optic neuropathy. This "neuroprotective" approach has been well-established in the laboratory but has not yet resonated in the clinic. This talk will concentrate on the following issues that are relevant to use of neuroprotection in clinic care of patients with glaucoma: (1) Where in the optic nerve and brain does a neuroprotective therapy need to act in order to translate to clinical efficacy? (2) Is it possible to design clinical trials to test neuroprotection in glaucoma within reasonable time and financial constraints? (3) Even if clinical trials showed efficacy, is there a clinical need given the availability of excellent IOP lowering therapies?

Neuroprotection: Where are We Now?

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The realisation that lowering IOP is unable to prevent progressive vision loss in **all** glaucoma patients, has led to investigation of neuroprotection as an alternative or additional treatment option. Neuroprotection has gained renewed interest recently as a therapeutic approach to prevent neuronal degeneration and loss of function in glaucoma, since the publication of the LoGTS study. Although confirmation of neuroprotective effects by other randomized clinical trials is needed, there is now a demonstration of positive non-IOP dependent effects. Furthermore, it has been proposed as a treatment strategy in other ocular diseases, such as AMD. This talk will review the evidence for neuroprotection in the eye, and its future as a treatment strategy.

Targeting RGC Axons in Glaucoma

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The search for targets for neuroprotection or neuroregeneration is challenging and usually required multiple and different strategies. Neurodegeneration and neuroprotection are both important although different. Neuroregeneration is crucial when we already have RGC loss. Neuroprotection is important to protect sick RGC and to prevent progressive and future RGC loss. The focus of this lecture is protecting potential axonal targets in glaucoma. Promising axonal targets include:

- Neurotrophic factors (CNTF, BDNF, NGF)- for neuroprotection and neuroregeneration
- Glutamate-diminish axonal transport
- Ca²⁺- excessive calcium induce irreversible injury and degradation of axonal cytoskeleton
- Toxic reactive oxygen species (ROS)-endogenous mitochondrial repair mechanism is impaired with age and increased light exposure
- Axonal survival factors – IPA family members

AntiVEGF Use in Trabeculectomy Surgery - What is its Role and the Evidence

Tina Wong

Glaucoma, Singapore National Eye Centre, Singapore

The current adjunctive use of Mitomycin C and 5 Fluorouracil have greatly improved the surgical outcomes of trabeculectomies, but remain inadequate in individuals with a propensity to scar. There is increasing evidence to support the use of anti-VEGF agents for modulating the post-operative scarring response in primary glaucomas. However, the mechanism of antifibrotic action is as yet unclear, and the dosing regime of the anti-VEGF agent are still debatable.

Methods: The effect of bevacizumab on scarring are investigated using a murine model of subconjunctival scarring. Animals were treated with 2 consecutive injections of bevacizumab or IgG control at the end of surgery on Day 0 and Day 2 post surgery. The animals were followed up until the filtration surgery was observed to have failed. Bleb survival and the signs and activity of inflammation and fibrosis are revealed through RT-PCR, western blot, zymography and immunohistochemistry of the tissues.

Results: Bleb survival was prolonged with bevacizumab treatment. There was a significant reduction in early inflammatory cell recruitment to the surgical site with bevacizumab treated eyes. mRNA expression and activities of MMP-9, TGF beta and COX-2 were significantly reduced in the early stages of wound healing. However, bevacizumab treatment resulted in increased collagen I and SPARC expression at the later stages of wound healing.

Conclusion: The optimal timing of administration is essential to ensure that the appropriate antifibrotic effect from bevacizumab use in glaucoma filtration surgery is achieved.

IOP Lowering Effects of Single Drop Application of Five Drugs Classes in Rats With Steroid-Induced Ocular Hypertension

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Purpose: For screening IOP lowering effects of new drugs several animal models are in use but most involve invasive techniques and are expensive. We evaluated the pharmacological utility of the rat model of steroid-induced ocular hypertension (SIOH) by studying the time course of IOP lowering by single drop application of 5 classes of antiglaucoma drugs.

Methods: SIOH model was developed by bilateral topical application of dexamethasone 0.1% twice daily for 40 days after baseline IOP estimation. A rise of 20% from baseline was considered significant and these animals were included in the study.

IOP lowering effect of single drop application of pilocarpine 2%, timolol 0.5%, dorzolamide 2%, brimonidine 0.2% and latanoprost 0.005% was evaluated in five groups of SIOH rats (n=8). In each group, 10µl of test drug was instilled in one eye and contralateral eye served as control. IOP was estimated at regular intervals over 24 hours post-instillation.

Results: Significant IOP elevation (p<0.001) was observed in 80% of the dexamethasone treated animals at day 40. Single drop application of pilocarpine caused mean peak IOP reduction of 16.25% at 1.5 hours post-instillation. Timolol, dorzolamide and brimonidine produced mean peak IOP reduction of 19.66, 19.20 and 17.30% respectively at 2 hours post-instillation. Peak effect of latanoprost was observed at 10 hours post-instillation and amounted to 26.91%.

Conclusions: The study demonstrated that the rat model of SIOH is susceptible to changes in aqueous humor dynamics involving several different mechanisms and, therefore, is of significant pharmacological utility in screening investigational antiglaucoma agents.

Prior Prostaglandin Agonist Exposure and Conjunctival Hyperemia With Bimatoprost 0.03% Preservative-free and Bimatoprost 0.03% Solutions in a Randomized, Multicenter Study

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Background: Preservative-free (PF) formulations of topical intraocular pressure (IOP)-lowering medications are being developed as alternatives for patients with sensitivity or allergies to preservatives. In a 12-week, double-masked, multicenter study, bimatoprost 0.03% PF showed equivalent IOP-lowering and similar safety to preserved bimatoprost 0.03% (Lumigan).

Methods: Patients with glaucoma or ocular hypertension were randomized to receive either bimatoprost 0.03% PF or bimatoprost 0.03% ophthalmic solutions once daily. Prior to the baseline visit, those treated with topical IOP-lowering medications underwent a 4-week to 4-day washout period. Safety assessments included reports of treatment-related adverse events (AEs). In a post hoc analysis, the rate of conjunctival hyperemia was compared between patients who had prior prostaglandin analog washout and those who had not.

Results: 596 patients were treated (301 bimatoprost PF, 295 preserved bimatoprost). Of the 363 patients who were washed out of prostaglandin agonists (PGA), over half being latanoprost, 18% were reported to have a hyperemia AE when receiving bimatoprost 0.03% preservative-free, while 21% reported the same for the preserved formulation. Hyperemia was significantly lower in this subgroup than in the group of 233 patients not on prior PGA; 34% in bimatoprost 0.03% PF (p=0.002) and 33% in preserved bimatoprost 0.03% (p=0.022).

Conclusions: Patients with prior PGA exposure reported less frequent hyperemia after treatment with bimatoprost. The cause for this difference is unknown; caution should be exercised when comparing hyperemia rates across studies that do not include similar enrollment criteria.

MRZ-99030, a β -Amyloid Aggregation Modulator, Protects Axons and RGCs in a Rodent Model of Glaucoma - PK/PD Relationship

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Background: MRZ-99030 is a small molecule with neuroprotective activity via modulation of β -amyloid (A β) aggregation and is currently under Phase I clinical development. The neurotoxic peptide A β has recently been implicated in retinal ganglion cell (RGC) apoptosis in glaucoma, with evidence abnormal amyloid precursor protein processing, increased expression of A β in RGCs and optic nerves in experimental glaucoma and also increased A β in the ganglion cell layer of glaucoma patients. It has been demonstrated that targeting different components of the A β formation and aggregation pathway can effectively reduce RGC apoptosis in vivo and therefore raises the possibility of neuroprotection in glaucoma. Based on these findings, we assessed the neuroprotective potential of MRZ-99030 in a commonly used rodent model of glaucoma.

Methods: Ocular hypertension was induced in rats by two injections of hypertonic saline into the episcleral veins, resulting in progressive loss of RGCs and axonal degeneration. Daily topical administration of MRZ-99030 for 6 weeks was followed by counting of previously retrograde-labelled RGCs in whole-mounts and assessment of optic nerve sections. For evaluation of PK/PD relationship, retina concentrations of MRZ-99030 were assessed in rats and monkeys.

Results: MRZ-99030 dose-dependently and significantly reduced loss of RGCs and axonal degeneration compared to vehicle control with a maximal effect size of 95%. Pharmacokinetic studies revealed sufficient retina concentrations of MRZ-99030 above in vitro affinity in both rats and monkeys.

Conclusions: Modulation of A β aggregation may be a promising avenue for neuroprotection and axoprotection in glaucoma.

Novel Strategies for Limiting Retinal Vascular Injury and Pathological Neovascularization

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Ischemic retinopathies, such as diabetic retinopathy, retinopathy of prematurity and branch vein occlusion, follow a similar pathological progression, beginning with oxidative stress, vascular inflammation, death of the vascular endothelial cells (EC) and ischemia which may progress to pathological angiogenesis, fibrosis and retinal detachment. Increased activity of the urea/ornithine pathway enzyme arginase has been linked to peripheral vascular disease and injury during diabetes, aging and hypertension. Excessive arginase activity reduces the supply of L-arginine needed for EC growth and repair. L-arginine depletion also alters activity of nitric oxide synthase (NOS), causing it to produce superoxide instead of NO which reduces blood flow and promotes vascular inflammation. Elevated arginase activity also can increase polyamine formation, leading to polyamine oxidation with generation of hydrogen peroxide and reactive aldehydes. To determine the involvement of the arginase pathway in retinal injury and dysregulated vascular growth and repair, we performed studies in ischemic retinopathy models using arginase inhibitors and arginase knockout mice. Our results show that oxidative stress, vascular inflammation, EC senescence and death, neuronal degeneration and pathological angiogenesis are correlated with activation of the arginase/polyamine pathway and that arginase blockade limits these effects. Furthermore, overexpression of arginase is prevented by blockade of NOX2 NADPH oxidase. These observations suggest that NADPH oxidase-induced activation of the arginase pathway has a key role in causing vascular inflammation and premature EC senescence, limiting vascular repair and promoting retinal neovascularization during ischemic retinopathy. Limiting the actions of arginase could provide a new strategy for treating this potentially blinding condition.

Therapeutic Role of AlphaB Crystallin in Retinal and Choroidal Angiogenesis

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Background: AlphaB crystallin (HSPB5) is a molecular chaperone for VEGF and member of the small heat shock family of proteins. We have shown that in HSPB5 knockout mice there is marked attenuation of laser induced choroidal neovascularization (CNV) and oxygen-induced retinopathy. In contrast, HSPB5 may function in the extracellular space to reduce inflammation by binding pro-inflammatory molecules. Therefore, we hypothesized that intraocular administration of recombinant HSPB5 might inhibit ocular angiogenesis. **Methods:** Laser-induced CNV was induced in C57BL/6 mice. Three photocoagulation lesions were delivered with a diode green laser in both eyes. 2 μ l (2 μ g) of recombinant HSPB5 or PBS was injected intra-vitreously at day 0 or d3 post-laser application. VEGF-164 antibody was included as a positive control. Fluorescein angiogram was recorded on a scale of 1-4 and CNV volume quantification were performed in the retinal flat mounts stained with isolectin B4 at day7.

Results: Intraocular injection of HSPB5 at d3 post-laser resulted in a statistically significant decrease in FA score and CNV volume (about 60% decrease; $p < 0.05$) that was similar to that found when animals were injected with anti-VEGF antibody. There was no inhibition of CNV when HSPB5 was injected on the same day as laser photocoagulation.

Conclusions: Intraocular injection of recombinant human HSPB5 inhibits laser induced CNV when given at d3 post laser – a time when inflammation is prominent. Despite its role as an intracellular chaperone for VEGF, HSPB5 should be considered for its therapeutic potential for inhibiting angiogenesis when delivered in the extracellular compartment.

Targeted Nanoparticle Therapy using Intraceptor Inhibition of Choroidal Neovascularization

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Age-related macular degeneration (AMD) and other retinal neovascular conditions are currently treated by monthly intraocular anti-VEGF injections are widely used to deliver protein-based drugs that cannot cross the blood-retina barrier. This invasive treatment carries significant risks, including bleeding, pain, infection, and retinal detachment; further, current treatments do not address subretinal fibrosis and scarring. A novel therapeutic strategy which improves outcomes in a less invasive manner, reducing risk, and providing long-term inhibition of angiogenesis is a felt medical need. Here we show that a single intravenous injection of targeted, biodegradable nanoparticles delivering a recombinant Flt23k intraceptor plasmid homed to neovascular lesions in the retina and regressed choroidal neovascularization (CNV) in primate and murine AMD models. Moreover, this treatment suppressed subretinal fibrosis, which is currently not addressed by clinical therapies. Most importantly, murine vision, as tested by OptoMotry®, significantly improved with nearly 40% restoration of visual loss induced by CNV. We found no evidence of ocular or systemic toxicity from nanoparticle treatment. These findings offer a nanoparticle-based platform for targeted, vitreous-sparing, extended-release, nonviral gene therapy which may suppress both CNV and fibrosis more effectively than intravitreal anti-VEGF therapy.

Notch and Jak/Stat Signaling Cascades in Astrocytes Regulate Remodeling of the Retinal Blood Vessels

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During development, the primary vascular layer in the retina is intimately associated with the underlying meshwork of astrocytes that emerge from the optic nerve. Although it has been suggested that the astrocyte template guides the endothelial cells to facilitate blood vessel growth, the molecular mechanisms underlying this process remain elusive. Our studies show that the loss of bA3/A1-crystallin in astrocytes affects the normal acidification of endolysosomal compartments, which is attributed to compromised activity of V-ATPase in these cells. Impaired endolysosomal pH in the endolysosomal compartments leads to reduced activity of g-secretase and consequently an inhibition of Notch signaling in the mutant cells. Overexpression of bA3/A1-crystallin in those same astrocytes restores normal activity of V-ATPase and endolysosomal acidification, thereby increasing the levels of g-secretase to facilitate optimal Notch signaling. Discrepancies in Notch signaling affects the astrocytes during development by downregulating the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and concomitantly inhibiting the transcription of glial fibrillary acidic protein (GFAP) and vascular endothelial growth factor (VEGF). We propose that bA3/A1-crystallin is a novel regulator of Notch/Jak/Stat signaling axis during astrocyte-mediated remodeling of retinal vasculature.

Potential Role of CLT-28643, a Selective $\alpha 5 \beta 1$ -Integrin Receptor Antagonist, in Neovascular Ophthalmic Diseases

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Background: Anti-VEGF therapy is mostly an anti-permeability therapy. Its anti-angiogenic and anti-inflammatory effect is limited and development of fibrosis is not inhibited directly by anti-VEGF drugs.

Methods: Experimental evaluation of the selective $\alpha 5 \beta 1$ -integrin receptor antagonist CLT-28643 (Clanotech) in different fibrosis indications, angiogenesis and inflammatory animal models.

Results: In the laser induced neovascularization mouse model CLT-28643 shows a CNV inhibition comparable to pan VEGF blockade s.c. administration. By oral administration of the compound, CNV inhibition increased up to 50%. A dose dependency and a stronger effect than pan-VEGF blockade are seen on neovascularisation in the ROP model. Physiologic vessel development does not appear to be affected by CLT-28643. In the bleomycin fibrotic lung model a significant reduction in the development of fibrosis is seen during treatment with CLT-28643. The same model indicates an effect on key inflammatory parameters (e.g. TNF- α , IL-1 β , COX-2, TGF- β).

Conclusions/Discussion: The experimental studies indicate a strong anti-angiogenic, anti-fibrotic and anti-inflammatory effect for CLT-28643 given topically or orally. $\alpha 5 \beta 1$ -integrin inhibition might therefore be a valuable approach as mono- or combination therapy for a range of ophthalmic diseases.

Involvement of Arginase in Diabetic Retinal Vascular Dysfunction

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Diabetes impairs retinal vascular endothelium-dependent relaxation, suggesting decreased availability of vasodilator nitric oxide (NO). However, studies have shown enhanced levels of NO products (nitrate/nitrite and ONOO) in diabetic retinopathy (DR). This study assessed retinal vascular function and bioavailable NO during DR and determined the role of arginase enzyme, which competes with NO synthase for L-arginine, in vascular dysfunction and reduced bioavailable NO. Studies were performed in STZ diabetic rats and mice and retinal vessels exposed to normal or high glucose (25 mM, HG) or transfected with adenoviral arginase 1 cDNA. In diabetic retinas, total NO products (NT and nitrate/nitrite) were increased, but a NO biomarker nitrite was reduced. Imaging using NO indicator DAF-2DA and superoxide (SO) detector DHE showed decreased NO in diabetic retinas, accompanied by increased SO. Diabetic retinas also showed elevation of arginase activity and expression (arginase1). Studies in knockout mice showed that deleting one copy of arginase 1 enhanced NO and reduced SO formation in diabetic retinas. EC-dependent relaxation of diabetic retinal arteries was impaired vs control. Exposure of arteries (24 hr) to either HG or adenoviral arginase cDNA increased arginase activity/expression, reduced NO release and impaired vascular endothelial relaxation. An arginase inhibitor prevented or reversed diabetes/HG effects in retinal vessels and EC. In conclusion, diabetes-induced oxidative stress is associated with increased arginase activity and expression (arginase1), decreased bioavailable NO, increased SO formation and retinal vascular dysfunction (decreased flow). Inhibition or arginase 1 deletion blocks these changes, suggesting a role for arginase in DR.

The Effect of Intravitreal Triamcinolone on Macular Edema in Eyes with Retinal Vascular Disease Unresponsive to Intravitreal Bevacizumab

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Background: Eyes with macular edema (ME) are treated with intravitreal injections of anti-vascular endothelial growth factor agents. In some eyes, ME fails to improve despite repeated injections of intravitreal bevacizumab (IVB). In this study the ME in those unresponsive eyes was monitored after treatment with intravitreal triamcinolone (IVT).

Methods: This retrospective study included eyes with ME secondary to diabetes (DM) or retinal vein occlusion (RVO) between January 2006 and June 2011. Data was collected before IVT, and one and four months following treatment and included visual acuity (VA), tonometry and optical coherence tomography (OCT).

Results: The study included 34 eyes from 33 patients with ME. Mean logMAR VA before IVT was 0.89 for DM and 0.79 for RVO. Four months following IVT, the mean change in VA was -0.13 logMAR for DM ($P < 0.002$) and -0.02 for RVO (NS) patients. OCT measured reduced central macular thickness (CMT) for both DM eyes (-146 μm , $P < 0.001$) and RVO eyes (-64 μm , $P = 0.20$). No correlation was found between the magnitude of the CMT reduction and VA improvement ($P = 0.01$). In 3/34 eyes (9%) increased intraocular pressure (IOP) necessitated topical treatment. One year after IVT, cataract progression requiring surgery occurred in 5/16 eyes (31%).

Conclusions: In our small limited cohort, ME secondary to DM showed a significant improvement both anatomically and functionally following treatment with IVT. In RVO eyes vision remained stable and a trend towards reduced CMT was found. The magnitude of anatomical improvement on OCT did not predict visual response in both groups.

Monosodium Urate Promotes Retinal Inflammation and Progression to Diabetic Retinopathy

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Background: Clinical studies have shown that hyperuricemia is associated with worsening progression to diabetic retinopathy (DR). Monosodium urate (MSU), the circulating form of uric acid (UA), is known to promote the activation of the macromolecular complex of the NLRP3-inflammasome. Here we investigated the effect of MSU in promoting retinal inflammation by activating the NLRP3-inflammasome on retinal cells in culture and evaluating the therapeutic effects of blocking UA formation and activity in the diabetic retina.

Methods: We determined the effects of MSU treatment (100-500mg/ml) in retinal endothelial, Muller and retinal pigmented epithelial cells (RPE) in culture. Western blotting and co-immunoprecipitation techniques were utilized to determine the expression levels of NLRP3 and its association with TXNIP and the ASC. ELISA assay was conducted to measure interleukin-1 β production. Streptozotocin-induced diabetic rats (STZ-rats) were treated with allopurinol, an inhibitor of UA synthesis, in the drinking water (daily, 50 mg/kg). Immunohistochemistry, Western blotting and ELISA analyses were conducted to measure inflammasome activation and tissue injury in the diabetic rat retinas.

Results: Treatments of retinal cells with MSU increased NLRP3 expression and interaction with ASC protein and TXNIP and promoted IL-1 β production. STZ-rats treated with allopurinol (4 weeks) decreased hyperglycemia-induced expression of ICAM-1, VEGF, NLRP3 and IL-1 β in comparison to untreated STZ-rats.

Conclusion: MSU is a critical mediator of inflammatory responses in the diabetic retina. Our results suggest that UA blockers are potential therapeutic strategies to prevent hyperglycemia-induced retinal inflammation and injury.

Intravitreal Autologous Plasmin in Proliferative Diabetic Retinopathy

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Background: The objective of this study is to establish the efficacy and safety of primary intravitreal injection of plasmin in the treatment of optic disk new vessels in proliferative diabetic retinopathy.

Methods: A comparative, prospective, interventional study in which ten diabetic patients with bilateral symmetric neovascularization of the optic disk secondary to proliferative diabetic retinopathy were submit to a intravitreal injection of 0.2 ml of autologous plasmin in the right eyes. The left eyes were used as controls. The primary measures were the changes in new vessel angiographic diffusion area (NADA).

Results: All patients completed the two-month follow-up. NADA decreased significantly after injection of $16.56 \pm 6.31 \text{ mm}^2$ to $7.16 \pm 4.98 \text{ mm}^2$ ($p < 0.001$). Ophthalmoscopically, regression was complete in five cases (50%), partial in two (20%), and there was no response in three (30%). No significant changes were seen in the new vessels of the control contralateral eye. No side effects or loss of visual acuity were seen in any case.

Conclusions: Intravitreal injection of autologous plasmin as primary treatment is safe and effective on the short term to obtain regression of most optic disk new vessels in proliferative diabetic retinopathy. Future studies are required to confirm its efficacy and relapses on the long term, it's possible role in initially resistant cases, and the need for adding pan-retinal photocoagulation to prevent potential relapses.

Lipoxygenase Pathway as a Therapeutic Target in Diabetic Retinopathy

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Background: Features of diabetic retinopathy (DR) include hyperpermeability and retinal neovascularization (RNV). Recently we demonstrated upregulation of 12/15 lipoxygenase (12/15-LOX) and its lipid metabolites, 12- and 15-HETEs in DR contributes to RNV via disrupting VEGF/PEDF balance. The goal of our study is to investigate whether 12/15-LOX contributes to retinal inflammation during DR via activation of NADPH oxidase, ER stress response, and VEGF-R2.

Methods: Effect of 12- and 15-HETE on retinal endothelial cell (REC) barrier was examined using FITC-dextran flux assay and electrical cell-substrate impedance sensing (ECIS). ROS production was measured by dihydroethidium (DHE) and dichlorofluorescein reactions. Western blotting (WB) was used to evaluate the expression NOX2, ER stress proteins, phospho-VEGF-R2 and phospho-SHP1. *In vivo* studies were performed using Ins2^{Akita} mice treated with or without the 12/15-LOX inhibitor baicalein (75 mg/kg in drinking water). LC/MS and Multiplex Immunoassay were used to measure HETE production and inflammatory mediators respectively.

Results: There was significant increase REC permeability and reduction in the transcellular electrical resistance (TER) by 12- and 15- HETEs compared to the control. This was associated with marked increases in ROS generation, NOX2 expression and levels of ER stress response proteins and p-VEGF-R2 expression. There was also a significant decrease in the levels of p-SHP1. *In vivo* studies demonstrated marked reduction in retinal HETEs, adhesion molecules (ICAM-1 and VCAM-1), IL6, ROS generation and NOX2 expression in diabetic mice treated with baicalein.

Conclusion: 12/15-LOX contributes to vascular hyperpermeability during DR via NADPH oxidase-dependent mechanism which involves activation of ER stress response and VEGF-R2.

Agreement on Heidelberg Retina Tomograph (HRT) Topographic Change Analysis (TCA) Glaucoma Progression Interpretations

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Purpose: HRT TCA reports the topographic change from baseline in the optic disc (ONH) and the peripapillary area. The purpose of this study was to evaluate agreement among 3 glaucoma experts of TCA printout interpretations of glaucoma progression and explore methods for improving agreement.

Methods: 100 eyes of glaucoma, glaucoma suspect, and healthy subjects with 8805;5 visits and 2 good quality HRT scans acquired at each visit were enrolled to this study. Three experts independently graded randomly ordered TCA's printouts as progressor or non-progressors. Each grader was presented with 2 sets of tests: a randomly selected single test from each visit and with both tests from each visit. Furthermore the TCA printouts were classified with and without using common criteria by each user. The criteria to assess a TCA print-out progression was to look for the red and green spots inside the ONH and for the consistency in the follow-up, not to consider the peripapillary red spots, to check the position of the vessels, the steepness of the rim, and to check for scan distortion.

The agreement was modeled using common factor error models for ordinal data and was described by assuming that there was a latent progression factor that was on a continuous scale.

Results: When 2 scans for session without criteria were used in the analysis, significant difference in slope (range: 1.35-1.59) and intercept (range: -0.38- -0.78) was found among the 3 experts. Slightly better agreement was found when only one scan without any criteria was used (slope (range: 0.81-1.12) and intercept (range: -0.40- -1.16)). However a good agreement was found when one scan with criteria was used, no significant difference in slope (range: 0.84-0.99) and intercept (range: -0.00- -0.04) was found among the 3 experts.

Conclusions: Among the TCA reports two scans for session do not improve the agreement among experts, but to have some progression TCA criteria improved the results.

Study on Possible Relationship between Serum Zinc Level, C-Peptide and Hyperglycemia in Type II Diabetics' Subjects from Bangladesh Population.

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Zinc plays a clear role in the synthesis, storage and secretion of insulin as well as conformational integrity of insulin in hexameric form, the decreased Zn, which affects the ability of the islet cell to produce and secrete insulin, might then compound the problem, particularly in Type II diabetes.

A total 60 consecutive type II diabetics' individuals and normal individuals were included in the study. There was no specific predilection for race, religion and socioeconomic status. Fasting blood glucose, two hours after breakfast glucose was measured by glucose Oxidase method and percentage of HbA1c was measured by Boronate affinity method. Zinc level is determined by using Semi Biochemistry Analyzer and C-peptide is measured by using the IMMULITE machine.

The levels of fasting plasma glucose (FPG) and two hours after breakfast (ABF) glucose were significantly ($p < 0.05$) higher in the hyperglycaemic group than those in the control subjects. The levels of HbA1c were also higher in the former group. The C-peptide levels in the control and hyperglycaemic groups were 3.58 ± 0.96 and 0.68 ± 0.13 (ng/l), respectively. The zinc level was 56% lower in the hyperglycaemic group than in the controls. Finally, the regression analyses revealed an inverse relation between zinc level and those of the FPG, ABF glucose, HbA1c and C-peptide.

Thus the results of the present study demonstrate that plasma zinc level could act as one of the predictors of type 2 diabetes complicated with hyperglycaemia.

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, 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 the possibility to convert different retinal cell types into "artificial photoreceptors" by targeting their genetically encoded light sensors. Artificially stimulated retinal activity enabled rd mice to perform visually guided behaviours 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.

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. In 90-95% of all cases, the disease is caused by mutations in the photoreceptor-specific ABCA4 gene. After subretinal administration of viral vectors containing the human ABCA4 gene, improved retinal morphology and function have been observed in animal models of Stargardt 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. Recently, a genetic approach for delivering cell type-specific optical control, known as optogenetics, has been shown to restore the visual function of the remaining defective or "dormant" cone photoreceptors in retinal degenerative disease. Having the distinct advantage of being independent of the underlying genetic defect, optogenetics opens new horizons for treatment of Stargardt disease and other currently untreatable blinding diseases.

PBN Inhibits RPE65 Activity and Protects the Retina from Stress-Induced Degeneration

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A2E and related toxic molecules are generated from all-*trans*-retinal and phosphatidylethanolamine, and are part of lipofuscin found in the RPE in AMD eyes. A novel therapeutic approach for AMD involves slowing down the visual cycle, which could reduce the amount of all-*trans*-retinal produced and thus the amount of A2E in the RPE. This can be accomplished by inhibiting RPE65, which produces 11-*cis*-retinol from all-*trans*-retinyl esters. Over ten years ago, we discovered that phenyl-N-*tert*-butylnitron (PBN), a spin trap agent, protects the retina from light-induced retinal degeneration. We recently showed that PBN and its derivatives (PBNDs) inhibit RPE65 in bovine RPE microsomes. PBN and PBNDs injected intraperitoneally into rats slowed the rate of rhodopsin regeneration and recovery of the a-wave response of the electroretinogram, consistent with a slowing of the visual cycle. Under these conditions, there was no effect on the photoresponse of cones. We propose that PBN and PBND are candidate drugs for the treatment of retinal degenerations in which accumulation of A2E and other toxic retinoid products may contribute to the pathophysiology of the disease.

Measuring the Intravitreal Mobility of Nanoparticles to Aid in the Rational Design of Gene Therapeutics for Retinal Disorders

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Background: Loss of vision can usually be attributed to genetic defects in the retina, and could in theory be cured with gene therapy. Delivery of nanotherapeutics to the posterior segment appears feasible via intravitreal injection, granted these nanoparticles remain mobile in the vitreous humour. To quantify and compare this intravitreal mobility, an *ex vivo* assay was optimized in this work.

Methods: Excised bovine eyes were used in combination with single particle tracking microscopy. In this model, the fragile vitreous structure was preserved, while it allowed for the determination of the intravitreal mobility of both model polystyrene beads with different sizes and surface groups, as well as gene nanomedicines composed of poly(amido amine)s and plasmid DNA.

Results: For both the model beads and the gene nanomedicines, we noticed that cationic charge drastically affected intravitreal mobility, while negatively charged particles remained mobile. This electrostatic effect was complemented by an increase in mobility after shielding of the particle surface with the hydrophilic polymer polyethylene glycol (PEG), suggesting hydrophobic interactions also influence the particle mobility.

Conclusions: Given the importance of intravitreal mobility of nanomedication for posterior segment diseases, we present an *ex vivo* assay to study nanoparticle mobility in intact vitreous humour by single particle tracking microscopy. This showed that cationic surface charge limits intravitreal diffusion of nanoparticles by binding to biopolymer structures, while anionic and PEGylated nanoparticles remain mobile. These results and the newly developed methodology should help in the rational design of nanomedicines used for intravitreal drug delivery.

Nanotechnology Guided Targeting and Triggered Release of siRNA within Ocular Neovascular Lesions

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Clinical translation of siRNA for management of retinal vascular diseases has been limited due to a lack of siRNA delivery strategies featuring high efficacy with limited off-target effects. We have developed a series of biocompatible nanocarriers targeted against endothelial cell surface biomarkers focally upregulated within ocular neovascular lesions. These nanocarriers can bear imaging or therapeutic payloads and deliver them to the cytoplasm of dysfunctional endothelial cells via recognition of disease-specific cell surface biomarkers. The goal of this study was to demonstrate the utility of targeted nanocarriers for site-specific delivery of antiangiogenic siRNAs in two animal models of retinal neovascularization. Targeted nanocarriers bearing VEGFR2 siRNAs were synthesized and characterized to determine optimal size, surface charge, and encapsulation efficiencies. Cytotoxicity, delivery efficiency, and functional knockdown of several molecular targets were determined in retinal microvascular endothelial cells. Biodistribution and efficacy of nanocarriers in animal models of laser-induced choroidal neovascularization and oxygen-induced retinopathy were analyzed. Antibody and/or peptide-targeted nanocarriers were capable of specific binding to cell surface molecules such as VCAM-1 on inflamed retinal endothelial cells *in vitro*, followed by triggered release of siRNA upon internalization. Specific targeting of neovascular endothelial cells was observed in both animal models of vascular disease. Knockdown of molecular targets via siRNAs was achieved *in vitro* and *in vivo* without adverse effects on cell and tissue function. Targeted nanocarriers are a promising framework for the delivery of diverse imaging and therapeutic payloads to diseased retinal endothelial cells *in vivo* for treatment of ocular neovascularization and similar pathologies.

Dynamic Observation of Total VEGF Level in Hyperglycemia Mouse Eyes after Intravitreal Injection of a Novel Anti-VEGF Drug KH902

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KH902, a novel VEGF inhibitor, is a recombinant, soluble, VEGF receptor protein. We observed the dynamic changes of VEGF in hyperglycemia mouse eyes after intravitreal injection of KH902.

112 five-week-old C57BL/6 mice were divided into two groups. After intraperitoneally injection of streptozocin (60mg/kg) for three consecutive days, mice were defined hyperglycemia once blood glucose exceeded 13.9mmol. The left eyes were injected with KH902 (20µg) or PBS and the right eyes were untreated. The total VEGF (free plus combined) and KH902 levels of the eyes were detected with ELISA. Data were analyzed with ANOVA with Bonferroni correction.

Ocular KH902 concentration changes were similar in the hyperglycemia and control groups. KH902 increased at 1 hour, reached their peaks at 24 hour. Afterwards they decreased and were not detectable starting from 192 hour. Interestingly, KH902 levels increased from 48 to 96 hour in the contralateral untreated eyes and were about 0.8~1.5% of the injected eyes. Total VEGF levels, including free VEGF and VEGF-KH902 complex, reached their peaks at 24 hour, decreased at 96 hour and returned to pre-injection levels from 192 hour. The VEGF levels were similar in the hyperglycemia and control groups. VEGF levels increased at 1 hour after KH902 injections, reached their peaks at 24 hours. The VEGF concentrations decreased gradually afterwards.

After intravitreal injection of KH902, the ocular KH902 and VEGF level changes were similar in hyperglycemia and normal mice. The VEGF levels transiently increased after KH902 administration, presumably because of an augment of a combined form of VEGF.

Improved Vitreous Stability and Retinal Delivery of Modified Cx43 Mimetic Peptides for the Treatment of Optic Neuropathies

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Background: Optic neuropathy is associated with retinal ganglion cell (RGC) loss leading to optic nerve damage and visual impairment. Recent research has shown that transient block of connexin43 (Cx43) hemichannels by mimetic peptides (MP) after retinal ischemia may inhibit uncontrolled hemichannel opening and may provide improved RGC survival. However, high hydrophilicity and poor peptide stability can limit efficient delivery in a clinical setting. The present study aimed to increase stability and thus efficacy of Cx43 MP by chemical conjugation to C₁₂ lipoamino acids or glucose.

Methods: Blockage of hemichannel opening was assessed by propidium iodide uptake into NT2 cells under low calcium conditions. Peptide stability in bovine vitreous was measured at 37°C for up to 4 hours by RP-HPLC and peptide half-life was determined.

Results: Propidium iodide uptake experiments revealed that inhibition of hemichannel opening by modified peptides was comparable to unmodified Cx43 MP and carbenoxolone, a known (but non-specific) hemichannel blocker, proving functionality of the molecules. Stability studies showed improved vitreous half-life for modified peptides (t_{1/2} between 299 to 359 min) compared to unmodified Cx43 MP (t_{1/2} = 122 min).

Conclusion: Peptide conjugation to C₁₂ lipoamino acids or glucose does not affect the functionality of Cx43 MP, but results in increased peptide stability and may therefore offer improved delivery of these molecules to the ocular tissues. We are now using a retinal ischemia-reperfusion rat model to determine the *in vivo* efficacy of unmodified and modified Cx43 MP, assessing RGC survival in retinal whole mounts.

Evaluation of Oculohypotensive Activity of Resveratrol in Rat Glaucoma Model

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Background: Elevated intraocular pressure (IOP) is one of the primary risk factor in the development of glaucoma. We evaluated the IOP lowering effects of resveratrol, a polyphenol, in normotensive and hypertensive rat eyes.

Method: Oculohypotensive effects of resveratrol in normotensive eye were evaluated using 8 groups of Sprague-Dawley rats (n=6). Highly aqueous insoluble resveratrol was solubilized in water with the aid of polyvinylpyrrolidone as carrier with mild sonication to produce a stable solution. Eight different concentrations ranging from 0.05-4% were prepared for topical application. Rats received 20µl of different concentrations of resveratrol in the test eye (TE) and vehicle in contralateral eye (CE). To evaluate effects in hypertensive eyes, rat model of steroid-induced ocular hypertension (SIOH) was used. The concentration producing maximum IOP reduction in normotensive eyes was evaluated. Three groups (n=8) of SIOH rats were used with TE receiving 20µl of vehicle, resveratrol or timolol, while CE received vehicle. IOP was estimated at baseline and at regular intervals post-instillation.

Result: All resveratrol concentrations produced significant oculohypotension peaking at 1.5 hour(H). Maximum mean IOP reduction of 15.1% was achieved with resveratrol 0.2% and was significantly higher than other concentrations (p<0.01). Oculohypotension was first observed at 0.5-1H and lasted for 4-5H. In SIOH rats, mean peak IOP reduction was achieved with resveratrol 0.2% at 1.5H amounting to 25.2% compared to peak reduction of 22.7% at 2H (p<0.05) with timolol.

Conclusions: Resveratrol lowers IOP in normotensive and oculohypertensive eyes. Further investigations are needed to evaluate possible mechanisms of its IOP lowering effects.

Transforming Growth Factor beta (TGF-β) Inhibitors as Anti-Ocular Fibrotic Agent, an *in vitro* Evaluation

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Background: Fibrotic processes have devastating effects on ocular integrity and function. The cytokine transforming growth factor-β (TGF-β) is a pivotal player in the process of fibrosis. Two TGF-β inhibitors; LY364947 (LY) and SB 202190 (SB) were evaluated for an antifibrotic effect on ocular cells involved in this process.

Methods: The drugs were evaluated in human Tenon's fibroblasts (HTFs) and retinal pigment epithelium (RPE) cell culture settings. MTT, BrdU test and wound scratch assay were used to assess cellular viability, proliferation and migration. RPE transdifferentiation was examined with alpha smooth muscle actin (α-SMA), β-catenin and F-actin antibodies.

Results: The inhibitory concentrations (IC 50) were 17µM for SB and 20µM for LY. Compared to control, BrdU staining revealed a reduction of cellular proliferation when cells were treated with LY at 100 µM and, SB at 50 and 100 µM concentrations, (t-test, p-value < 0.05). Both LY and SB had anti-migration effect. However, SB was associated with intracellular vacuoles formation. LY inhibited RPE transdifferentiation, partly suppressed α-SMA expression, and increased β-catenin expression at the cell-cell junctions. F-actin expression was not markedly affected since differentiation and cellular shape and polarity could be maintained.

Conclusion: This study shows that TGF-β inhibitors can play a promising role in modulation of fibrotic processes involving ocular cells. LY and SB may be considered against fibrotic processes such as proliferative vitreoretinopathy or after glaucoma filtering surgery.

The Experimental Study of Effects of Ginkgo Biloba Extract on L-Type Calcium Channel Currents in Rat Retinal Ganglion Cells

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Objects: To investigate the effect of GBE on L-type calcium channels in acutely dissociated rat RGCs by using whole-cell patch-clamp techniques so as to provide evidence in the cellular level for developing GBE in retinal protection. **Methods:** Individual RNC was dissociated by enzymatic and mechanical methods. Effects of GBE on L-type calcium channels were studied by using whole-cell patch-clamp techniques. **Results:** GBE at concentrations of 0.1µg/ml, 1µg/ml, 10µg/ml, 100µg/ml, and 500µg/ml decreased the current amplitudes L-type calcium channels to 101.22±18.74%, 91.13 ±5.03% (p<0.01), 7.53 ±30.53% (p<0.01), 32.26 ±15.13% (p<0.01), and 6.13 ±6.77% (p<0.01) of control respectively. The difference in calcium channel currents from the difference of GBE is statistically significant (p<0.01). **Conclusion:** 1. GBE whose concentration are 0.1µg/ml, 1µg/ml, 10µg/ml, 100µg/ml and 500µg/ml exhibits inhibitory effect on calcium channel currents in a concentration dependent manner. 2. GBE exhibits protective effect on RGCs from rats. The mechanisms may be related to inhibit calcium influx so as to inhibit apoptosis of cells.

Quantitative and Qualitative Label Free Imaging using Mass Spectrometry in the Context of an Ophthalmic Application

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Mass spectrometry imaging (MSI) permits the label-free study of several compounds of interest simultaneously on the surface of biological tissues at 20µm of resolution. Recently, numerous studies have dealt with the growing interest in combining quantitative and distribution analyses using MSI. This application may play a significant role in early phases of pharmaceutical discovery to evaluate small molecule concentration, notably drugs. Moreover, unlike classical imaging and quantification techniques, MSI can provide precise and selective quantitative information at micrometer level to differentiate fine histological structures. Our approach will be applied in an ophthalmic study to assess the distribution and quantification of Benzalkonium chloride (BAK) compound in specific areas of the eye after instillation. The distribution of two BAK compounds (BAK C12 and BAK C14) were investigated in small specific histological regions of the eye (such as iridocorneal angle or sclera, choroid, retina regions) in order to estimate efficiency of action or adverse effects of the treatment. High spatial resolution images were performed at cells level (30 µm). Molecular distribution was also correlated to tissue histology using H&E staining. Then, our methodology of quantification by MSI was applied. Local Drug concentration differences were observed according to histological area and position on the eye section (anterior, posterior, temporal or nasal side). In conclusion, MSI offers new insight in ocular therapeutic/pharmaceutical research, especially for high-precision distribution and quantification studies.

Adenosine A3 Receptor Agonist Prevents Retinal Ganglion Cell Degeneration

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Background: A significant number of glaucoma patients continue to lose vision despite successful intraocular pressure control. Therefore, novel strategies to save retinal ganglion cells (RGCs) are needed.

The modulation of adenosine receptors (ARs) can be neuroprotective against brain insults. We investigated the potential neuroprotective role of adenosine A3 receptor (A3R) activation against RGC degeneration.

Methods: Propidium iodide (PI) and TUNEL assays were performed in cultured retinal explants. PI-positive cells were counted at DIV2 (before NMDA incubation) and DIV4. We also used a partial optic nerve transection (pONT) model. Eyes were injected with 2-Cl-IB-MECA or PBS before transection and imaged using DARC (Detection of Apoptosis in Retinal Cells) after 7 days.

Results: RGCs express A3R as detected by immunohistochemistry. NMDA (300µM; for 48h) significantly increased PI-positive cells ratio (DIV4/DIV2) in retinal explants. Pre-treatment with the A3R agonist Cl-IB-MECA (1µM) prevented the increase in PI-positive cells ratio. The A3R antagonist (MRS1191; 1µM) prevented this protective effect. Similarly, NMDA increased the number of TUNEL-positive cells in RGC layer and Cl-IB-MECA (1µM) exerted a significant neuroprotection. Pre-incubation with MRS1191 also prevented this protective effect.

In retinal slices from pONT eyes the immunoreactivity of A3R was downregulated. DARC imaging showed that Cl-IB-MECA (1.2µM) significantly reduced RGC apoptosis by 50% compared to untreated pONT eyes.

Conclusions: A3R activation is neuroprotective against RGC death. Thus, targeting A3R in RGCs may have potential in the management of glaucoma. **Support:** FCT (PEst-C/SAU/UI3282/2011 and SFRH/BD/47947/2008), Portugal, and COMPETE.

A Comparison of On-Demand and Continuous Treatment with Bevacizumab Every Four or Eight Weeks in Age-Related Macular Degeneration

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Background: Age-Related Macular Degeneration (ARMD) is treated in myriad of treatment schedules. In this study we set out to compare if an on-demand treatment of Bevacizumab every four weeks or eight weeks is non-inferior to a continuous treatment of Bevacizumab every four or eight weeks.

Methods: In the Rotterdam Eye Hospital a non-inferiority, randomized controlled trial was conducted with 248 ARMD patients that were treated with Bevacizumab for One year. At inclusion all patient were randomized into four treatment groups. Group 1 (n=64) and group 2 (n=64) were treated every four (group 1) or eight weeks (group 2) in a continuous treatment schedule. Group 3 (n=60) and 4 (n=60) were treated with Bevacizumab on an on-demand basis every four (group 3) or eight weeks (Group 4). Main end points were best corrected visual acuity gain measured in Visual Acuity Score (VAS) and change in Central Foveal Thickness (CFT) on OCT.

Results: VAS increased in all treatment groups with respectively 1.9±13.8 (Group 1), 6.0±8.9 (Group 2), 5.6±10.4 (Group 3) and 4.5±11.8 (Group 4). There was a reduction in CFT for all treatment groups ranging from -61±93 (Group 3) to -109±90 (group 1). There were no significant differences between the treatment groups for VAS change and CFT change. Mean number of injections in group 3 were 8.5±2.3 and in group 4 were 5.8±1.0.

Conclusions: On-demand treatment of ARMD with bevacizumab is non-inferior to continuous treatment in either an every four or eight week treatment schedule.

Comparison of Very Low Fluence and Low Fluence Photodynamic Therapy in Chronic Central Serous Chorioretinopathy

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Purpose: To investigate the safe effective light dose for photodynamic therapy (PDT) in the treatment of chronic central serous chorioretinopathy (CSC).

Methods: Thirty-five eyes of 34 patients with chronic CSC were recruited for this study. From November 2009 to July 2010 and from April 2011 to August 2011, PDT was performed using 50% and 25% of the full light dose in 27 eyes of 27 patients (group I) and 8 eyes of 7 patients (group II), respectively. The minimum follow-up period was six months. Mean change of best corrected visual acuity (BCVA) and central retinal thickness, hyperpermeability change from abnormal choriocapillaris, success rate, recurrence rate, and complications were analyzed.

Results: Group I showed that BCVA (logMAR) improved significantly from 0.33 ± 0.17 to 0.14 ± 0.15 at 6 months ($p < 0.001$). However, there was no significant improvement of BCVA ($p = 0.176$) in group II. The one eye of 27 eyes (3.7%) in group I and the 4 eyes of 8 eyes (50.0%) in group II showed recurrence until 6 month follow-up ($p = 0.010$). After initial PDT, hyperpermeability from abnormal choriocapillaris was decreased or disappeared at 95.5% in group I, 62.5% in group II at month 3 ($p = 0.048$). None showed severe adverse events in both groups.

Conclusions: 50% energy of PDT seems to be less recurrent, safer and more effective method compared with 25% energy of PDT in the treatment of chronic CSC.

Visual Acuity (VA) Outcomes with Pharmacologic Resolution of Vitreomacular Traction (VMT) or Full-Thickness Macular Hole (FTMH) Closure

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The ocriplasmin MIVI-TRUST program included two phase 3, multicenter, randomized, double-masked, placebo-controlled trials to determine efficacy and safety for treatment of VMT. An analysis was performed to determine the effect of pharmacologic VMA resolution or FTMH (equivalent to stage II) closure on VA outcomes in the MIVI-TRUST program.

Patients with VMT were randomized to receive a single intravitreal injection of 125 µg ocriplasmin ($n = 464$) or placebo ($n = 188$). The primary end point was anatomic VMA resolution at 28 days post-injection. Selected secondary end points included pharmacologic FTMH closure and best-corrected VA (BCVA) improvement of ≥ 2 or ≥ 3 lines.

Pharmacologic VMA resolution at day 28 was observed in a significantly larger proportion of the ocriplasmin group (26.5%) compared to placebo (10.1%; $P < 0.001$). Pharmacologic FTMH closure at day 28 was observed in a greater proportion of patients in the ocriplasmin group (40.6%) compared to placebo (10.6%). BCVA improvement of ≥ 2 lines at 6 months occurred in 41.5% of responders (ie pharmacologic VMA resolution at 28 days) compared to 20.2% of nonresponders. Respective ≥ 3 -line gain rates were 19.7% and 8.1%. BCVA improvement of ≥ 2 lines at 6 months was observed in 68.8% of patients with FTMH closure compared to 26.9% of patients who did not achieve this outcome. Respective ≥ 3 -line gain rates were 47.9% and 11.5%.

A single injection of ocriplasmin achieves higher rates of VMA resolution and FTMH closure compared to placebo. BCVA gains at 6 months were greater in patients with who achieved these outcomes compared to those who did not.

Intravitreal Bevacizumab for Retinopathy of Prematurity: Refractive Error Results

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Purpose: To evaluate refractive error in infants who underwent intravitreal bevacizumab injection for treatment of threshold retinopathy of prematurity (ROP).

Design: Non-randomized interventional comparative study.

Methods: The study group included all infants who consecutively received a single intravitreal (0.375 mg or 0.625 mg) bevacizumab injection for therapy of threshold ROP in fundus zone I or zone II. The control group included infants who had previously undergone retinal argon laser therapy of ROP. The follow-up examination included refractometry under cycloplegic conditions.

Results: The study group included 12 children (23 eyes; mean birth weight: 622 ± 153 g; gestational age: 25.2 ± 1.6 weeks) and the control group included 13 children (26 eyes; birth weight: 717 ± 197 g; gestational age: 25.3 ± 1.8 weeks). Both groups did not differ significantly in birth age and weight and follow-up. At the end of follow-up at 11.4 ± 2.3 months after birth, refractive error was less myopic in the study group than in the control group (-1.04 ± 4.24 diopters (median: 0 diopters) versus -4.41 ± 5.50 diopters (median: -5.50 diopters); $P = 0.02$). Prevalence of moderate myopia ($17 \pm 8\%$ versus $54 \pm 10\%$; $P = 0.02$; OR: 0.18 (95% CI: 0.05, 0.68) and high myopia ($9 \pm 6\%$ versus $42 \pm 10\%$; $P = 0.01$; OR: 0.13 (95% CI: 0.03, 0.67) was significantly lower in the bevacizumab group. Refractive astigmatism was significantly lower in the study group (-1.0 ± 1.04 diopters versus 1.82 ± 1.41 diopters; $P = 0.03$). In multivariate analysis, myopic refractive error and astigmatism were significantly associated with laser therapy versus bevacizumab therapy ($P = 0.04$ and $P = 0.02$, respectively).

Conclusions: In a one-year follow-up, a single intravitreal bevacizumab injection as compared to conventional retinal laser coagulation was helpful for therapy of ROP and led to less myopization and less astigmatism.

Anti-Inflammatory and Anti-Angiogenic Effects of NOV C-ter in Experimental Models

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Purpose: to study the possible mechanisms of action involved in the anti-inflammatory and anti-angiogenic effects of NOV C-ter (Sisene, France).

Methods: Models were performed on Lewis male rats (6-8 weeks old). Intravitreal injections (5 µl) were performed at the same time as uveitis induction, inflammation was assessed at 16h, and irises and ciliary bodies were extracted. The groups included: LPS, NOV C-ter 1.25 µg, NOV C-ter 2.5 µg and NOV C-ter 5 µg. In the corneal micropocket assay, LPS pellets (Sigma-Aldrich, France) were implanted into the corneal stroma followed by sub-conjunctival injections every other day for 8 days. Angiogenesis was assessed clinically, and corneas and conjunctivas were extracted. The groups were: no treatment, PBS, bevacizumab 250 µg, NOV C-ter 5 µg, NOV C-ter 10 µg and NOV 2 µg. Real-time PCR analysis was performed for all.

Results: Compared to PBS, NOV C-ter exerted a significant anti-inflammatory effect for the doses 1.25 µg ($P < 0.01$) and 2.5 µg ($P < 0.05$). PCR analysis showed no significant effects on the expression of VEGF, VEGF-R1, VEGF-R2, COX-2, Hey-1, Notch-1 and Jagged-1. IL-6 ($P = 0.009$), IL-1β, TNF-α, and MCP-1 were significantly downregulated. NOV C-ter 10 µg and NOV 2 µg significantly reduced LPS induced angiogenesis ($P < 0.05$). IL-6 was downregulated by NOV 2 µg and NOV C-ter 10 µg ($P < 0.0001$), CD31, TNF-α, and connexin-43 were down-regulated by NOV 2 µg ($P < 0.05$).

Conclusion: Anti-inflammatory and anti-angiogenic effects observed for NOV C-ter seem to be mediated by a downregulation of pro-inflammatory cytokines, mainly IL-6.

Intravitreal Bevacizumab for Choroidal Neovascularisation in Degenerative Myopia: a Retrospective Study in Real Life

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Photodynamic therapy (PDT) has been the mainstay of therapy for choroidal neovascularization (CNV) secondary to degenerative myopia. The surge of anti-VEGF has improved the clinical outcome of CNV in AMD. Intravitreal injections of anti-VEGF are considered now a potential alternative treatment for myopic lesions.

36 patients treated with IV injections of bevacizumab (Avastin®) 1,25 mg (0,05 cc) were included in this retrospective study. The results were collected from charts with a complete ophthalmological examination.

The results were recorded before and 12 months after treatment. The sample includes 14 men and 22 women (median age 59.6 years). The delay between the first symptoms and the treatment was on average 36 days. The average distance BCVA was initially 1.00 ± 0.69 logMAR and finally 0.75 ± 0.68 logMAR ($p=0.001$) with 2.3 ± 1.2 injection. At 12 months, 94% ($n=34$) of the patients presented with a stabilization or improvement of distance BCVA. The central macular thickness on OCT was reduced but without statistical significance.

This study shows a satisfying efficacy of IV injections of bevacizumab in the treatment of myopic CNV at the anatomical and functional level. The treatment with PDT resulted in a statistically significant stabilization of the BCVA in 72% of the treated eyes at 24 months. The treatment with anti-VEGF seems to be an interesting alternative in the treatment of CNV secondary to pathological myopia, based on recent publications as in the present study. Prospective and randomised trials should be however realised between the anti-VEGF injection and PDT.

In Vivo Molecular Imaging of Retinal Vascular Diseases

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Molecular imaging strategies for characterization of retinal vascular diseases are needed for early detection, improved timeliness of therapeutic interventions, and assessment of therapeutic response. Approaches for molecular imaging of the retina have been limited by a lack of molecularly-targeted imaging agents capable of targeting disease biomarkers in vivo with sufficient sensitivity and safety. To address this need, hairpin nucleic acid functionalized gold nanoparticles (hAuNP) featuring optical contrast agents and RNA-specific nucleic acid targeting sequences were developed for noninvasive imaging of any messenger RNA or microRNA biomarker in the retina. The goal of this study was to evaluate the utility of hAuNP for longitudinal imaging of mRNA and microRNA biomarkers in an animal model of laser-induced choroidal neovascularization (LCNV), to evaluate hAuNP as clinically-relevant retinal molecular imaging agents. hAuNP were demonstrated to be effective contrast agents for in vivo optical imaging of multiple hypoxia and inflammation-associated mRNA and miRNA biomarkers in mouse models of CNV, and were not associated with adverse effects on cell viability and function in animal models. hAuNP are promising nanoscale imaging agents which can be utilized in conjunction with clinically-available ophthalmic imaging instrumentation for noninvasive, high sensitivity, and high specificity imaging of RNA disease biomarkers in retinal vascular disease. These nanoparticles are amenable for imaging virtually any RNA target in the retina, are candidates for clinical translation, and may also be valuable for elucidating molecular mediators of retinal disease in preclinical studies.

Longterm Efficacy of Ciliary Muscle Gene Transfer of Three sFlt1 Variants in a Rat Model of Laser-Induced Choroidal Neovascularization

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Background: Inhibition of vascular endothelial growth factor (VEGF) has become the standard of care for patients presenting wet age-related macular degeneration. However, monthly intravitreal injections are required for optimal efficacy. We have previously shown that electroporation enabled ciliary muscle gene transfer results in sustained protein secretion into the vitreous for up to 9 months.

Methods: Here we evaluated the long-term efficacy of ciliary muscle gene transfer of three soluble VEGF receptor-1 (sFlt-1) variants in a rat model of laser-induced choroidal neovascularization (CNV). Fluorescein angiography (FA) were performed to evaluate vascular leakage. CNV growth was evaluated using retinal pigment epithelium (RPE)/Choroid flatmount and intracranial angiography. Intra-ocular VEGF levels were measured using ELISA. The mRNA expression of VEGF was quantified in the RPE/Choroid complexes.

Results: All three sFlt-1 variants significantly diminished vascular leakage and neovascularization as measured by FA and flatmount choroid at 3 weeks. FA and intracranial angiography demonstrated that inhibition of CNV was maintained for up to 6 months after gene transfer of the two shortest sFlt-1 variants. Throughout, clinical efficacy was correlated with sustained VEGF neutralization in the ocular media. Interestingly, treatment with sFlt-1 induced a 50% down-regulation of VEGF mRNA levels in the RPE and the choroid.

Conclusion: We demonstrate for the first time that non-viral gene transfer can achieve a long-term reduction of VEGF levels and efficacy in the treatment of choroidal neovascularization.

Monitoring Pathological Changes in Cone Outer Segment Structure Using Adaptive Optics Retinal Imaging

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Background: The purpose of this study was to characterize pathological changes in outer segment (OS) structure using adaptive optics (AO) imaging.

Methods: Four patients with multiple evanescent white dot syndrome (MEWDS) and two suffering from acute macular neuro-retinopathy (AMNR) were examined using OCT (Spectralis, Heidelberg Engineering, Germany) and AO imaging (rtx1, Imagine Eyes, France). Cone photoreceptor density was measured using automated software and analyzed in comparison with OCT findings. The procedure was repeated after one month. One MEWDS and one AMNR patients were re-examined after 10 months.

Results: At the first visit, OCT images showed irregularities in the OS tip line in all cases and in the IS/OS line in several cases. In the same regions where OS was shortened, AO revealed marked decreases in cone density, which dropped from over 30000 cells/mm² to less than 10000 cells/mm². In the MEWDS cases, the locations of cone defects in AO images also corresponded with hypo-fluorescent areas observed in the late phase of ICG angiography. At follow-up visits, the return of the IS/OS and OS tip lines back to normal in OCT images was correlated to an increase in cone density in all cases. However, in MEWDS cases, cone mosaic abnormalities were still visible after the OCT lines were restored.

Conclusion: AO allowed analyzing damage and recovery of cone OS structure in MEWDS and AMNR. In these diseases, AO appeared to be more sensitive than SD-OCT for monitoring changes in the cone mosaic.

Cataract and Diabetic Macular Edema: a Prospective Comparative Trial Investigating Phacoemulsification Associated with Intravitreal Micronized Triamcinolone Acetonide or Bevacizumab

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Purpose: To investigate macular thickness and visual acuity changes after 1 intravitreal injection of micronized triamcinolone acetonide (mTA) or bevacizumab (B) at the end of phacoemulsification in naïve eyes with cataract and diabetic macular edema (DME).

Methods: One hundred naïve eyes with cataract and diabetic macular edema were randomly assigned to receive at the end of phacoemulsification 4mg of mTA (Vitreal S, Sooft Italia) or 0.5 mg of B (Avastin, Roche). Comprehensive ophthalmic evaluation was performed preoperatively and at 1, 4, 12 and 24 weeks postoperatively. Main outcome measures included central macular thickness (CMT) and best-corrected ETDRS visual acuity (BCVA). Complications were recorded.

Results: All the patients completed the 24-week study visit. The 2 group did not show significant preoperative differences in CMT ($p>0.05$) and BCVA ($p>0.05$). Mean CMT decreased significantly at the end of follow-up in mTA group ($p<0.05$), but not in B group ($p>0.05$). Mean BCVA increased significantly in both groups versus baseline ($p<0.05$). The BCVA gain was greater in mTA group than B group. Intraocular pressure increased only in 4% patients in mTA group. No other complications were recorded.

Conclusion: There preliminary data showed that intravitreal mTA is more effective than intravitreal B in management of DME in eyes undergoing cataract phacoemulsification. Further studies with longer follow up are required.

Autologous Serum Treatment for Ocular Surface Disease in Allergic Conjunctivitis

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Introduction: Allergic conjunctivitis is expressions of ocular immune hypersensitivity against allergens characterized by ocular surface inflammation responsible for the changes as Papillae, Trantas Horner Dots and Hyperemia, we propose the use of autologous serum eye drops to achieve this end.

Objectives: To demonstrate the effect of autologous serum eyedrops in resolution of signs associated with two types of allergies: Perennial allergic conjunctivitis (PAC) and vernal keratoconjunctivitis (VKC).

Methods: We performed a prospective series of 20 cases, Preparation was performed with a concentration of 100% autologous serum. Quantification of the signs of bulbar conjunctival hyperemia, papillae and Trantas Dots was performed using the standard grading scales of CCLRU (30 and 60 days).

Results: Bulbar hyperemia was present in 85% of cases and after 30 and 60 days decreased to very mild hyperemia (mean scale: 1.3 to 1.1, with clinically and statistically significant difference ($T\leq t$; $P = 0, 00126$). The baseline presentation on Papillae were mild (half scale 1.12) (SD 0.71, 0-2) and had no clinically significant changes after eyedrop administration. The effect on limbal nodule presentation Trantas Dots obtained a significative decrease in scale: From moderate to nearly absent ($T\leq t$; $P = 0.199$). **Discussion:** The effect restorative and anti-inflammatory of autologous serum on allergic conjunctivitis, according to studies by Fox et al, is due to its ability antiapoptotic able to repair persistent epithelial defects, corneal ulceration associated disorders neurotrophic and corneal burns. The use of autologous serum eyedrops 100% presents a dramatical reduction of signs.

A Phase 3 Study (OPUS-1) Evaluating Lifitegrast Ophthalmic Solution, 5.0% versus Placebo for the Treatment of Dry Eye Disease

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Background: Dry eye disease (DED) is a condition of ocular surface inflammation leading to symptoms of discomfort. Lifitegrast is an investigational drug targeting LFA-1 (CD11a/CD18; $\alpha L\beta 2$) to inhibit binding to ICAM-1 (CD54) - a key step in chronic T-cell mediated inflammation observed with DED.

Methods: A randomized, double-masked, placebo-controlled study enrolled 588 dry eye subjects randomized 1:1 to lifitegrast or placebo (vehicle) applied BID for 84 days. Eligibility included no active lid margin disease, STT ≥ 1 and ≤ 10 mm, and worsening of fluorescein staining and symptoms upon exposure to a controlled adverse environment. Co-primary endpoints were inferior corneal staining score (ICSS, sign) and visual-related function subscale of the Ocular Surface Disease Index (VR-OSDI, symptom) at Day 84. Supportive endpoints included fluorescein/lissamine staining and patient-reported symptoms (7-item visual analog scale and discomfort).

Results: Lifitegrast demonstrated superiority to placebo ($P=0.0007$) in improvement in ICSS at Day 84; this was supported by reductions in total corneal staining ($P=0.0184$) and improvements in nasal lissamine staining at Day 14 ($P=0.0018$) with maintenance through Day 84 ($P=0.0039$). The VR-OSDI score did not achieve significance ($P=0.7894$); however, significant improvements were observed for discomfort ($P=0.0273$) and dryness ($P=0.0291$) - the most severe symptoms at baseline. There were no serious ocular adverse events (AE); the most common AE was transient irritation upon the initial dose (Day 0) of lifitegrast.

Conclusion: Lifitegrast demonstrated significant improvements in signs/symptoms of DED versus placebo and appears safe when administered over 84 days.

Comparative Investigation of Chronic Blepharitis Combined Treatment Regimen Effectiveness

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Background: Meibomian gland obstruction in patients with blepharitis and dry eye contributes to poor results of antiinflammatory therapy.

Purpose: To evaluate influence of different components of combined treatment regimen in management of chronic blepharitis.

Methods: 6 months study involved 90 patients (180 eyes) with chronic blepharitis. The 1st group was treated by dexamethasone ointment and artificial tears. Patients in the 2nd group received artificial tears and a course of hot compresses with lid massage, accompanied by every day lid hygiene with blephagel. The 3rd group received the same course of lid massage and hygiene and dexamethasone ointment, but without artificial tears. Among investigative methods were: patients' questionnaire, biomicroscopy, TBUT test, Shimer test.

Results: patients in the 1st group mentioned improvement already during the first week, but the persistence of the effect stayed only for 2.5 months. In the 2nd group the effect was slower, but lasted for longer period (up to 6 months). Patients in the 3rd group gained very fast result already on the first week, but it was also short lasting. Shimer test results changed chaotically. TBUT test showed more stable tear film in all groups.

Conclusions:

1. On terms of combined treatment regimen, the use of dexamethasone ointment to a greater extent promotes faster improvement. Blephagel causes longer persistence of the positive effect. Artificial tears contribute to a longer remission period.
2. Shimer test is not of great value in treatment effectiveness evaluation.
3. Hot compresses and lid massage dramatically improves persistent remission.

Anti-Inflammatory Effect of Eyelid Cleanser Based on *Melaleuca Alternifolia* in Non-Infectious Blepharitis

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Introduction: Blepharitis is a chronic disorder producing inflammation of the anterior and posterior lid margin, with involvement of skin and others structures: eyelash and meibomian glands. The inflammatory etiology in non-infectious blepharitis, refers absence to current infection associated with altered meibum lipid composition. Eyelid hygiene keep lid margins clean and free from debris.

Objectives: To demonstrate the effect of eyelid cleanser based on *Melaleuca Alternifolia* in resolution of signs associated with noninfectious blepharitis as erythema, debris and edema and symptoms as itching.

Methods: We performed a prospective series of 30 cases. Quantification of the blepharitis signs as lid hyperemia, edema, crusting was performed using the standard grading scales of CCLRU and Marx's line. Observations were made before beginning treatment with eyelid cleaner based on *Melaleuca Alternifolia* or Tea Tree Oil after 30 days.

Results: The average age of patients was 55 years old. Basal erythema, crusting, edema and itching decreased significantly from mild to absent (CCLRU 2,6 to 0,7) clinically and statistically significant results: Pearson 0,62; $p < 0,080$; Crusting and itching were the most noted finding in 68,9%, and had been reduced from absent or very slight (CCLRU 2,6 -1,2; 1,96-0,3; SD 0,17). The reduction in the symptoms and crusting were dramatic, showing the grade of improved.

Discussion: Anti-inflammatory effect of eyelid cleanser based on *Melaleuca Alternifolia* was successful treatment to blepharitis non-infectious. This study supports the eyelid margin cleansing is useful in controlling the symptoms and inflammatory signs of cronic blepharitis.

Matrix Therapy in Regenerative Medicine: from Basic Science to Cornea therapy

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Tissue homeostasis, our ability to replace identically a dead cell by a new cell, is regulated by the local cellular microenvironment. Proper signals stored in the extracellular matrix will trigger cell migration and multiplication to achieve a perfect replacement or regeneration. Heparan sulfates (HS) play a pivotal role in the regulation of tissue homeostasis by binding, bridging and protecting the matrix proteins as well as by storing and protecting most communication peptides such as growth factors, cytokines, chemokines... Hence this glycosaminoglycan is the keystone of extracellular matrix architecture.

However this order is challenged when many cells die after tissue aggression as response leave traces called scar or fibrosis. Destruction of HS leads loss of quality as the original communication peptides are no more protected, are destroyed and replaced by the emergency signals brought by inflammatory/circulatory cells. We engineered large biodegradable nanobiopolymers to mimic HS named RGTA (for ReGeneraTing Agent). When introduced after tissue injury RGTA would restore the matrix scaffold and proper initial microenvironment leading in some cases to a real regeneration process.

Recently CE marketed eye drop (CACICOL20®), this biopolymer showed excellent tolerance, rapid pain reduction and corneal healing in a pilot clinical trial with persistent epithelial defects resistant to standard therapies. Cohort studies on patients with neurotrophic ulcers have indicated that this eye drop could be an alternative to amniotic grafting. Case reports showed strong benefits in healing corneal alteration from wide etiological diversities as predicted from the scientific rational. On going RCT should evidence these observations.

Topical Azythromycin Promotes Corneal Allograft Survival

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Purpose: The antibiotic azythromycin (AZM) is known to have anti-inflammatory capacity during inflammation of the eyelid margins and in experimental dry eye disease. The anti-inflammatory efficacy of topical AZM was analyzed following keratoplasty in the rat model.

Methods: Corneal transplants were performed between Lewis recipient and Fisher donor rats. Recipients were treated topically for two weeks with AZM. Control animals received topical myglol or dexamethasone in an allogeneic or AZM in the syngeneic setting. All transplants were monitored clinically. Infiltration of CD45, CD4, CD8, CD25, CD161 and CD163 was stained histologically. Cytokine profiles were analyzed in lymphatic organs by qPCR.

Results: AZM significantly promoted corneal graft survival ($p < 0.01$) with an equivalent capacity of dexamethasone. However, some AZM-treated recipients rejected whereas all dexamethasone-treated rats survived throughout the experiment. No negative side effect was observed in AZM-treated syngeneic rats. Histology confirmed the clinical finding with massively reduced numbers of all infiltrating leukocyte populations that were analyzed ($p < 0.01$). Systemically, no differences of cytokine profiles in lymphoid organs of AZM- compared to control recipients were observed.

Conclusions: Topical azythromycin has a strong anti-inflammatory effect following keratoplasty that can be compared to topical dexamethasone. This effect occurs locally and is sufficient to promote allograft survival in rat keratoplasty. Therefore, we suggest the additive use of topical AZM following keratoplasty.

Evidence of Epithelial Remodelling in Chronic Ocular allergy by Means of Immunohistochemistry and *In Vitro* Studies may Suggest New Treatment Strategies.

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Background: The spectrum of ocular allergy includes reversible conditions and irreversible chronic severe forms of disease involving the cornea (vernal and atopic keratoconjunctivitis). It is suggested that remodelling may play a role in the pathogenesis of chronic ocular allergic disease. In Chronic asthma it is suggested that EGFR overexpression and increased activation of the epithelial-mesenchymal trophic unit (EMTU hypothesis) may participate in disease development accounting for chronicity, severity and poor response to steroid treatment.

Methods: Conjunctival biopsies of healthy subjects, seasonal allergic conjunctivitis, giant papillary conjunctivitis (group A) were compared to atopic and vernal keratoconjunctivitis (group B) and expression of EGFR, TGF α and CD44 was assessed by means of immunohistochemistry. Furthermore, cells of two epithelial conjunctival cell lines (IOBA-NHC, CHwK) were treated with various agents and expression levels of EGFR, VEGF, CD44, and p21waf were assessed by means of ELISA. Statistical analysis was performed using Mann-Whitney test for immunohistochemistry data and t-test for the ELISA results where appropriate and all experiments were performed at least twice.

Results: There is increased expression of all markers in the chronic forms of ocular allergic disease reflected also by the production levels of the markers assessed by ELISA in the two epithelial cell lines. This was statistically significant ($p < 0.05$) and disease severity seems to correlate with expression levels.

Conclusions: There is evidence that epithelial conjunctival remodelling may be responsible for disease severity in ocular allergic disease as shown in chronic asthma. New treatment strategies may be suggested to prevent or inhibit disease perpetuation.

Efficacy of Extended-Release Oral Diclofenac in Postoperative Pain Management after Photorefractive Keratectomy

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Purpose: Inadequate pain control after photorefractive keratectomy (PRK) surgery can be a source of distress for patients and ophthalmologists. The purpose of this study was to evaluate the efficacy of extended-release diclofenac for the management of pain after PRK surgery.

Methods: In this prospective clinical trial study, patients in the case group were given extended-release diclofenac pre- and postoperatively, and patients in the control group were given acetaminophen and ibuprofen photophobia, and functional deficit scores were evaluated subjectively for each patient. The surgeon evaluated lid swelling, conjunctival injection, and epithelial healing. pre- and postoperatively. Patients were examined 2 days after PRK surgery. Pain,

Results: Among the 62 patients enrolled in the study, 33 patients were given extended-release diclofenac (case group) and 29 patients were given acetaminophen and ibuprofen (control group). The pain score was reduced in the case group compared to the control group (4.32 ± 2.72 vs. 6.52 ± 1.99 , respectively; $p < 0.001$). Photophobia, functional deficit scores, lid swelling, and conjunctival injection were significantly reduced in the case group compared to the control group.

Conclusion: The results indicate that oral diclofenac (preoperatively) is more effective than other routine analgesics in the management of pain in PRK surgery.

The Use of 0.05% Cyclosporine in Management of Herpes Viral Recurrent Erosions

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Background: Herpes viral recurrent erosions are caused by the sum of various factors – dry eye, chronic allergic reaction to used drugs, not adequate reparative therapy and others. In most of the cases chronic inflammatory process is persisted.

Purpose: To reduce and control the level of inflammation and corneal epithelial edema without use of corticosteroids.

Methods: Study involved 22 patients with recurrent erosions of herpes viral origin with severe exacerbations occurs more often than once in 4 month. Additionally to regular therapy all patients were receiving courses of 0.01% -0.001% Dexamethazone for 2 month. All patients underwent dry eye tests. BUT test was decreased and severe Lissamine green coloring was found. At the beginning of the study corticosteroid treatment was canceled and 0.05% Cyclosporine (Restasis®) was administered twice a day for 7 month. The follow up period was 1 year with monthly check-up visits.

Results: In 1 year period 4 patients had 1 recurrence of erosion, 3 patients had 2 or more recurrences, 1 patient developed geographic keratitis. In 2 cases there were obvious needs to continue corticosteroid treatment. In 5 cases the administration of Cyclosporine was prolonged over 7 month period because of dry eye complains. Therefore 14 patients (64%) did not have any erosion recurrence and in 12 patients (54%) the effect was stable in 5 month period after Cyclosporin discontinuation.

Conclusions: The use of local Cyclosporine in cases of herpetic recurrent erosions is effective because of anti-inflammatory effect and reduction of aggressive autoimmune reaction alertness.

Posterior Capsule Opacification: Pharmacologic Prophylaxis with Kinase Inhibitors

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Purpose: Prevention of posterior capsule opacification (PCO) is a challenge for surgeons and researchers since it represents the major long-term complication after cataract surgery. We investigated the effect of the kinase inhibitors erlotinib and alkylphosphocholines on human lens epithelial cell behaviour in vitro and the feasibility of intraocular lens (IOL) coating with alkylphosphocholines for pharmacologic PCO prophylaxis.

Methods: Kinase Inhibitors were assessed for their biocompatibility on different human ocular cell types. To determine their effect on cell proliferation, the MTT test was performed. Chemotactic migration was analyzed with the Boyden Chamber Assay and chemokinetic migration by time lapse microscopy. Contraction was measured by a 3D matrix contraction assay and cell spreading by measuring the cell diameter on a fibronectin coated surface. IOLs of different design and material were incubated with Alkylphosphocholines and the number of human lens epithelial cells was determined.

Results: The IC50 concentrations of Erlotinib and Alkylphosphocholines were 8.8 μ M and 100 μ M, respectively, for human lens epithelial cells. Chemotactic migration ($p = 0.004$) and chemokinetic migration ($p = 0.001$) were reduced significantly in a concentration based manner. Cell mediated collagen matrix contraction ($p = 0.001$) and spreading on a fibronectin coated surface ($p = 0.001$) were attenuated. APC-coated intraocular lenses were able to reduce human lens epithelial cell proliferation significantly.

Conclusions: We were able to demonstrate that cellular features relevant for PCO formation were attenuated by kinase inhibitors in vitro. Drug delivery by coated IOLs seems feasible and might become a future option for pharmacologic PCO prophylaxis.

New Molecular Classes of Antibiotics Effective Against Drug Resistant Gram Negative Pathogens

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Antibiotic resistant pathogens particularly from *Pseudomonas* are being more commonly recognized in the ophthalmology clinic. However, currently there are few current antibiotics with good activity against these organisms. We have developed two classes of molecules, one a small non-natural peptide and the other a small molecule which overcome the issues with current therapies.

The development pathway has included microbiological testing with clinical strains of resistant forms of *Pseudomonas*, in vitro and in vivo toxicity testing as well as proof of efficacy in a mouse model of corneal infection with *Pseudomonas*. Additionally, biophysical studies and molecular dynamics has been used to understand the action at an atomic level.

Microbiological testing has compared the activity with a fourth generation fluoroquinolone, and found that MICs remained constant over 17 strains of tested bacteria while the quinolone MIC increased by up to X40. These drugs were shown to be non-toxic when put on the mouse and rabbit eye. For in vivo studies of the infected mouse cornea, these drugs were administered X3/day at 1 and 3mg/ml in PBS with the fluoroquinolone as a comparison. The peptide drug was found to be as effective as the quinolone at 1/3 the concentration, the small molecule concentration was similar. However, our new drugs B2088/99 and AM0052 killed *Pseudomonas* very rapidly and were able to avert resistance in a laboratory simulation. In conclusion, we have presented two new candidates effective against this emerging type of infection.

LentiVector®Platform: Clinical applications in ophthalmology

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Oxford BioMedica has developed ocular gene therapies using its proprietary LentiVector® platform which is based on recombinant Equine Infectious Anaemia Virus (EIAV). Currently we have three ocular therapies in clinical development: RetinoStat®, StarGen™ and UshStat®, for the treatment of age-related macular degeneration, Stargardt macula dystrophy and Usher Syndrome 1B respectively. Regulatory approval for Clinical Development has been received for StarGen™ in the US and France, and for RetinoStat® and UshStat® in the US. Phase I (RetinoStat®) and Phase I/IIa (StarGen™ and UshStat®) clinical evaluations are currently underway.

The dose-escalation phase of the RetinoStat® trial has been completed. For StarGen™ and UshStat® the dose-escalation phase is in progress. Subretinal administration of all three products has been well tolerated, causing no ocular inflammation or immune responses in any patients. Transduction of the retina following subretinal injection of RetinoStat® rapidly produced high levels of both transgenes detectable in the aqueous. These levels are substantial, show dose dependence and long term expression.

The platform has proved to be a highly effective delivery system for relatively large genes into target retinal cells, resulting in stable and long-term expression.

Applications of Nanocarriers in Drug Delivery: an Update Review

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Drug delivery is the method of administering a pharmaceutical compound to achieve a therapeutic effect in patients. Drug delivery technologies are patent protected formulations that modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety. Nanocarrier delivery systems are extensively being investigated as a drug delivery strategy in the pharmaceutical research from the last 3 decades. Nanocarriers, such as nanoparticles, have the capacity to deliver ocular drugs to specific target sites. Nanoparticulate technologies offer good benefits as solubilization of hydrophobic active pharmaceutical ingredient (API), improvement in bioavailability, improved pharmacokinetics of API and protection of API from physical, chemical or biological degradation. Nanocarriers release drug at constant rate for a prolonged period of time and thus enhance its absorption and site specific delivery. The advantages of using nanoparticles include improved topical passage of large, poorly water-soluble molecules as glucocorticoid drugs or cyclosporine for immune-related, vision-threatening diseases. Other large and unstable molecules, as nucleic acids, delivered using nanoparticles offer promising results for gene transfer therapy in retinal diseases. This review presents an overview on nanocarrier technology to deliver drugs.

Relationship Between the Metabolic Syndrome in Patients with Type 2 Diabetes and Diabetic Retinopathy in Deficiency of Vitamin D

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Today there are about 285 million impaired, of whom 90% live in developed countries. About 60 million people in the European Region of WHO diabetes patients: 10.3% of men and 9.6% of women aged 25 years and older. According to the International Diabetes Federation, the most important pathogenesis factors in the development of the metabolic syndrome are abdominal obesity and insulin resistance.

Purpose - to determine the relationship between the degree of manifestation of the metabolic syndrome in patients with type 2 diabetes and severity of DR against deficiency of vitamin D3. Under our observation were 39 patients (69 eyes) aged from 35 to 62 years. Experience of illness ranged from 5 to 18 years. Among examined 25 patients had NPDR and 14 - PRD. Among patients 64.1% had insufficient vitamin D3 and 35.9% experienced its deficiency. In the group of patients with NPDR mean 25 (OH) was 58.8 nmol / l, while in PRD rate dropped to 37.5, indicating the presence of severe deficiency of vitamin D3. Patients with deficiency of vitamin D3 (64.1%, 25 patients) NPDR met in 23% of cases, PPDR - in 25.8%, and 15.3% of GAD in patients. There was a correlation between the level of 25 (OH) and BMI, fasting glucose and indicators of metabolic syndrome.

There was the relationship between BMI and severity of DR, the higher the weight, you are more pronounced DR. It should be noted that patients with metabolic syndrome was observed more severe form of diabetic retinopathy.

In Vivo Assessment of Pharmacologic Vitreolysis in Rabbits with the Digital Fluoroscopy System

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Backgrounds: To demonstrate in vivo assessment of plasmin-induced posterior vitreous detachment (PVD) and vitreous liquefaction in rabbits using the Digital Fluoroscopy System (DFS). **Methods:** Twenty eyes of 10 New Zealand white rabbits were divided into five groups. In each group, one rabbit received an intravitreal injection of 2.0U plasmin in the right eye and 0.5U plasmin in the left eye. Intravitreal injection of 0.1ml balanced salt solution (BSS) was performed in the right eye and no injection was performed in the left eye of the other rabbit taken as a control. Intraocular fluid dynamics was assessed by the DFS with a contrast agent in each group at different time intervals (6, 12 hours, 1, 3, and 7 days). After the rabbits were sacrificed, both eyes were enucleated. Scanning electron microscope was used to confirm the morphologic alterations of vitreoretinal interface observed in the DFS.

Results: Complete PVD was observed after 12 hours with 2.0U plasmin injection, while complete PVD was observed only after 3 days with 0.5U plasmin injection. The eyes with BSS injection or without injection failed to show complete PVD even after 7 days. Complete vitreous liquefaction was observed after 7 days with 2.0U plasmin injection, but no eyes with 0.5U plasmin or BSS injection showed complete vitreous liquefaction. The DFS images provided clear visualization of PVD and vitreous liquefaction, and correlated well with the histologic changes.

Conclusion: The DFS is a useful tool for the evaluation of pharmacologic vitreolysis considering clear in vivo visualization of PVD and vitreous liquefaction.

Topical Treatment with Cyclosporine 0,05% (CsA) for Subepithelial Infiltrates Secondary to Adenoviral Keratitis

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Purpose: To evaluate the topical treatment with 0,05% Cyclosporine A, in patients with subepithelial corneal infiltrates.

Methods: We retrospectively reviewed the records of 19 patients (22 eyes) before and after treatment with cyclosporine 0,05% drops three times daily. All patients had been treated with topical corticosteroid previously without any improvement. All data were recorded including visual acuity, intraocular pressure, medications used, evaluation of infiltrates.

Results: Twelve males and 7 females with mean age 39±10 years were included in this study. Mean follow up was 16 months. There was statistically significant reduction in the improvement of foreign body sensation and glare, while the number of corneal infiltrates had significantly reduced as well. Five patients noted no improvement. Overall patients were satisfied with the cyclosporine drops treatment.

Conclusions: Topical CsA 0,05% treatment can be considered as a quite effective alternative for the treatment of adenoviral subepithelial infiltrates which may insist for a long time after the initial infection.

The Relationship between the Cannabinoid CB Receptor System and Protection Against A2E Photo-Toxicity in Age Related Macular Degeneration (AMD)

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Background: The fluorophore A2E, a pyridinium bisretinoid, accumulates in retinal pigment epithelial cells (RPE) as a major component of lipofuscin. A2E has the potential for causing RPE cell damage observed in age related macular degeneration (AMD). Degradation of A2E produces reactive oxygen species (ROS) that leads to cell damage.

The endocannabinoid CB receptor system (ECBR system) is comprised of specific cannabinoid receptors (CB1; CB2). Cannabinoid receptors have been detected in neuron cells and proposed as potential therapeutic agents in neurodegenerative disorders because of their involvement in controlling neural cell survival and death. The anti-oxidative property of cannabinoids was also confirmed.

A central hypothesis of this work is that oxidative stress followed by A2E photo-oxidation and degradation can be prevented by cannabinoids.

Methods: Cells model: A2E-laden RPE cells following blue light irradiation. Cannabinoids were screened for their ability to modulate the frequency of nonviable cells, directly and in selective manner, using selective agonist.

Results: We have synthesized, purified, and characterized the fluorophore A2E. This permit cells model with RPE cells. Photo-oxidation of A2E leads to generation of ROS that activate apoptosis and RPE cell damage. We found that pretreatment of the RPE cells with synthetic cannabinoids, (HU-210, a potent non-selective receptor agonist, and HU-308, a CB2 specific agonist) protected the cells from oxidative stress and intracellular ROS generated by A2E photo-oxidation.

Conclusions: Significant differences were found in the oxidative damage caused by A2E photo-degradation in RPE cells, in presence and absence of cannabinoids, indicating potential protection through the ECBR system.

Algorithm Approach for Severe Keratoconjunctivitis Sicca Diagnosis

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Introduction: The incidence of Keratoconjunctivitis sicca (KCS) has a social and economic impact. Both diagnosis and classification of KCS severity represent challenges not only in patient management, but also in KCS study design, due to the lack of standardised diagnostic methods.

Methods: The ODISSEY European Consensus Group experts reviewed 14 signs (CFS, osmolarity, Schirmer test, cytology, keratitis, conjunctival staining, visual function, inflammation, blepharospasm, TBUT, aberrometry, confocal microscopy, inflammatory markers and disease treatments) in order to establish an algorithm on severe dry eye diagnosis. These criteria have been discussed in relation to their specificity for severe dry eye and their association with the severity of the disease.

Results: Considering the multifactorial nature of KCS, the experts have defined a simple, but comprehensive diagnostic tool – the **Severe KCS diagnostic algorithm**. After tear secretion assessment and dry eye diagnosis, evaluating OSDI (Ocular Surface Disease Index) score and CFS (Corneal Fluorescein Staining) grade is sufficient to diagnose severe KCS for most patients. Experts have established that additional tests are necessary when these two criteria are not correlated.

Conclusions: The ODISSEY algorithm facilitates the KCS diagnosis and establishes the disease severity. In patients with correlation between symptoms and signs, diagnosis of severe KCS is easy, but when dissociated, diagnosis is more of a problem. In such cases, a simple and specific approach is now established in severe KCS, thanks to the additional criteria defining our diagnostic algorithm.

Macular Pigment Optical Density (MPOD) in Macular Health and Visual Function: Bridging the Gap between Clinical Research and Clinical Practice

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Purpose: Clinical research shows MPOD to be associated with a decreased risk for age-related macular degeneration (AMD) and benefits in visual function. Since MP is entirely of dietary origin it seems important to educate health professionals on the role of MP and to introduce MPOD measurement into clinical practice.

Method: An interdisciplinary panel of five international experts in the area of retinal diseases and macular carotenoids met to discuss the latest science and their own clinical and research experience on four specific points: *i)* the relevance of MPOD as a potential biomarker for AMD; *ii)* the value of measuring MPOD and the technologies available to measure it reliably and objectively; *iii)* the relationship between lutein and zeaxanthin consumption and MPOD and *iiii)* the influence of MPOD on visual function in healthy individuals.

Results: After age, genetic predisposition and smoking, low MP is the next most important risk factor for AMD. Proper intake of lutein and zeaxanthin through diet and/or supplementation can, in most cases, influence the MP and can be an adequate means to modulate this risk factor. An increase in MPOD is linked to better visual performance (visual acuity, contrast sensitivity and glare discomfort).

Conclusion: Nutritional intervention with dietary carotenoids is a well-established way to fortify the antioxidant defences of the macula which may reduce the risk and/or progression of AMD, positively impacting visual health and function. It is imperative to integrate this valuable scientific knowledge into clinical practice, where it can have a beneficial impact.

Tolerance of a Sub-Conjunctival Injection of XG-102 in Ocular Inflammation

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We have evaluated XG-102, a protease-resistant peptide that selectively inhibits JNK activity in a phase Ib study to assess its safety and tolerability after sub-conjunctival injection in patients with post-surgery or post-traumatic intraocular inflammation. Patients and methods: It was an open label phase Ib study designed to assess the safety and tolerability of a single sub-conjunctival injection of XG-102. Twenty patients were included with four dose escalating groups of five patients each. The decision to proceed to the next dose group was taken by the Data Safety Monitoring Board (DSMB) based upon the tolerability and safety data collected for the preceding dose group. Patients were followed up to 28 days after administration of study treatment (24 hours, 48 hours, 8 days, and 28 days). Results: The sub-conjunctival injection of XG-102 was well tolerated by all patients and in all dose groups. None of the reported events were considered to be related to the study treatment. All patients experienced a decrease in the intra-ocular inflammation as of visit 1 and this decrease was sustained up to visit 4. No patient required an intravenous (iv) or sub-conjunctival administration of corticoids subsequent to the administration of XG-102. Conclusion: XG-102 administered as a sub-conjunctival injection in patients with recent post surgery or trauma intraocular inflammation is safe and well tolerated. A phase II is ongoing to demonstrate the efficacy of XG-102 in ocular inflammation

Bioactivity in Retinal Cells of GDNF-Loaded Microspheres Intended for Intravitreal Administration

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Purpose: To compare the bioactivity of GDNF released from PLGA microspheres (MS) in retinal cells prepared using two different variants (W/O/W and S/O/W) microencapsulation emulsion methods.

Methods: GDNF-loaded PLGA MS were prepared following an emulsion-solvent extraction evaporation method by a W/O/W emulsion (MS-1) or by a S/O/W emulsion (MS-2). For *in vitro* bioassays, retinas from postnatal day (10 B6 mice) were isolated and exposed to media released from different GDNF loaded MS from formulation 1 and 2. At 40h post plating, cultures were fixed and analysed via tunel labelling to determine the percentage of cell death.

Results: The microencapsulation methods used led to production yield of 72.4±7.0% for MS-1 and 79.7±4.4% for MS-2 formulation. While MS-1 showed big porous on the surface, MS-2 had non-porous smooth surfaces. The protein entrapment was 30.0±0.9% for MS-1 and 23.4±0.5% for MS-2. A three-phasic sustained GDNF *in vitro* release was obtained for both formulations for 133 days. *In vitro* bioassays showed that significantly less retinal cell death (P 0.001) was always observed at 40 h post-plating when cells were cultured in the presence of GDNF released from MS-2. While values of retinal cell death from MS-1 of 20.4 % were obtained, for MS-2 a lower value (15.9%) was observed.

Conclusions: The inclusion of GDNF in its solid state during the microencapsulation procedure increases its biological activity in target cells.

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Procoagulant and Anticoagulant Agents in Patients with Retinal Vein Occlusion Combined with Cardiovascular Disease

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Purpose: The study of homeostasis (coagulation and fibrinolytic systems) in patients with retinal vein occlusion (RVO) and a history of hypertension and systemic atherosclerosis.

Materials and Methods: The study involved 25 patients (25 eyes) with non-ischemic type (Group 1) and 15 patients (15 eyes) with ischemic type (Group 2) central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

Patients had compensated hypertension and systemic atherosclerosis and had not used medication affecting homeostasis.

Control group consisted of 30 patients of similar age without RVO.

Results: Patients with a history of hypertension and systemic atherosclerosis and ischemic RVO had lower antithrombin III levels (94.25±0.25) compared to patients with non-ischemic RVO (102.13±2.4) and the control group (100.577±1.04, p≤0.05). Patients from Group 2 had changes in coagulation system: high levels of thrombogenicity index (4.167±0.035) and Hageman factor-dependent fibrinolysis (16.5±1.5) while in Group 1 the values were 1.04±0.06 and 13.67±3.8 respectively and in control group 0.945±0.03 (p≤0.05) and 10.923±1.45 (p≤0.05) respectively.

Conclusion: Ischemic type of CRVO and BRVO in patients with hypertension and systemic atherosclerosis is associated with significant disturbances in homeostasis that can possibly lead to worse clinical course.

Acute Angle-Closure Glaucoma After Bronchodilator Nebulization

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Purpose: To report bilateral acute angle-glaucoma with ipratropium bromide and salbutamol nebulizer treatment.

Results: An 70 years old man was admitted in the ER with acute dyspnoea and edema of the glottis, was treated with hydrocortisone, ipratropium bromide and salbutamol nebulizer, metamizol and diazepam. Next day was admitted again in the ER with marked headache and vomiting and referring decrease in visual acuity bilaterally. On observation showed intra-ocular pressure 60 mmHg right eye and 52 mmHg left eye, corneal edema and bilateral narrow angle. He was treated with mannitol, and acetazolamide and pilocarpine and were performed goniotomy and iridotomy in both eyes. After resolution of the acute glaucoma underwent phacoemulsification with implantation lens in posterior chamber.

The nebulized ipratropium bromide and salbutamol can trigger acute angle closure glaucoma in susceptible patients (low anterior chamber, farsightedness, glaucoma, chronic angle closure) in these patients is important to minimize the absorption of topical drugs to decrease the risk of developing acute angle-closure glaucoma.

Preventing Outbreaks of Herpetic Keratitis with L-Lysine

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Some studies suggest that the amino acid L-lysine oral supplement may be helpful in reducing the rate of recurrences for Herpes Simplex Virus (HSV) muco-cutaneous infections, especially when accompanied by a high-lysine, low-arginine diet. L-lysine is an essential amino acid highly water soluble. Oral administration is the preferred route for lysine supplementation. It is absorbed in the small intestine, and then moves to the liver.

The amount of the estimated daily requirement for lysine varies from study to study, from 60 mg/day to 3,000 mg/day, or even more.

L-arginine is an amino acid required for the replication of HSV. Both lysine and arginine compete for absorption in the intestine; thus, lysine reduces the availability of arginine for HSV.

Keratitis caused by HSV is a major cause of blindness from corneal scarring and opacity worldwide. Since lysine is effective in the prevention of outbreaks of HSV muco-cutaneous infections, we decided to treat HSV Severe Keratitis (HSV-K) in the same way. In our clinical study, we prescribed 200 mg per day, which proved to be effective for the prevention of HSV-K in the five patients studied over a period of one to thirteen years.

It has been observed that when a patient's serum lysine concentration exceeds 165 nmol/ml, there is a corresponding significant decrease in the recurrence rate.

In conclusion, we can state that oral lysine is also effective in the treatment of HSV-K.

Assessment of the Therapeutic Value of Phloroglucinol in Stargardt's Disease

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Background: Autosomal recessive Stargardt's disease is the most common cause of macular dystrophies due to mutations in *abca4* gene. When ABCA4 activity is impaired, all-*trans*-retinal (atRAL) accumulates and triggers formation with phosphatidylethanolamine of A2-PE, by carbonyl and oxidative stress. Daily photoreceptor outer segments (POS) phagocytosis by retinal pigment epithelium (RPE) leads to A2E accumulation, causing RPE death and progressive photoreceptor loss. Our goal is the design and selection of powerful chemicals against carbonyl and oxidative stress (anti-COS).

Methods: Phloroglucinol (benzene-1,3,5-triol) was first assessed for its efficacy as anti-COS. ARPE-19 cell line and rat RPE primary cultures were pre-incubated with phloroglucinol before incubation with oxidative (H₂O₂ and A2E) and carbonyl (atRAL) stressors. Cell viability was measured using tetrazolium compound (MTT) assay. Alternatively, phloroglucinol was co-incubated with atRAL. Test-tube experiments were carried out to inhibit the synthesis of A2E from atRAL and ethanolamine in the presence of phloroglucinol. Adducts formed between phloroglucinol and atRAL were identified by NMR and mass analysis.

Results: Exposure of RPE cells to stressors caused dose-dependent decreases in cell viability, whereas pre-treatment with phloroglucinol significantly reduced the decline. Co-treatment of RPE cells with phloroglucinol and atRAL drastically prevented RPE cell death. In the presence of atRAL and ethanolamine, phloroglucinol led to complete inhibition of A2E synthesis.

Conclusions/Discussion: Phloroglucinol has a dual action as anti-carbonyl stress and anti-oxidant in RPE cells. The proposed mechanism for the anti-carbonyl stress action is the trapping of all-*trans*-retinal. Lower protection observed during pre-incubation compared to co-incubation suggests a low bioavailability of phloroglucinol.

Evaluation of Fast-Dissolving Matrices Containing Platelet-Lysate for Corneal Lesions Treatment

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Background: The fields of application of topically administered platelet derivatives are numerous. Platelet lysate (PL) is generally administered in form of eye drops to patients and this type of preparation has to be stored in a freezer for all time of treatment. We developed fast dissolving solid matrices prepared by freeze-drying based on mucoadhesive polymers, both for making easier the storage and for prolonging the contact time of PL with the damaged corneal tissues, thus increasing its therapeutic effect.

Methods: The matrices were formulated with polyacrylic acid (PAA) and polyvinylpyrrolidone (PVP) and were prepared by freeze-drying of polymeric dispersions containing PL. The polymeric dispersions were characterized from technological point of view. The biological evaluation consisted of an in-vitro wound-healing test performed on human corneal epithelial cells using insert and μ -Dish Ibidi. The wound healing properties were evaluated taking microphotographs at prefixed time and measuring the cell invasion in the gap.

Results: The freeze-dried matrices showed a rapid dissolution time (PVP matrices dissolved in about 2 minutes). After 6 hours, the cells were migrated in the gap for 187, 190 and 170 μ m, respectively with PVP and PAA matrices and with the reference serum free medium. The cell proliferation completely filling the gap in 10 hours with LP loaded matrices, compared to 12 hours with reference.

Conclusion: Freeze-drying technique appeared useful for developing ready-to-use fast-dissolving matrices for topical administration of LP on the cornea. The solid matrices could favour the storage of LP at room temperature and patient compliance could be increased.

Impact of the Routes of Administration on the Effects of Cyclosporine in an Experimental Rat Model of Dry Eye

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Dry eye syndrome is a relatively common disease with multifactorial causes. It has been shown that rodent models of dry eye experimentally induced by scopolamine, a tropane alkaloid drug with muscarinic antagonist effects, could be helpful to test and select therapeutic candidates in the disease.

Here we propose to compare the action of cyclosporine A, an inhibitor of T-cell activation and inflammatory cytokine production, after oral and topical administrations.

Experimental dry eye was induced in female albino rats by a systemic and continuous delivery of scopolamine (20 mg/day) over 21 days via osmotic pumps implanted subcutaneously on day 1. Animals were divided in three groups of five animals: The first two groups were instilled either saline or cyclosporine 0.05% eye drops and the third group received 20mg/kg/day cyclosporine by oral administration.

Tear production was measured with the phenol red thread test, tear break-up time was studied under slit-lamp, and corneal defects were examined by slit-lamp observation using blue light after 0.5% fluorescein eye drop instillation and in vivo confocal microscopy. These examinations were performed in both eyes at baseline and on days 7, 14 and 21.

Cyclosporine orally or topically administered significantly reduced clinical signs of dry eye by increasing lacrimation and decreasing corneal defect.

Cyclosporine appears to show efficacy in this model, regardless of the mode of administration.

Role of Diagnostic Tests for Dry Eye in Patients with Blepharospasm

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Background: The goal of the study is to value diagnostic tests for KCS for the patients with blepharospasm.

Methods: A prospective study included 60 female patients older than 40 years with blepharospasm, divided into two groups according to the clinical symptoms.

Results: 63.3% of the patients from the control group and 3.3% of the patients from the intervention group had Schirmer's test values between 5 and 10 mm. 96.7% of the patients from the intervention group had Schirmer's test values above 10 mm. In the control group the mean of the TBUT test of the right eye was 3.5 and of the left eye was 4. In the interventional group the mean of the right and the left eye was 2.5. Impressionist conjunctival cytology showed that all the subjects of intervention group were having abnormal findings of epithelial surface, whereas in the control group were women with a normal conjunctival surface. By comparing the fluorescein test staining between the two groups of patients it could be observed that only conjunctiva stains with fluorescein, were recorded in the interventional therapy group, whereas corneal surface stains with fluorescein, were also recorded in the control group. There was a statistically significant difference in staining lissamine green, the median lissamine test was 4.86 in the intervention group and 5.71 in the control group.

Conclusion: Comparison of diagnostic tests for KCS that were used in this study under the ROC curve, it can be concluded that fluorescein test has the best sensitivity and specificity.

Corticosteroids-Induced Toxicity and Cell Death Mechanisms in Vascular Endothelial Cells

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Glucocorticosteroids (GCs) have been widely used in the treatment of many diseases. They are injected at strong doses directly in the eye or systemically to treat macular oedema, neovascularization and numerous general inflammatory states.

The purpose of this research is to study the toxic effects of the GCs on endothelial cells. We performed our study on cells of the human microcirculation (HMEC), on bovine retinal endothelial cells (BREC) and Ex-vivo using flat mounted rat retinas. Four glucocorticosteroids were tested: Hydrocortisone, Dexamethasone, Dexamethasone phosphate and Triamcinolone Acetonide. The expression of the glucocorticoid and mineralocorticoid receptors was verified by Q-PCR. The DL50 relative to these drugs was estimated by the MTT test. Mechanisms of cells death have been explored using the evaluation of lactate dehydrogenase release, DNA electrophoresis, immunohistochemistry and western blot.

We found a decrease of cell viability in the presence of GCs. The most hydrophobic GCs were the most toxic. The cell origin was also important. The endothelial cells of the general microcirculation are more sensitive than the retinal endothelial cells. The study of the mechanisms of cell death showed an activation of caspases dependent or independent cell death. All the in vitro results were confirmed on the ex-vivo model.

So that, therapeutically used doses of GCs are toxic for endothelial cells. This should be kept in mind in the clinical use of these compounds.

Functional and Structural Retinal Abnormalities Associated with Didanosine-Induced Retinopathy

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Background: Didanosine is a nucleoside analogue of guanosine with antiretroviral activity against the Human Immunodeficiency Virus. This drug is used instead of azidothymidine in cases of intolerance or refractory disease.

Retinal toxicity cases were first described in 1992.

Since little is known on the exact toxic mechanism, close ophthalmologic follow-up is required. The purpose of our study is to describe functional and structural abnormalities associated with didanosine-induced toxic retinopathy.

Methods: We report three cases of didanosine-induced retinopathy. Visual acuity, visual fields, electrophysiologic assessment, fundus autofluorescence and spectral domain Optical Coherence Tomography (SD-OCT) are provided for each patient, as well as the cumulative dose and use of other nucleoside analogues.

Results: All patients had normal visual acuity but some of them had visual field constriction or peripheral vision difficulties under scotopic conditions. Full-field electroretinogram revealed mild rod-cone dysfunction. Fundus examination revealed mottling and well circumscribed round atrophic lesions with hyperpigmented borders in the mild periphery. These changes were better seen using fundus autofluorescence imaging with a peculiar granular pattern. SD-OCT showed irregularity of the retinal pigment epithelium and photoreceptor outer segment structure in the peripheral retina. Toxic effects appear to be related to peak and cumulative dosage as well as in association with other nucleoside analogues.

Discussion: Didanosine-induced retinopathy suggest rod-cone degeneration in peripheral retina with a characteristic autofluorescence pattern. The exact mechanism(s) of toxicity is unknown, but may involve impairment of outer

segment renewal and/or of retinal pigment epithelium phagocytic function.

The Role of RAGE in *in vivo* Angiogenesis and AMD

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Background: The receptor for AGEs (RAGE) evokes pro-inflammatory signalling responses in the retina. This study investigated RAGE modulation associated with neovascular age-related macular degeneration (nvAMD) progression.

Methods: Serum levels of RAGE ligand, S100B and soluble RAGE (sRAGE) from patients with nvAMD in at least one eye (n=51) were compared to age-matched controls without AMD in either eye (n=52). C57Bl/6 control (WT) and RAGE null (RAGE^{-/-}) mice, were photocoagulated to induce CNV. Fundus photography and fluorescein angiography evaluated lesion progression. Post-mortem retinal flat-mounts were evaluated for CNV lesion morphology, occurrence of RAGE-ligand (S100B) and inflammatory cell infiltration. In parallel in vitro, the angiogenic response of human endothelial cells was assessed. In vitro RAGE knockdown (via siRNA), S100B-mediated angiogenesis and NFκB transcription were analyzed.

Results: S100B was altered in patients with nvAMD when compared to control. Retina from RAGE^{-/-} mice exhibited significantly reduced CNV lesion size when compared to WT control (p<0.05). Activated microglia were considerably less abundant in RAGE^{-/-} CNV lesions when compared to WT counterparts (p<0.001). S100B immunostaining was higher around CNV lesions of WT mice when compared to RAGE^{-/-} mice. S100B-treated HMECs showed increased migration/tube formation (p<0.001) and subsequent NFκB transcriptional activation. siRNA-mediated knockdown of RAGE significantly prevented HMEC responses to S100B.

Conclusions: Pro-inflammatory and angiogenic responses appear mediated by S100B-RAGE interactions. This study highlights the role of RAGE in inflammation-mediated outer retinal pathology in CNV progression.

Efficacy Analysis of Preservative-Free Tafluprost and Timolol in Open-Angle Glaucoma and OHT Patients in a Phase-III Study

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Background: To determine whether baseline intraocular pressure (IOP) and prior therapy significantly influence efficacy of preservative free tafluprost (PFTAF) and timolol (PFTIM)

Methods: The efficacy of PFTAF 0.0015% q.h.s. and PFTIM 0.5% b.i.d. was analyzed in 610 randomized OAG and OHT subjects in a double-masked, three-month study. Post hoc efficacy analyses were completed after stratifying patients by prior treatment and by baseline diurnal (mean of 8 AM, 10 AM, and 4 PM) IOP, including "Low" (<24 mmHg), "High" (≥26 mmHg), and "Moderate" (25 to 27 mmHg) IOP groups.

Results: PFTAF (N=298) lowered mean diurnal IOP 6.9 mmHg (28%, baseline 24.9 mmHg) vs. 6.6 mmHg (27%, baseline 24.7 mmHg) by PFTIM (N=312). Prior treatments did not influence efficacy except in patients (n=262) naïve to prostaglandin therapy: PFTAF lowered diurnal IOP 7.2 mmHg (28%) vs. 6.5 mmHg (26%) by PFTIM (0.7 mmHg difference, p=0.044). Baseline evaluations showed PFTAF lowered IOP by 5.6 mmHg (25%) vs. 9.1 mmHg (32%) in the "Low" (n=125) and "High" (n=88) groups, respectively (3.5 mmHg difference, p<0.001). In the "Low" groups, PFTAF and PFTIM (n=132) each lowered IOP 5.6 mmHg (25%, p=0.958). In the "High" groups, PFTAF (n=88) and PFTIM (n=90) lowered IOP 9.1 mmHg (32%) and 7.9 mmHg (29%), respectively (1.1 mmHg difference, p=0.020). In "Moderate" patients, PFTAF (n=76) lowered mean diurnal IOP 7.8 mmHg (30%) vs. 7.2 mmHg (28%) by PFTIM (n=79).

Conclusions: The magnitude of IOP reduction by PFTAF and PFTIM is dependent on baseline IOP and may be influenced by prior treatments.

Histologic Changes in the Retina and the Choroid After Atelocollagen Gel Injection into the Suprachoroidal Space of Rabbit Eyes

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Background: Drug delivery to the suprachoroidal space has been focused as a new potential approach to diseases in the posterior segment of the eye. Atelocollagen gel is known to be in the gel state at 4 degrees, but it becomes solid at body temperature. Atelocollagen might be a useful carrier of the drug to the eye because it takes longer time to be degraded when a drug is mixed with atelocollagen instead of liquid. In this study we histologically investigated effects of injected atelocollagen gel into the suprachoroidal space on the retina and the choroid in rabbit eyes. **Methods:** Under general anesthesia the sclera of the rabbit eye was exposed and cut about 2mm. After the cut reached the choroid, a microcatheter was inserted into the suprachoroidal space and atelocollagen gel was injected. Immediately after the surgery, and at 1week, 1 month, 2months, and 4 months after the surgery, the rabbits were euthanized and the eyes were removed and processed for paraffin sections. **Results:** Sixteen rabbit eyes were used in this study. The injected atelocollagen was observed in the suprachoroidal space and in the choroid of paraffin sections until 2 months after the surgery. The retina and the choroid showed no apparent damages after the surgery. At 4 months after the surgery, the atelocollagen was not detected in the choroid. **Conclusions:** The injected atelocollagen remained in the choroid and the suprachoroidal space until 2 months after the surgery without apparent damages to the retina.

The Change of Retinal Ganglion Cells and Expression of Vascular Endothelial Growth Factor in Diabetic Rat Model

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The purpose of this study was to examine the changes of the RGCs and the expression of vascular endothelial growth factor (VEGF) in retina of diabetic rat model. Diabetes was induced with a single injection of 60 mg/kg streptozocin (STZ). RGC apoptosis was apparent by TUNEL staining after induction of diabetes in the rat. The GFAP induction occurred both in astrocytes and muller cells during diabetes. Furthermore VEGF protein expression was increased throughout the retina. Diabetic changes induce RGC apoptosis. Elevation of VEGF expression and activation of glial cells in the retina were observed. The effect of modulating VEGF on the diabetic retina need further investigation.

Synaptic Plasticity of the Retinal Cells in Experimental Glaucoma Model

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Glaucoma is known to be an irreversible disease that causes blindness. The purpose of this study was to examine the expression of synaptophysin, an important molecule closely related to synaptic activities, and synaptic plasticity in a chronic ocular hypertension rat model. Chronic ocular hypertension was induced by three episcleral vein cauterization. The intraocular pressure (IOP) remained elevated in the cauterized eyes for the 8-week experiment, whereas it was not elevated in the contralateral control eyes. The average number of RGCs decreased significantly, and TUNEL-positive cells were detected in the ganglion cell layer. Synaptophysin immunoreactivity was found in the inner part of the outer nuclear layer and outer plexiform layer. The distribution of synaptophysin was present within the outer nuclear layer at the early stage, and increased transiently. This data suggest that there is increase in synapses between retinal cells after chronic ocular hypertension. The role of this phenomenon needs further investigation.

The Extract of *Litsea japonica* Ameliorates Blood-Retinal Barrier Breakdown in db/db Mice

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Background: Loss of blood-retinal barrier (BRB) properties is an important feature in the pathology of diabetic retinopathy. Endothelium integrity is important for the normal functioning of vessels. *Litsea japonica* (Thunb.) Jussieu, a Korean native plant, has potential health benefits, including antioxidant, anti-inflammatory and anti-cancer effects.

Methods: In the present study, we evaluated the ability of an ethanol extract of *L. japonica* to prevent retinal vascular leakages in db/db mouse, an animal model of type II diabetes. *L. japonica* extracts (LJE, 100 and 250 mg/kg) were treated once a day orally for 12 weeks.

Results: Vehicle-treated db/db mice exhibited hyperglycaemia and retinal vascular leakage. However, LJE treatment blocked diabetes-induced blood-retinal barrier breakage and decreased retinal VEGF expression in db/db mice. It also inhibited degradation of occludin, an important tight junction protein.

Conclusion: Taken together, our findings suggest the potential therapeutic usefulness of *L. japonica* for retinal vascular permeability diseases.

Long-term Outcomes of Intravitreal Triamcinolone Injection or Vitrectomy for Macular Edema Associated with Branch Retinal Vein Occlusion

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Background: Macular edema is one of the major causes of visual loss associated with branch retinal vein occlusion (BRVO). The purpose of this study is to investigate the effects of the intravitreal injection of triamcinolone acetonide (IVTA) and vitrectomy for macular edema associated with BRVO.

Methods: Retrospective review of the medical records of 59 eyes with BRVO. Twenty eyes underwent IVTA (4mg) and 19 eyes underwent vitrectomy as the first treatment for macular edema due to BRVO. Twenty eyes were observed without treatment. Follow-up visits were scheduled before the treatment and at the postoperative 1, 3, 6 and 12 months. The main outcomes to evaluate efficacy were best corrected visual acuity (BCVA) and mean central retinal thickness (CRT).

Results: In the IVTA group, the mean BCVA didn't change at 1 month, and improved significantly at 3, 6 and 12 months after the injections in comparison with the baseline. The mean CRT decreased significantly at 1-12 months after treatment. In the vitrectomy group, the mean BCVA improved significantly at 1-12 months after treatment, and the mean CRT decreased significantly at 1-12 months after treatment. In the natural course group, the mean BCVA improved and the mean CRT decreased significantly at 3 months in comparison with the baseline.

Conclusions: IVTA and vitrectomy were improved BCVA and CRT in patients with macular edema associated with BRVO earlier significantly in comparison with the natural course. The long-term effects were not different significantly between the IVTA and the vitrectomy groups.

Comparison of Spectral Domain and Swept-Source Optical Coherence Tomography in Pathological Myopia

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Background: Optical coherence tomography (OCT) detects subtle pathology in myopic fundi. This study aims to compare OCT images obtained with swept-source OCT (SS-OCT) and spectral domain OCT (SD-OCT) in pathological myopia.

Methods: Five patients with pathological myopia underwent SD-OCT and SS-OCT imaging. SS-OCT was performed using a prototype system (Topcon Medical Systems). SD-OCT was performed using enhanced depth imaging on the Heidelberg Spectralis OCT. The closest corresponding scans from the central subfield were compared.

Results: Eight eyes of five patients with pathological myopia were included (mean spherical equivalent -16.00±4.70D). Clear visualization of the choroid in the staphyloma was possible in 8/8 SS-OCT images compared to 1/8 SD-OCT images ($p<0.001$) while clear visualization of the sclera was possible in 5/8 SS-OCT images and 3/8 SD-OCT images ($p=0.35$). The IS/OS line was clearly seen in 6/8 eyes with SS-OCT, compared to 1/8 with SD-OCT ($p=0.009$). The external limiting membrane was clearly seen in 7/8 scans with SS-OCT and 2/8 with SD-OCT ($p=0.009$). SS-OCT demonstrated foveoschisis in 4 eyes, with 1 of these not visible on SD-OCT. The wider SS-OCT scan revealed additional pathology not visible using SD-OCT along the staphyloma walls in 4/8 images. These included incomplete posterior vitreous detachment in 1 eye, and peripheral retinoschisis in 3/8 eyes. Vitreoschisis was visible in 3/8 SS-OCT images but not the SD-OCT images.

Conclusion: SS-OCT is useful for imaging the posterior staphyloma of pathological myopia, providing greater detail than SD-OCT.

Polymicrobial versus Monomicrobial Keratitis: a Retrospective Comparative Study

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Objectives: To compare risk factors, clinical characteristics, microbiological profile, and treatment outcomes of polymicrobial versus monomicrobial keratitis.

Methods: In this retrospective comparative case series, eyes with polymicrobial and monomicrobial keratitis were identified from microbiological records from January 2002 to December 2010. Various parameters including demographics, risk factors, clinical and microbiological characteristics and treatment outcomes were analyzed.

Results: Twenty-one eyes each with polymicrobial and monomicrobial keratitis were included. Contact lens usage was the commonest predisposing factor in both groups. Systemic (23.8%) and multiple (33.3%) risk factors were involved in polymicrobial group only. Mean age of patients, mean size of corneal infiltrates and mean duration for infection resolution were significantly greater in the polymicrobial group. Medical treatment was successful only in 80.9% of eyes with polymicrobial keratitis, whereas all monomicrobial keratitis patients responded to it. A total of 44 organisms belonging to 18 species (bacteria=13, fungi=5) were isolated from the polymicrobial group, and *Pseudomonas aeruginosa* and *Candida albicans* were the most frequently isolated bacteria ($n=12$) and fungi ($n=5$) respectively. In the polymicrobial group, gram-negative organisms were most sensitive to gentamicin (87.8%) and ciprofloxacin (78.7%), while gram-positive organisms were 100% sensitive to ciprofloxacin and cefazolin.

Conclusions: A high index of suspicion of polymicrobial keratitis should be made in patients with multiple and systemic risk factors. Contact lens usage was the most common risk factor in both groups. Corneal infiltrate size is a reliable indicator for suspecting polymicrobial keratitis. Prolonged course of disease and decreased antibiotic sensitivity were other notable features of polymicrobial keratitis.

A Novel Device for Depicting Metamorphopsia Pattern

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Background: Maculopathy is usually combined with metamorphopsia. Though the patients complain of metamorphopsia, it is often difficult to present what the distorted configuration seen by the patients. Most of time, Amsler grid is used to test if the metamorphopsia exists, revealed by the patients' own perception; however, in terms of demonstrating the distorted configuration as an image, it is of no use. Previously, several rationales had been proposed to reveal the metamorphopsia pattern, but they were not widely applied to test the patients. To fulfill the clinical requirements as assessing the extent or severity of the metamorphopsia, and evaluating the preoperational and postoperational condition, it is necessary to develop a device capable of handling such investigations.

Methods: We constructed a device, based on a notebook computer running Windows 7 with a LCD screen, and composed the software codes in Matlab. With a particular algorithm, the device was realized and utilized to depict the metamorphopsia pattern. The acquired patterns were further compared and judged by the patients' fundus abnormality.

Results: Several kinds of maculopathy had been investigated including cellophane maculopathy, age-related maculopathy, diabetic maculopathy, and retinal vein occlusion, etc. More clinical data were accumulated and proved the device's clinical efficacy as depicting the metamorphopsia pattern.

Conclusions/Discussion: As far as we know, the algorithm we developed is a novel one in depicting metamorphopsia. The clinical efficacy is proved through several kinds of maculopathy. Though still under further refinement, the device is promising to become a tool for evaluating macular function.

Assessment of the Efficacy of Topical Cyclosporine for Dry Eye Disease Induced by Mustard Gas using Tear Osmolarity Measurement

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Introduction: The aim of this study was to evaluate treatment effectiveness of topical cyclosporine on dry eye disease induced by mustard gas using tear osmolarity measurement.

Material & Method: In our prospective clinical study 36 eyes of 36 patients exposed to mustard gas with severe dry eye resistant to artificial tears enrolled the study. Before and after treatment with topical cyclosporine 0.05% twice daily for 3 months, they were evaluated using the Ocular Surface Disease Index for improvement in symptoms as well as tear breakup time, Schirmer testing and osmolarity measurement for improvement in signs of the disease.

Results: The mean OSDI score before treatment was 0.74 ± 0.15 . After treatment it reduced to 0.64 ± 0.15 ($p < 0.001$). The mean TBUT at baseline was 1.9 ± 1.4 seconds which increased to 2.7 ± 1.5 seconds ($p < 0.001$). However this difference was not clinically significant. Results of mean Schirmer test were 4.6 ± 1.3 mm at baseline and 5 ± 1.3 mm after treatment ($p < 0.001$). There was a reduction in tear osmolarity of patients after 3 months of treatment with cyclosporine. The mean osmolarity measures were 301.7 ± 11.5 before treatment and 286.3 ± 7.9 after 3 month treatment ($p < 0.001$).

Conclusion: We concluded that topical cyclosporine 0.05% is effective in tear osmolarity reduction and improving the symptoms of dry eye disease in patients affected to mustard gas.

Intravitreal Bevacizumab for Myopic Choroidal Neovascularization: Long Term Results

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Background: Myopic choroidal neovascularization (CNV) is one of the main causes of blindness in developed countries and still remains a therapeutical challenge. The purpose of this study was to compare the outcome at two years of myopic CNV treated with photodynamic therapy with verteporfin (PDT) and intravitreal bevacizumab (IVB). **Methods:** A prospective, randomized, multicenter, masked, phase III study was performed in 55 myopic eyes with subfoveal or juxtafoveal CNV. Eyes were randomized either to IVB (Group 1) or conventional PDT (Group 2) and followed up 24 months. Primary outcomes were best-corrected visual acuity and macular thickness. Fluorescein angiography was performed at baseline, and with CNV activity. **Results:** Both groups were found to be similar for age, spherical equivalent, sex, ratio of pseudophakic eyes, ratio of eyes with previous PDT, LogMAR BCVA, ETDRS letters read and central foveal thickness at baseline. The average number of letters read at baseline in Group 2 was 53.0 (SD 16.8) vs. 62.4 (SD 16.1) at month 24 ($p = 0.002$). The average number of letters read at baseline in Group 1 was 52.8 (SD 13.9) vs. 49.5 (SD 18.2) at month 24 ($P = 0.84$). 64% of eyes in Group 2 gained 10 or more letters vs. 25% in Group 1 ($P = 0.008$). Mean number of IVB during the first and second year was 3.5 and 0.6 respectively.

Conclusions: IVB is a useful procedure as a first line therapy to treat CNV associated with high myopia, improving the results obtained with PDT during the first and second year follow-up.

How to do the Microbial Characterization of a New Preservative Free Multi-Dose Devices for Ophthalmic Formulations?

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Background: Preserved formulations in multi-dose containers are standard for treatment of ophthalmic disorders. The most widely used benzalkonium chloride (BAC) is safe at low concentrations and for short term treatment. Challenges for preserved formulations are associated with chronic conditions like dry eye or glaucoma. Multi-dose devices which make preservatives dispensable will provide benefits for these patients. The Ophthalmic Squeeze Dispenser (OSD) is such a device and various pharmaceutical companies have recently launched artificial tears using the OSD. The system relies solely on mechanical measures to sustain the microbial integrity of the formulation. For such an innovative technology it is essential to provide convincing and reliable data on microbial stability during storage and use. When using eye drops, microorganisms can potentially contaminate the medication via the dosing orifice or via the venting air equilibrating the volume of the dispensed drops.

Methods: Although guidelines have been established for preserved multi-dose and preservative-free single dose containers, no guideline is available so far on microbial testing of preservative-free multi-dose devices. Consequently, convincing test methods need to be developed. One procedures use a very agile germ (*Pseudomonas aeruginosa*) to challenge the dosing orifice, another uses the tiny spores of *Bacillus atrophaeus* to demonstrate the whole package integrity. For the tests devices filled with broth medium were used to provide optimum growth conditions for the germs in case of any contamination.

Demonstrated outcome: no microbial contamination of bottle content or subsequent drops.

Conclusion: The OSD is a save multi-dose device for unpreserved ophthalmic formulations.

Ca Channel Blockers Effect on Visual Field in Normal and Hypertensive Primary Open Angle Glaucoma

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Purpose: The purpose of this study is to investigate the Ca channel blockers effect on visual field performance in normal and hypertensive glaucoma patients.

Methods: Clinical, observational, prospective study on 2 groups of patients:

· Group I (study group): 28 patients with normal and hypertensive POAG which have received oral therapy with nimodipinum 30mg x 2/day – 12 months

· Group II (control group): 28 patients with normal and hypertensive POAG with placebo treatment.

Both groups were homogeneous about age and sex and had not any ocular or general pathology associated.

Each patient had a complete ocular examination every 3 month including: intraocular pressure measurement, fundus examination, blood pressure and pulse rate measurements. We performed the visual field analysis and colour Doppler imaging of central retinal artery.

Results: During 12 month period the IOP averaged was 14.3 mmHg in the study group and 14.0 mmHg in the placebo group and no significant changes was seen in blood pressure or pulse rate. The estimated slope of change in the MD was less negative in nimodipinum group than in placebo group (-0.40 vs. -1.6 decibels/year).

The systolic velocity peak (PSV) in central retinal artery had a medium increase by 2.42 ± 0.18 cm/s in nimodipinum group comparing with the placebo group and the end diastolic velocity (EDV) had also ameliorated values in the same group by 0.83 ± 0.23 cm/s.

Conclusions: Vascular modulation by Ca channel blockers seems to have a positive effect on ocular perfusion associated with visual field stabilisation.

Expression Pattern of Kinin-Dependent Genes in Peripheral Blood Mononuclear Cells after Age-Related Macular Degeneration Treatment with Ranibizumab

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Background: The purpose of this study was to evaluate the effectiveness of treating neovascular AMD patients with intravitreal injections of ranibizumab (as compared to control subjects), as well as to identify differences in kinin-dependent gene expression patterns in the peripheral blood mononuclear cells (PBMCs) of these patients.

Methods: 27 eyes of 27 patients with exudative AMD were examined both before and after three months of ranibizumab injection. Total RNA was extracted from PBMCs using TRIzol reagent (Invitrogen, Carlsbad, CA). Microarray data analysis was performed with the use of GeneSpring 12.0 platform (Agilent Technologies UK Limited, South Queensferry, UK).

Results: Average visual acuity before drug administration was: 0.2048 Standard Deviation: 0.1609

After three injections mean visual acuity was: 0.3274 Standard Deviation: 0.1451 The changed expression of 11 genes was identified (t test, $p < 0.05$) by an arbitrary cut off of at least 2-fold change. The overexpression of 4 kinin-related genes (CSK, GNAS, GNB2, MAP2K2) and inhibition of 7 genes (ADCY2, ADCY3, BRAF, EGFR, GNA13, GNG13, RRAS) were demonstrated in AMD.

Conclusions: Expression changes of kinin-related genes in PBMCs of neovascular AMD patients may be associated with intravitreal ranibizumab therapy. Gene expression changes in PBMCs patients after ranibizumab treatment might indicate the potential systemic effect of therapy for AMD. The signaling pathways of kinin receptors also seem to be possible therapeutic target.

Two Patients with Optic Disc Granuloma due to Cat Scratch Disease

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Cat scratch disease (CSD) is a granulomatous disease caused by Bartonella. In eyes it can present as oculoglandular syndrome or neuroretinitis. Optic nerve granuloma is not common, mainly seen in neuro-sarcoid, TB, less in Churg Struass and other diseases.

Purpose: to present two patients with optic nerve granuloma (atypical NAION like) caused by CSD.

Methods:

Patient 1: 53 y-o healthy man, presented with visual loss in the left eye (LE). On examination Visual acuity 2 MFC, positive RAPD, regional elevation and infiltration of the optic disc, which leaked on fluorescein angiogram (FA).

Patient 2: 55 Y-O lady, complained of painless LE visual loss. H/O recent febrile illness and owns a cat. On examination: Visual acuity 2 MFC, positive RAPD and infiltrated lower nasal region of the optic disc. FA showed leakage mainly at the infiltrated region with some staining of the veins coming to the disc at that region (Granuloma with branch periphlebitis).

Each of the patients underwent extensive work up for granulomatous, autoimmune, infectious diseases and a thrombophilic panel. Bartonella Henselae IgG and IgM AB titers were elevated. Patients were treated with antibiotics and corticosteroids.

Results: Patient one showed partial response, but patient 2 who was treated primarily with corticosteroids and 2 weeks later with antibiotics did not respond. Both patients remained with a significant visual field defect.

Conclusion: In patients with visual loss and atypical optic disc swelling, one should suspect a granulomatous disease including CSD. Early antibiotic treatment followed by CS might be beneficial.

Retinal and Peripapillary Nerve Fiber Layer Thickness in Eyes with Thyroid-Associated Ophthalmopathy

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Although the orbital and histopathological structural changes associated with thyroid-associated ophthalmopathy (TAO) are well documented, no significant change in retinal and/or nerve fiber layer (RNFL) thickness has been demonstrated.

Aim: To compare retinal and peripapillary RNFL thickness values in TAO patients with those of normal subjects and to assess the correlation between the severity of the disease and the changes observed in macular and RNFL thickness.

Methods: 21 patients with TAO (mean age 44.1 years) and 41 healthy controls (mean age 42.9 years) were evaluated. The participants underwent ophthalmological and OCT examinations (including measurements of macular and RNFL thicknesses).

Results: The inner macula was significantly thinner (270.4 ± 17.27 μ m) in 40 eyes of 21 patients compared to 281.79 ± 15.2 μ m in 63 eyes of the 41 controls ($p=0.001$). The average RNFL thickness was significantly greater in the TAO group ($n=42$, 110.06 ± 33.3 μ m) compared to the controls ($n=73$, 96.25 ± 9.42 μ m) ($p=0.013$). The superior, inferior and nasal quadrant RNFL thicknesses were significantly greater in the TAO group (136.7 ± 45.73 , 137.95 ± 35.03 , and 99.38 ± 65.85 , respectively) compared to controls (118.47 ± 14.25 , 125.52 ± 13.55 , and 71.91 ± 13.95 , respectively). There was also a correlation between these changes and the clinical severity of the disease.

Conclusions: Eyes of patients with TAO have a thinner macula and a thicker peripapillary RNFL as demonstrated by OCT. There is also a correlation between the clinical severity of the disease and these changes. Retinal thinning may be secondary to mechanical compression on the retina by orbital contents. OCT may serve as a noninvasive tool for the diagnosis and follow-up of TAO.

The Novel Antioxidant SkQ1 is an Effective Protector of Lacrimal Gland from Aging and Dry Eye Syndrome Development

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One of the major causes of dry eye syndrome is lacrimal gland (LG) dysfunction. We studied the effect of Visomitin, new SkQ1-containing eye drops, upon LG of senescent rats.

We used four groups of animals: control rats – 8 and 11 months (no treatment) and rats which got eye drops with Visomitin and without it (placebo) in the period from 8- to 11 months. To reveal Visomitin effect, we compared the state of LG in all groups, taking into account morphology of acinar and ductal cells, rate of LG acinus degradation, lymphocyte infiltration and fibrosis. Using digital image analysis, we estimated the ratio between LG tissue emptiness that reflected cell death and relative squire of a total LG parenchyma. In the group of 11 month rats, the ratio was 30% higher as compared with that in 8 month animal group. In placebo it was equal with the ratio for 11 month control animals but in the Visomitin group it was close to the ratio of 8 month rats.

Our results suggest that the treatment by SkQ1-containing drops Visomitin during three months could protect rat LG from age-related degradation and keep the tissue in the state of that in younger rats. Comparable effect was found when we compared the number of inflammation focuses in LGs of animals of different groups.

Thus, Visomitin has obvious protective effect on LG tissue of aging rats and suggest its inhibiting role in the development of dry eye syndrome. This work was supported by grant from the Institute of Mitoengineering of the Moscow State University.

A New Method of Neural Retina Cultivation *in vitro* Efficient in Detection, Activation of Hidden Cell Sources for Retinal Regeneration

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To study of cell sources for regeneration of the retina and factors stimulating of them the “in vivo-like in vitro” models are needed. We applied the novel method of 3D organotypic culturing of isolated neural retina (NR) of the adult rat. The method was chosen in order to maintain of tissue long term viability and induce of cell regenerative responses. To study of obtained, cultured NR samples we applied methods of morphology, BrdU assay and immunohistochemistry. We first succeeded in collecting of viable NR spheroids and then described their cells behavior and type of tissue restoration in vitro. In NR spheroids after 10 days in vitro cells in G1, S- and M phases were observed. Among them we determined at least two cell populations different in localization and phenotypic features: retinal microglia and Müller cells. Cells capable of DNA synthesis were non-neuronal except photoreceptors actively synthesized mitochondrial DNA in their inner segments. There were not any signs of cell growth from the NR undifferentiated periphery while we registered the translocation of cell bodies between nuclear layers. Therefore, applied in vitro conditions induced cell proliferation and efforts to be inserted to NR structure. This approach seems to be an applicable new technique in study of genes and signal molecules that regulates NR cell regenerative responses. It could enable us also to study the effect of various exogeneous factors maintaining of NR cells' viability and function.

Efficient Delivery of siRNA by Atelocollagen in a Murine Laser-induced Choroidal Neovascularization Model

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Purpose: Previous studies have shown that siRNAs could suppress angiogenesis via stimulation of toll-like receptor (TLR) -3. The purpose of this study was to determine the efficacy of atelocollagen to deliver siRNA without TLR3 stimulation in the laser-induced choroidal neovascularization (CNV) model.

Methods: CNV was induced by laser injury in C57BL/6J mice, and volumes were measured 7 days later. Non-targeted siRNA, 21 nt (nucleotides) siRNA-*Luc* (Luciferase) and 21 nt siRNA-*Vegfa* were injected into the vitreous following injury. Atelocollagen was incubated with naked 21 nt siRNAs before injection. To block TLR3 endosomal activity, chloroquine was injected intravitreally after laser injury.

Results: The mean CNV volumes were significantly smaller in the naked siRNA-*Luc*, naked siRNA-*Vegfa*, or siRNA-*Vegfa* /atelocollagen complex compared with PBS, atelocollagen, or siRNA-*Luc*/atelocollagen complex-injected mice ($p < 0.05$).

Conclusion: These findings demonstrate that atelocollagen may deliver siRNA without non-specific TLR3 stimulation in the murine laser-CNV model.

Comparison of Soluble Tear Muc-16 as a Clinical Endpoint for Dry Eye Studies in Mice and in Humans

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Purpose: To compare the feasibility of soluble Muc-16 as a clinically relevant endpoint for dry eye studies in a mouse model and in human dry eye and normal subjects.

Methods: Mice were subjected to Ora's optimized dry eye model for 13 days and compared to controls. Corneal staining was assessed on days 0, 4, 8, and 12 using a modified Micron III imaging system. Tear washes were analyzed for soluble Muc-16 by ELISA. Human tears from 8 normal and 26 dry eye subjects were analyzed for soluble MUC-16 using a similar ELISA. Additional measures for human subjects included Schirmer's, corneal staining, and tear film breakup time (TFBUT).

Results: Corneal staining was significantly increased ($p < 0.0001$) in dry eye challenged mice compared to controls by day 4 of the challenge and remained elevated throughout the entire study. Tear wash analysis at the conclusion of the challenge revealed a significant increase ($p < 0.0001$) of soluble Muc-16 in challenged mice compared to controls. There was also a significant correlation ($p = 0.0051$, $r^2 = 0.361$) between the final corneal staining score and Muc-16 levels. In the human subjects, there was a statistically significant inverse correlation between Muc-16 and Schirmer's and TFBUT for all subjects. Total staining, corneal staining, and conjunctival staining showed statistically significant positive correlations with Muc-16.

Conclusion: Preclinical work confirms that increases in soluble Muc-16 are conserved between the mouse dry eye model and the human clinical condition. Increased soluble Muc-16 values are positively correlated with dry eye symptomatology.

Focal/Grid Photocoagulation versus Bevacizumab Plus Laser for Diabetic Macular Edema (DME): a Randomized Trial

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Purpose: to compare 9-month outcomes of patients receiving either focal/grid photocoagulation or bevacizumab + laser for diffuse DME.

Methods: 51 eyes with DME involving the fovea and visual acuity (VA) 20/32 to 20/320 randomly received focal/grid photocoagulation (n= 29) or bevacizumab + laser (n=22).

Results: VA worsened by -5.12 ± 12.23 letters in the photocoagulation-alone group ($p=0.46$) and improved by $+7.8 \pm 1.6$ letters in the bevacizumab group ($p=0.05$). Mean central foveal thickness (CFT) decreased in both, the laser group, by 22.7 ± 94.52 ($p=0.09$) and the bevacizumab group, by 65.68 ± 73.25 μm ($p=0.08$).

Conclusions: bevacizumab + laser was significantly better to improve VA at 9 months than laser alone.

Intravitreal Injection of Transferrin Preserves Photoreceptors from Light-Induced Degeneration

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Age-Related Macular Degeneration is associated with iron accumulation in RPE and photoreceptors. We have demonstrated that light exposure induced an early mobilization of proteins regulating iron metabolism in the retina. We have also showed that transferrin (Tf), either intraperitoneally injected or genetically produced, protects photoreceptors against death due to genetic mutations. Here, we analyze the effect of Tf on a model of light-induced photoreceptors degeneration. Retinal degeneration was induced in rats by white light (10, 000 lux) for 24 hours, followed by one week of cyclic light. To test the effects of Tf, apo human Tf (hTf) was intravitreally injected at 4 concentrations prior to illumination. Then, eyes were fixed and sections of their retinas were analyzed to measure outer nuclear layer thickness and to stain iron. Levels of hTf were evaluated by ELISA in retinal tissues at different times after injection. The level of hTf in retina and eye cup is high at 6 hours, decreases at 24 hours, comparatively, in vitreous and aqueous humor, hTf increases between 6 and 24 hours. Intravitreally injected hTf has no toxic effect on retina. hTf protects the retina (especially photoreceptors) against the deleterious effects of light and decreases iron accumulation. Preservation of photoreceptors layer thickness is proportional to the amount of hTf delivered. hTf directly injected into the eye has a potent protective effect on photoreceptors degeneration induced by intense light. This result could be due to the iron chelating effect of Tf.

Giant Pituitary Adenoma – Mislead Diagnosis with Advanced Normal Tension Glaucoma

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This is the case of a 68 years old male patient, HG.

The patient was referred to our clinic as an advanced glaucoma patient, both eyes, for surgery.

He was examined in March 2007 and he was diagnosed with Normal Tension Glaucoma and put under treatment with PGA oid.

At the moment of the diagnosis: OD IOP=16mmHg, OS IOP=15 mmHg.

The patient was declared incompetent for performing automated perimetry, so he was referred to Goldmann perimetry.

He had 5 visual field exams over a period of 5 years, during which the treatment was gradually increased to maximal topical therapy, but the patient still developed a severe deterioration of the visual acuity, visual field and of the ocular fundus aspect.

During the hospitalization we performed automated perimetry that showed hemianopsia. The patient was referred for cerebral MR and diagnosed with giant pituitary adenoma. The patient had surgery, but he continued to lose visual acuity and optic atrophy installed both eyes.

In conclusion, every time when we deal with a patient suspected of having Normal Tension Glaucoma we have to exclude other causes, otherwise we can lose precious time and the patient can lose precious vision. Normal Tension Glaucoma should remain an exclusion diagnosis.

Outcomes of Combination Treatments in Refractory Neovascular Glaucoma. A retrospective Review in Patients with Advanced Proliferative Diabetic Retinopathy (PDR)

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Introduction: Neovascular Glaucoma (NVG) often appears as a refractory condition that is not well controlled by any medical treatment in advanced PDR. The purpose of this work is to review the outcomes of different treatment modalities in patients with PDR and NVG.

Material and Methods: Retrospective, interventional, consecutive case series of 17 eyes with refractory NVG secondary to uncontrolled PDR diagnosed between 2008 and 2011. Patients with a minimum follow up period of six months were included and divided into two treatment subgroups: Patients in group I went under medical treatment, panretinophotocoagulation (PRP) with or without bevacizumab and patients in group II were managed by PRP, bevacizumab and Ahmed valve. Treatment outcomes were compared and classified as success or failure according to specific criteria.

Results: 17 eyes with refractory NVG secondary to uncontrolled PRP were included. 10 in group I and 7 in group II. There were no differences in age, sex or initial IOP. The mean reduction in IOP in group I was 14.8 mmHg while in group II was 30 mmHg, with an interval between 10 and 47 mmHg. At six months 79.6% of the eyes in group I and only 46.5% in group II ($p<0.05$) needed concomitant hypotensive treatment. No differences in visual outcomes or complications during the follow up period were detected.

Conclusion: The implantation of Ahmed devices provides an effective reduction of IOP even in severe refractive secondary glaucoma; however, further studies with long term follow up are necessary.

Safety, Tolerability and Efficacy of Topical Delivery of a Recombinant Human Growth Hormone (rHGH) in a Corneal Debridement Model

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Background: Persistent corneal defects are difficult to treat, resource intense, often require surgery, and can result in blindness. rHGH is a well accepted protein known to accelerate growth and healing. A standardized corneal debridement model (CDM) was used to test the safety and efficacy of topical rHGH 4x/day. rHGH was selected based on its ability to up regulate and modulate growth factors, i.e. insulin growth factor and epidermal growth factor, that have been shown to be involved in corneal re epithelization.

Methods: A standard CDM was created in 9 New Zealand White rabbits. All 18 eyes received 50 µl drop of dexamethasone (dex) postoperatively QID for 5 days. Dex alone vs Dex & balances salt solution (BSS) vs topical rHGH (100ug/ml) (50 µl) was evaluated. Safety and tolerability were assessed daily. Twice daily slit lamp exams with photos were employed to measure time to complete healing and daily percent healing across all arms. Histopathology was evaluated.

Results: Topical rHGH was well tolerated. Histopathology was normal with no inflammation or angiogenesis. Although a small n, in eyes receiving the topical rHGH an efficacy trend was seen with a faster corneal healing rate as early as Day 3. On Day 4, 100 % of eyes with Dex/rHGH were completely healed vs 40 % of Dex/BSS vs 0% of the dex alone.

Conclusions: Topical rHGH was well tolerated with an efficacy signal for faster corneal wound healing in a CDM. rHGH should be explored as a treatment for corneal defects with impaired healing.

Successful treatment of Recurrent Conjunctival Papillomatosis by using Topical Interferon Alfa-2b Eye Drop Solution

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Background: An off label use of Interferon alpha-2b (IFN-α2b) injection, as IFN-α2b eye drop solution has recently been shown to be successful in conjunctival papillomas and conjunctival intraepithelial neoplasia (CIN). Generally, the lesions are treated by surgical excision and/or cryotherapy. Interferon usually is not considered effective in treating large tumors without surgery. The aim of this paper is to report a case of conjunctival squamous cell papilloma successful treatment in topical using IFN- α2b eye drop solution as hospital preparation.

Case: A 45 year-old male presented with multiple cauliflower like tumors on his right conjunctiva. He underwent excision of conjunctival tumor 4 years previously.

The patient was instilled eye drop solution including the INF-α2b five million units per one drop, dosage is four times a day every 6 hours, and eye drops therapy was followed at 2-week intervals. Biopsy revealed squamous cell papilloma. The lesions had significantly decreased in size 7 months after treatment initiation. The tumors have not recurred 6 months after excision quitting IFN-α2b eye drops. No systemic or local treatment side effects developed.

Conclusions: Instillation of IFN-α2b is effective for treating conjunctival squamous cell papilloma as neoadjuvant therapy.

Ophthalmic Manifestations of Prothrombin G20210A Mutation

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Introduction: The G20210A mutation in the prothrombin gene is an established risk factor for venous thrombosis. There is a controversy of the role of this mutation in arterial thrombotic disease. The association of peripheral capillary non-perfusion with prothrombin G20210A mutation has never been reported before.

Case Report: We present the case of 34-year-old man who presented with a peripheral capillary non-perfusion. The fundus examination of his RE revealed an epiretinal membrane, peripheral (mainly temporally) retinal hemorrhages, exudates and microaneurismal alterations of the vascular bed. Fluorescein angiography demonstrated an extended area of capillary non-perfusion distal to the microaneurismal lesions. Evaluation revealed a mutation of the 20210G/A prothrombin gene and MTHFR mutation.

Conclusion: Screening for hereditary thrombophilia should be considered, regardless to patient age, in patients with peripheral retinal ischemia. The prothrombin G20210A mutation, a genetic risk factor, may be associated with peripheral capillary non-perfusion.

Predictive Factors for Visual Outcomes after Intravitreal Bevacizumab for Diabetic Macular Edema: a Spectral Domain Optical Coherence Tomography Study

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Background: The purpose of this study is to identify optical coherence tomography features predictive of visual outcomes after IVB treatment. **Methods:** This retrospective chart review included patients affected by DME and treated with IVB (1 mg/ 0.04 mL) based on fluorescein angiography (FA), clinical appearance and spectral domain optical coherence tomography (SD-OCT). Patients received an injection at baseline and were then followed-up for 12 months. Re-treatment was performed at investigator discretion. The primary outcome was change in best corrected visual acuity (BCVA, logMAR). Secondary outcomes include central retinal thickness (CRT) and the number of injections. Correlation between SD-OCT appearance and final visual outcomes was statistically analyzed. **Results:** The study included 55 consecutive eyes of 43 patients. Data from a 12-month follow-up are available for all patients. Mean BCVA (logMAR ± SD) improved by -0.03 ±0.19 logMAR at the end of follow-up. Retinal thickness (µm ±SD) decreased on average by 67.3 ±160 µm at 12 months. During the follow-up, patients received 3.2 injections, on average. A significant correlation was found between final BCVA and baseline BCVA (r = 0.807, p<0.01). Final BCVA was influenced by macular volume (r = 0.13, p<0.05), presence of cystoid macular edema (r = 0.14, p<0.05), epiretinal membrane (r = 0.19, p<0.05), disruption of photoreceptor IS/OS junction (r = 0.15, p<0.05). **Conclusions:** Intravitreal bevacizumab is an effective therapy for the treatment of DME. Baseline BCVA and SD-OCT appearance may be helpful in predicting the final visual outcome.

Protective Effects of Agmatine on Lipopolysaccharide-Injured Microglia

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Background: Activated microglia are one of the main causes of neuroinflammation. In this investigation, we evaluated whether agmatine reduces lipopolysaccharide (LPS)-induced microglial damage in vitro and in vivo.

Methods: For in vitro study, BV2 cell line was exposed to LPS in the presence of agmatine. The cell viability and nitrite production were determined. For in vivo study, agmatine was intraperitoneally administered and LPS was microinjected into the corpus callosum of adult ICR mice. Brain tissue was evaluated by immunohistochemistry for microglial marker of ionized calcium binding adaptor molecule 1 (Iba1) and inducible nitric oxide synthase (iNOS).

Results: Agmatine significantly reduced the LPS-induced BV2 microglial cytotoxicity and nitrite production (both, $p < 0.001$). It also decreased the activities of microglia and iNOS induced by LPS microinjection into corpus callosum.

Conclusion: Our findings reveal that agmatine attenuates LPS-induced microglial damage and suggest that agmatine may serve as a novel therapeutic strategy for neuroinflammatory diseases.

Effects of Rho-Kinase Inhibitor (Y-27632) on Extraocular Muscle Surgery in Rabbits

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Purpose: This study was performed to evaluate the usefulness of Rho-kinase inhibitor (Y-27632) on the postoperative inflammation and adhesion after extraocular muscle (EOM) surgery in rabbits

Methods: Both eyes of ten rabbits underwent reinsertion of the superior rectus muscle (SRM). After reinsertion of SRM, the right eye of each rabbit received a subconjunctival Rho-kinase inhibitor injection. As controls, normal saline was injected subconjunctivally in the left eye. To assess acute and late inflammatory changes in SRM using an Ki-67 antibody, anti-CD11 β + antibody, F4/80 antibody at postoperative 3 day and 4 weeks respectively. At 4 weeks, the sites of muscle reattachment were evaluated grossly for postoperative adhesion score and histopathologically for collagen formation.

Results: The Ki-67 antibody, anti-CD11 β + antibody expression was not statistically different in Rho-kinase inhibitor group compared to the control group at postoperative 3 days and 4 weeks. But F4/80 antibody expression was statistically different in Rho-kinase inhibitor group at both 3 day and 4 weeks ($p = 0.038, 0.031$). The differences in adhesion score of SRM/conjunctiva between the two groups was statistically significant ($p = 0.070$). But adhesion score of SRM/sclera between the two groups was not statistically significant ($p = 0.178$) at 4 weeks after surgery. In microscopic findings, the stain of collagen in Masson trichrome stain at postoperative 4 weeks was diminished in the Rho-kinase inhibitor group.

Conclusion: Intraoperative Rho-kinase inhibitor subconjunctival injection may be considered to be secure and effective as an adjunctive management to decrease inflammation and fibrosis after EOM surgery.

Serum Vascular Endothelial Growth Factor and Ischemia Modified Albumin Levels after Unilateral and Bilateral Intravitreal Bevacizumab Injections

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Background: Previous reports have demonstrated that the serum levels of vascular endothelial growth factor (VEGF) are reduced after intravitreal injections of bevacizumab. This study aimed to determine the serum levels of VEGF and ischemia modified albumin (IMA), a marker of ischemia, following unilateral versus simultaneous bilateral intravitreal injections of bevacizumab.

Methods: This was a prospective controlled study. Blood samples were drawn prior to injection and at 1, 7 and 30 days after injection.

Results: A total of 11 patients participated in this study: 8 in the unilateral subgroup and 3 in the bilateral subgroup. Overall, mean serum VEGF levels were lower than baseline throughout the follow-up period (from 307.45 ± 273.45 pg/ml at baseline to 159.55 ± 120.68 pg/ml at Day 30), however there was no significant difference between the two subgroups. Mean serum IMA levels were also lower than baseline during follow-up, but measurements varied significantly between the subgroups.

Conclusions: In this study, both serum VEGF and IMA levels were lower after intravitreal bevacizumab. There was a small yet significant difference in IMA levels between the unilateral and bilateral groups, whose clinical consequence is unclear. The study's limitations and its small size warrant further investigation.

Efficacy of Bevacizumab for Macular Edema following Branch Retinal Vein Occlusion Stratified by Baseline Visual Acuity

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Backgrounds: To investigate efficacy of intravitreal bevacizumab in patients with macular edema following branch retinal vein occlusion (BRVO) stratified by baseline best corrected visual acuity (BCVA).

Methods: One hundred ten eyes of 109 patients treated by intravitreal bevacizumab due to macular edema following BRVO were retrospectively studied. All patients had minimum follow-up period of 6 months. The patients were stratified by baseline BCVA (group I: 17 eyes, $<20/200$, group II: 62 eyes, $20/200-20/40$, group III: 30 eyes, $<20/40$). Reinjections were performed if recurrent macular edema was diagnosed. Changes in BCVA, central macular thickness (CMT), and number of injections were noted.

Results: Mean change from baseline BCVA at 6 month was significantly improved in all three groups. The percentage of patients who gained three lines or more in BCVA at 6 month was 88.2% (15 eyes) in group I, 71.0% (44 eyes) in group II, and 6.7% (2 eyes) in group III ($p < 0.000$ for group I or group II vs group III). There was no difference among three groups in mean change of CMT at 6 month and number of injections.

Conclusions: Intravitreal bevacizumab can be effective treatment for macular edema following BRVO irrespective of baseline BVCA although patients with fair baseline visual acuity shows slightly limited visual improvement after treatment.

A Novel Presentation of Zoster Ophthalmicus, HHV 3 (VZV)

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Background: The Human HerpesVirus family (HHV 1- 8) include viruses that may cause very serious diseases to human beings.

Methods: This is a case study of a patient with Zoster Ophthalmicus that shows novel features that, to the best of my knowledge, have not been described before.

Seventy five year old immuno-competent female suffered left Zoster Ophthalmicus. She received systemic anti-herpes treatment only after 2-3 weeks from presentation because initially she just had mild blepharitis and stromal keratitis that responded to topical treatment. A few weeks later she developed painless upper eyelid ptosis and ocular motility abnormalities. In her most up date follow up visit the patient real concern was the hallmark symptom of myasthenia "fatigability= worsening as the day wears off".

Results: This is a case of left Zoster Ophthalmicus. It was very unusual to see this disease causing the above eyelid and ocular motility signs in the left eye of this patient. This is a case of ocular myasthenia following Zoster Ophthalmicus.

Conclusion: Zoster Ophthalmicus (HHV 3) is known to cause various ocular inflammations. It is very well known that virus diseases are common triggers of auto-immune reactions and diseases. Viruses are obligatory intracellular parasites that are capable of inducing genetic changes that lead to synthesis of different (foreign) protein. This foreign protein acts as an antigen that triggers auto-immune response.

Madarosis as Sinusitis Complication and the Medical Treatment

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Eyelids are cutaneous-musculous-membranous formations that cover and protect the eye. On the cusp of each cap are placed Eyelashes with protective and aesthetical function. This study presents the case of a child with a skin disease, unilateral madarosis on the upper lid, with paranasal sinusitis and medical treatment.

The Purpose of the Study: The purpose of this study is to present Sinusitis as cause of Madarosis, and its medical therapeutic treatment and paranasal sinusitis.

Material and Methods: The patient visited pediatrician, and all the laboratory tests had normal values the EEG test results were in physiological boundaries. After 5 – 6 months the problems were repeated and the eyelashes of the right eye upper lid had dropped. The patient was brought to the Ophthalmologist, undergoing the fundus examination, conjunctival swab for fungus but, the results returned negative. Patient was referred to otorhinolaryngologist, undergoing a series of examinations, including paranasal cavity Roentgen. The patient suffered from Paranasal Sinusitis.

Patient is treated with Valeclor sir.250 mg/5ml, for two weeks in parenteral way and inhalation. The eyelids were treated with: Sol. Dexa – Gentamycin for two weeks and Ung. Dexa - Gentamycin for 2 months once a day. After two months the eyelashes begun to emerge.

Results and Conclusions: During treatment no complications appeared and the Eye pressure was normal. Here we conclude that Madarosis can occur as a complication of paranasal sinusitis or other lid skin manifests like redness, edema and itching.

Key Words: Madarosis, paranasal sinusitis, treatment.

Dexamethasone Intravitreal Implant for Persistent Diabetic Macular Edema in Vitrectomized Eyes

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Purpose: To evaluate the effects of intravitreal dexamethasone implant in vitrectomized eyes with persistent diabetic macular edema (DME).

Patients-Methods: We present 3 cases with persistent DME after vitreoretinal surgery for rhegmatogenous retinal detachment. Main outcome measures included changes in best-corrected visual acuity (BCVA) and cube average thickness (CAT).

Results: All patients had undergone previous treatments for DME (laser photocoagulation and/or intravitreal injection of anti-VEGF). One of the three patients presented retinal detachment after the fourth anti- VEGF injection and following that he underwent vitrectomy. At baseline the BCVA was 1/10, CF and 1/10 and the CAT 613µm, 426µm and 341µm respectively. Best corrected visual acuity was improved to 2-3/10, 1/20 and 2/10 and the mean CAT to 294µm, 365µm and 299µm respectively on the first month and after 2,3 and 4 months. Two patients needed retreatment within six months. One of them developed increased intraocular pressure, successfully managed with topical IOP-lowering medications.

Conclusion: Dexamethasone intravitreal implant might be an effective treatment option in persistent DME in vitrectomized eyes.

Pilot Study of Bromfenac 0.09% and Difluprednate 0.05% on Macular Volumes and Retinal Thickness after Uncomplicated Cataract Surgery

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Purpose: To investigate whether topical bromfenac 0.09% qd with difluprednate 0.05% is efficacious in controlling retinal thicknesses and macular volumes after uncomplicated cataract surgery in the initial postoperative period.

Methods: Randomized, prospective investigator masked pilot study of 6 patients with SDOCT measured preoperatively, pod1, pod7, and pod 42. Patients were given bromfenac 0.09% qd 3 days prior to surgery and bromfenac 0.09% qd with difluprednate 0.05% qd for 21 days following cataract surgery.

Results: Mean central subfield thicknesses (micrometers), cube volume (mm cubed) and cube average thicknesses(micrometers) measurements were 260.8, 9.85 and 275.2 at baseline, 259.8, 9.75 and 272.8 at pod 1, 266.3, 9.88, and 277.2 at pod 7 and 272.8, 10.25 and 287 and pod 42.

Conclusions: Bromfenac/difluprednate qd is an efficacious perioperative treatment. Central subfield thickness showed a strong trend for reduction compared to baseline at pod 1, 7 and 42. Cube average thickness showed a weak trend towards reduction at week 6 only. Further study is warranted to determine ideal dosing and how this regimen may compare to other perioperative regimens.

Clinical Characteristics of Choroidal Neovascularization of Younger Patients in Taiwan

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Purpose: Sharing experience of diagnosing and treating CNV of young patients (age ≤ 50 years) in our hospital.

Methods: Retrospective chart review of patients of CNV from January 2007 to August 2012 in Shin Kong Wu Ho-Su Memorial hospital was done. Best corrected visual acuity (BCVA) by snellen charts and Early Treatment Diabetic Retinopathy Study (ETDRS) charts were recorded. If patients received anti-vascular endothelial growth factor treatment, the following data were recorded: total numbers of injections, types of drugs, preoperative and final BCVA, ETDRS, central retinal thickness, and total follow-up time. Two-tailed paired t tests were used to compare mean changes in BCVA and central retinal thickness on OCT.

Results: 63 eyes of 55 patients under 50 years diagnosed as CNV were enrolled. Mean age was 36.8 ± 10.0 years. 18 patients were male and 36 patients were female. 41 CNV lesions were subfoveal, and 22 were juxtafoveal. Mean total follow-up time was 18.5 ± 19.9 months. Mean total number of injection was 1.9 ± 1.6 . Pathologic myopia is the most commonly seen CNV in young patients in our hospital (50.8%), followed by ICNV (15.9%), IPCV (15.9%), PIC (11.1%), chronic CSCR (3.2%), and angiod streaks (3.2%).

Conclusion: We reviewed 63 eyes of CNV in younger patients. We described common etiologies and responsiveness to anti-VEGF treatment in this group. Understanding the common etiologies of CNV and different prevalence comparing to western countries may help to early diagnose CNV-related problems and avoid further morbidity in younger patients.

Acuvue Oasys for Astigmatism Contact Lenses for the Correction of Residual Ametropia Following Intacs Implantation in Keratoconus

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Purpose: To evaluate the performance of Acuvue Oasys for Astigmatism (Johnson & Johnson Inc, USA) contact lenses in the correction of residual ametropia following INTACS implantation in keratoconus.

Methods: This retrospective study comprised all patients with keratoconus and contact lens intolerance who had INTACS implantation (with or without collagen crosslinking, CXL) and were fit with Acuvue Oasys for Astigmatism lenses to correct the residual ametropia.

Results: Six eyes of 4 patients were fit with the Acuvue Oasys for astigmatism contact lenses. Two patients were fit 1- and 3-years after INTACS implantation, and 2 patients were fit 3- and 6-months after INTACS implantation and CXL. The period of time between CXL and INTACS implantation in these eyes were 9- and 10-months. In all patient eyes excellent centration and movement could be attained with the contact lenses. All patient eyes could be fit with one trial lens and perfect orientation was accomplished with no rotation more than 5 degrees at 5 minutes following CL fit. The mean UDVA increased from 0.44 ± 0.29 LogMAR to 0.13 ± 0.10 LogMAR following contact lens wear. All patients continued to wear their contact lenses 10 to 12 hours/day and graded comfort with their contact lenses as "excellent" at the last follow-up examination. No unwanted side effect was observed.

Conclusion: Acuvue Oasys for Astigmatism contact lenses are easy to fit, increase visual acuity effectively and can provide day-long comfort when used for residual ametropia correction following INTACS implantation (with or without CXL) in keratoconus.

Corneal Collagen Crosslinking Following Intrastromal Corneal Ring Segment Implantation for Keratoconus: One Year Follow-Up Results

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Purpose: To evaluate the safety and efficacy of riboflavin and UVA supported corneal collagen crosslinking (CXL) following INTACS implantation.

Methods: Nine eyes of six patients followed with the diagnosis of progressive keratoconus were included in this prospective study. Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction, slit-lamp examination, corneal topography, central corneal thickness (CCT) with ultrasound pachymeter and endothelial cell count with confocal microscopy were evaluated before and after INTACS implantation and at 1, 3, 6 and 12 months after CXL treatment.

Results: The mean age of patients was 24.2 ± 2.3 years. After INTACS implantation, the mean improvements in UDVA and CDVA were 3, and 1 Snellen line, respectively. The mean manifest refraction spherical equivalent decreased 4.6 D and the mean keratometry readings were flattened by 2.8 D ($p=0.04$). The mean time between CXL and INTACS implantation was 5.6 ± 3.5 months. At postoperative 12 month follow-up UDVA, CDVA, MRSE, mean keratometry readings and endothelial cell counts were stable ($p>0.05$). Postoperative CCT decreased during the first 3 months ($p=0.04$) but then increased significantly ($p=0.01$); at the last follow-up examination the CCT was close to the preoperative values.

Conclusion: In progressive keratoconus patients with contact lens intolerance, CXL following INTACS implantation seems to be safe and effective at 1 year follow-up.

Three-Year Follow-Up of Intacs in Keratoconus

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Purpose: To evaluate the long-term safety and efficacy of INTACS implantation in the management of keratoconic eyes with contact lens intolerance.

Methods: Seventeen eyes of 12 contact lens intolerant keratoconus patients who had INTACS implantation were included this prospective study. Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction spherical equivalent, slitlamp examination, keratometry, contrast sensitivity, corneal topography and corneal thickness measurement were performed before INTACS implantation and 1 day, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years and 3 years postoperatively. Follow-up was 3 years.

Results: The mean age was 32.3 ± 5.2 years. The mean UDVA was 0.84 ± 0.40 LogMAR before INTACS implantation and 0.41 ± 0.33 LogMAR at the end of the third year. The mean preoperative CDVA was 0.17 ± 0.18 LogMAR and improved to 0.12 ± 0.22 LogMAR at the end of the third year. The mean manifest refraction spherical equivalent decreased from -5.60 ± 3.20 D to -2.8 ± 2.7 D at first month and remained stable thereafter. Astigmatism decreased from -4.8 ± 2.7 D to -2.8 ± 2.6 D at the first month and remained stable thereafter. The mean keratometry decreased from 48.8 ± 5.30 D to 46.8 ± 4.20 D. The mean mesopic contrast sensitivity significantly increased at medium spatial frequencies.

Conclusion: At three years, INTACS implantation in keratoconus significantly improved vision and decreased the refractive error and keratometric values. INTACS seems to be safe and effective in the management of keratoconus patients with contact lens intolerance.

Pre-Operative Use of 0.05% Cyclosporine in Cases of Drug Induced Conjunctivitis in Glaucoma Patients

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Background: Prolonged use of hypotensive eye drops contributes to the formation of chronic irritation of the conjunctiva.

Purpose: Optimization for treatment of the patients with glaucoma and chronic irritation in pre-operative period.

Methods: 6 patients with glaucoma and chronic irritation of the conjunctiva were followed. Each of them was receiving two types of hypotensive eye drops (0.5% timolol, 0.005% latanoprost, 0.1% brinzolamide, etc.). For all patients the surgical treatment was administered, but was cancelled due to chronic irritation. For relief of the symptoms patients were periodically receiving anti-allergic and 0.01% self-prepared Dexamethasone eye drops. The usage of these drugs had been caused by the necessity of patients' comfort and led to certain IOP increase and dry eye symptoms. For purpose of replacing the corticosteroid therapy the 0.05% Cyclosporine (Restasis®) was administered twice a day.

Results: After 2 months of such therapy a sustained relief of chronic irritation of the conjunctiva in all patients was achieved. In 3 cases patients were able to maintain the low IOP only with the usage of only one hypotensive drug instead of 2 drugs which patients were receiving before. In two month all of the patients underwent scheduled glaucoma surgery.

Conclusions: The preliminary study supports the hypothesis that it is effective to use 0.05% Cyclosporine for treatment in cases of scheduled glaucoma surgery to avoid extra inflammatory factor contributing to poor surgery effect and patients discomfort.

Central Retinal Thickness Changes and Visual Outcome Following Uncomplicated Phacoemulsification Cataract Surgery in Diabetic Patients without Retinopathy and Normal Controls

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Background: Diabetic retinopathy is a risk factor for pseudophakic cystoid macular edema (PCME). However, the visual outcome and changes of central retinal thickness (CRT) in diabetic patients without retinopathy were not so definite. We compared the visual outcome and CRT changes after surgery in diabetic patient without retinopathy and normal controls. The relationship to HbA1c was also evaluated.

Methods: Patients underwent uncomplicated phacoemulsification cataract surgeries were enrolled during May 2009 to February 2012. CRT and Best-corrected visual acuity (BCVA) were obtained preoperatively, in week one, two, four, and eight.

Results: 101 eyes in control group and 58 eyes in diabetic group were enrolled. Increase in CRT was observed in week two ($p=0.038$), four ($p<0.001$), and eight ($p<0.001$) in control group as well as in DM group in week four ($p<0.001$), and eight ($p=0.005$). The percentage changes in CRT were different between both groups in week four ($p=0.043$), but the difference vanished in week eight ($p=0.152$). There was no difference in BCVA in all time periods. Besides, the CRT changes and visual outcome were not related to HbA1c level.

Conclusions: The final visual outcome in diabetic patient without retinopathy is as good as in controls. Significant increase in CRT postoperatively is noticed in both groups, but the diabetic eyes seemed to be more prominent and have delayed recovery in CRT change. Besides, the visual outcome and changes in CRT were not related to the level of HbA1c. Therefore, diabetes mellitus alone without retinopathy may not be a poor prognostic factor for post-cataract surgery visual recovery and PCME.

Functional and Structural Recovery after Intravitreal Anti-VEGF Antibody Treatment for Idiopathic Choroidal Neovascularization in Taiwan

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Purpose: To evaluate the functional and structural recovery of the retina after treatment of idiopathic choroidal neovascularization (CNV) using intravitreal injections of anti-VEGF antibody in Taiwan.

Methods: Retrospective charts review of nine eyes of eight patients with idiopathic CNV was done during March 2006 to August 2012 in Taiwan. All the patients received complete ophthalmologic examinations, including optical coherence tomography (OCT) and fluorescein angiography (FA). All the eyes were treated with intravitreal injections of anti-VEGF antibody (Bevacizumab for 2.5mg/0.1ml or Ranibizumab for 0.5mg/0.05ml). The post-operative visual acuity, OCT, and FA were obtained to evaluate the functional and structural recovery of the retina after treatment.

Results: The mean age was 34.22 ± 7.9 years. The majority of CNV located at subfoveal area (89%). Besides, the all the CNV were classic type. Mean numbers of injection was 1.8 ± 0.46 injections for each eye in our study with 67% single injection. After IVI of anti-VEGF antibody, there was statistically significant improvement in BCVA (Initial BCVA in Log MAR = 0.64 ± 0.57 , final BCVA in Log MAR = 0.12 ± 0.33 , $p=0.004$). Besides, the initial central retinal thickness (CRT) was $272.89 \pm 44.50 \mu\text{m}$ improved to $209.22 \pm 23.53 \mu\text{m}$ in the end of follow-up ($p=0.003$).

Conclusions: The intravitreal injection of anti-VEGF antibody is effective for stabilizing or improving vision in patients with idiopathic CNV. Besides, compared to CNV caused by other etiologies especially the age-related macular degeneration, idiopathic CNV required fewer injections and relatively long-term stabilization.

Evaluation of Topical SKQ1 in a Murine CAE™ Model of Dry Eye Disease

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Purpose: SKQ1 (Visomitin) is a novel mitochondrial-targeted anti-inflammatory drug in development. The goal of this study was to test a topical formulation of SKQ1 as a treatment for dry eye.

Methods: The study employed a murine model of dry eye disease that combines environmental (CAE™) and pharmacologic induction of pathologic signs of disease. SKQ1 (255ng/mL) was dosed topically either once (QD), twice (BID), or four times (QID) daily for a total of 14 days ($n=8-10$ per arm). The vehicle control arm was dosed BID throughout the study. Fluorescein staining evaluations were performed using Ora's novel Micron III imaging system at various time points throughout the study. Corneal images were evaluated using Ora's proprietary clinical scale.

Results: SKQ1 significantly reduced corneal staining for the QD and BID doses compared to vehicle alone. QD administration of SKQ1 was statistically lower than vehicle at the Day 4 evaluations ($p<0.01$), whereas the BID regimen significantly reduced staining after Days 4 and 12 ($p<0.01$ and $p<0.05$, respectively). QID dosing of SKQ1 displayed a similar trend of reduced staining, but the observed reduction was not statistically lower than vehicle.

Conclusions: SKQ1 significantly reduces corneal staining in this mouse model of dry eye. QD dosing appears to reduce overall corneal staining early in the model, but cannot overcome the disease as it progresses. BID dosing reduces overall corneal staining compared to vehicle throughout the study. These data provide support for SKQ1 as a potential therapy for dry eye disease.

Expression of Efflux Transporters in Human Ocular Tissues

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Background: Some efflux transporters have been discovered in ocular tissues, but knowledge about these is limited, and some data are not in agreement.

Methods: Quantitative RT-PCR, western blotting, and immunohistochemistry were used to obtain the relative mRNA and protein expression profiles of various efflux transporters in human ocular tissues. Cornea, conjunctiva, iris-ciliary body, retina-choroid, human corneal endothelial cell line (HCEC), and human retinal pigment epithelial cell line (ARPE-19) were examined for the expression of multidrug resistance-associated protein 1-7, multidrug resistance protein 1, lung resistance protein, and breast cancer-resistance protein.

Results: There are great differences in the expression profiles of efflux transporters in mRNA and protein levels in ocular tissues, and the expression patterns of HCEC and ARPE-19 appear to be widely different from those of the native ocular tissues. There are also great differences in the expression sites of efflux transporters in ocular tissues, HCEC, and ARPE-19.

Conclusion: This is the first quantitative study on efflux transporters in normal ocular tissues and cell lines, and this study offers a more complete profiling of efflux transporter expression in human ocular tissues. The evidence of cross-ocular tissue transporter expression differences noted in this study supports the conclusion that efflux transporter expression variability should be taken into consideration to better understand ocular pharmacokinetic and pharmacodynamic data. This work also sheds light on the potential limitations of HCECs and ARPE-19 in predicting the corneal and retinal permeability of ophthalmic drugs and transporter substrates.

Diquafosol Tetrasodium Increases the Concentration of Mucin-Like Substances in Tears of Normal Human Subjects

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Purpose: The aim of the study is to determine the effect of topical application of diquafosol tetrasodium on the tear proteins including mucin-like substances in tears of a group of clinically normal subjects.

Methods: Tears were collected from both eyes of 10 normal volunteers. Diquafosol sodium solution 3% was applied once in the right eye and sodium chloride solution 0.9% (saline) in the left eye. Tears were collected by Schirmer test strips before the application and 5 min, 15 min, 30 min and 60 min after the application, respectively. The major tear proteins including secretory IgA, lactoferrin, lipocalin-1, lysozyme, and sialic acid were measured by the high performance liquid chromatography assay.

Results: Concentrations of total protein and some major tear proteins decreased at 5 min in both groups, and returned to the baseline levels. Concentration of sialic acid, a marker for monitoring mucin-like substances in tears, significantly decreased at 5 min after saline application, whereas significantly increased at 5 min after diquafosol application. No significant differences in sialic acid concentrations were seen after 15 min in both groups.

Conclusions: A single application of saline and diquafosol resulted in transient decrease of tear proteins possibly due to the wash out and dilutional effects. In contrast, a significant increase of sialic acid in tears was seen after diquafosol application. Although the effect of diquafosol on sialic acid concentration in tears is transient, our results suggest that diquafosol stimulates the secretion of mucins from ocular tissues of normal human subjects.

A Human Corneal Epithelium and Acellular Stroma Model Utilizing a Collagen Vitrigel Membrane and its Application to Drug Permeability Test

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Purpose: Drug permeability test is indispensable for development of ophthalmic drugs. The test has been performed by *in vivo* examinations using living rabbits. However, it is difficult to extrapolate permeability of human cornea due to species differences between human beings and rabbits. Meanwhile, a collagen vitrigel membrane (CVM) chamber we recently developed is a three-dimensional culture tool possessing a scaffold composed of high density collagen fibrils equivalent to connective tissues *in vivo*. In this study, we developed a human corneal model including epithelium and acellular stroma in the chamber using a CVM equal in thickness to human corneal stroma, and aimed to apply in drug permeability test.

Methods: First permeability of CVMs was measured using cyanocobalamin and FITC-dextran (FDs). Next a human corneal model was prepared by three-dimensionally culturing HCE-T cells (a cell strain derived from human corneal epithelium) in a 450µm thick CVM chamber. Subsequently, permeability of the model was measured using FD-4 before and after exposing 0.05% benzalkonium chloride (BAK).

Results and Conclusion: A CVM chamber indicated molecular size-dependent permeability similar to that of the corneal stroma. A human corneal model developed in CVM chamber possessed about 6 layers of HCE-T cells, and showed similar patterns in the expression of cornea specific proteins. Permeability of FD-4 to the model after exposing BAK was increased three times compared to before exposing BAK. These results suggest that a human corneal model including epithelium and acellular stroma using a CVM chamber may be useful for drug permeability test.

The Effect of Cataract Surgery on Ocular Dominance The Effect of Cataract Surgery on Ocular Dominance

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Purpose: To study the effect of cataract surgery on ocular dominance.

Setting: Ophthalmology department, Tel Aviv Medical Center, Tel Aviv, Israel

Methods: 37 cataract extraction candidates were assessed prior to cataract surgery including refraction, best corrected visual acuity, ocular dominance and a full biomicroscopic examination. Cataract surgery was performed and ocular dominance was assessed again one day, one week and one month after surgery.

Results: Of the patients examined 35% shifted their ocular dominance from one eye to the operated eye. Dominance shifting was positively related to improvement of visual acuity of the operated eye in comparison to the other eye. Most of the dominance shifting occurred one week after the surgery.

Conclusions: Ocular dominance can show plasticity, even in older adults and is related to the improvement in visual acuity after cataract surgery.

Twelve-Months Results from Clinical Practice of Epiretinal Strontium-90 Brachytherapy for the Treatment of Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

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Purpose: The Meritage trial proved that epiretinal strontium-90 brachytherapy in subfoveal choroidal neovascularization (CNV) due to AMD is effective in reducing the number of Bevacizumab injections needed to control exudation in patients receiving frequent injections. Patients followed at the Tel Aviv Medical Center, proven unresponsive to repeated injections, were offered this treatment. We report 12 months results of clinical use.

Methods: A retrospective case series of patients treated by strontium-90 brachytherapy for subfoveal CNV is presented. All patients underwent 23G pars plana vitrectomy. 24G brachytherapy using NeoVista device (Fremont, California) was applied for four minutes and anti-VEGF was injected intravitreal. Follow-up visits were at postoperative day 7 and monthly afterwards. Patients were eligible to receive anti-VEGF injections on PRN basis.

Results: 23 patients were treated. 13 had a follow-up of at least 12 months and are presented. In all cases, the surgical procedure was performed without complications or technical difficulties. Clinical results and twelve months follow-up will be gathered and presented at the meeting.

Conclusions: Epimacular brachytherapy is feasible in clinical practice. While some patients take benefit of the treatment and need significantly less PRN injections, others do not seem to react after one year of follow-up. Larger numbers of patients are needed to evaluate efficacy and which patients could take advantage of combined radiation and anti-VEGF therapy.

ECTOINE: a New Strategy to Control Allergic Conjunctivitis Symptoms

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Seasonal and perennial allergic conjunctivitis are very frequent in the general population. Several antiallergic drugs are currently available: they have different mechanisms of action although sharing some limitations concerning tolerability and compliance, especially in children.

Ectoine is a low molecular weight cyclic amino acid derivative of natural origin. It is produced by several extremophilic microorganisms who accumulate ectoine to protect themselves against harsh environmental conditions such as increased extracellular salt concentration or UV exposure.

Experimental studies showed that ectoine protects cell membranes from allergen-induced damage and decreases inflammation by forming a water shell (Ectoine Hydro-Complex) around the cells. It achieves its effect in a pure mechanical way: ectoine does not have any pharmacological, immunological or metabolic mechanism of action.

Ectoine has recently been developed as a 2% ophthalmic solution, indicated to prevent and treat symptoms of allergic conjunctivitis. It has been proven effective and safe in clinical studies. In adults, it decreases symptoms of allergic conjunctivitis (TOSS score decrease of 24.44% in ectoin treated subjects and of 15.80% in the placebo group; Treatment difference = -1.45; p=0.023; 95% CI: [-2.68, -0.21]). In a comparative clinical study after one-week treatment Ectoin has been found to be as effective as azelastine, as the change in the scores of individual symptoms showed no significant difference. Even in children and adolescents, ectoine 2% is effective, safe and well tolerated. Ectoine 2% eyedrops can be a new therapeutic strategy for allergic conjunctivitis, very well tolerated and safe.



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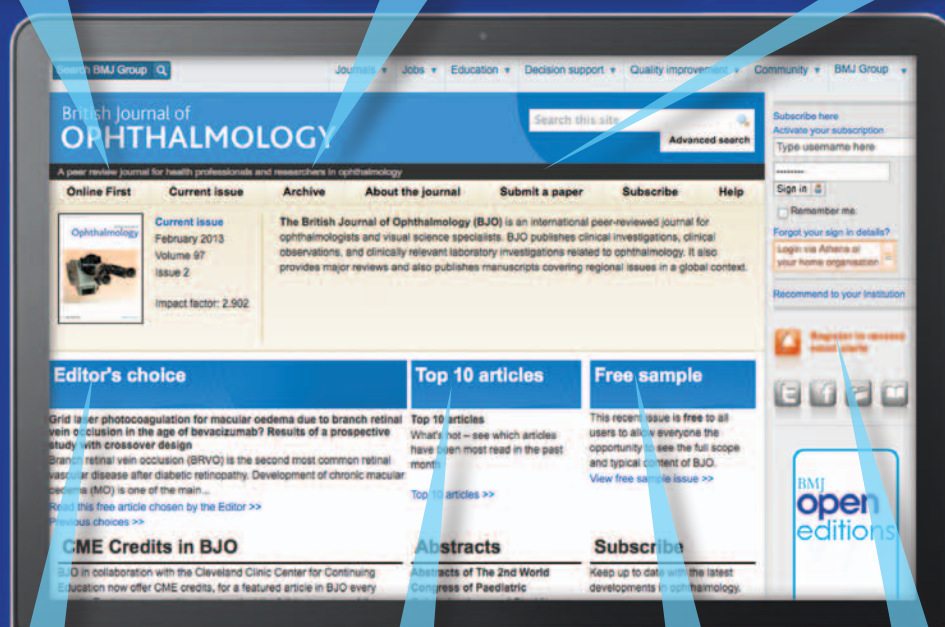
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