12th ISOPT Clinical

The International Symposium on Ocular Pharmacology and Therapeutics

Berlin, Germany
July 9-12, 2015
Program & Abstracts

www.ISOPTclinical.com

	Thursday 09.07		Friday 10.07			Saturday 11.07			Sunday 12.07
	A	B	A	B	C	A	B	C	B
08:00-09:00			Dry AMD (II)	Glaucoma Viewed by Other Sub-Specialties	Inhibition of Diabetic Retinopathy	Innovation	Anti-Angiogenesis	Neuro Ophthalmology	Infection Free Papers
09:00-09:45	Dry AMD I	Not All Steroids Are Equal	Gene Therapy (II)	More than Disc Cupping	Uveitis - Clinicl Studies Design		Stem Cells	Glaucoma Therapeutic Advances	Retina Free Papers
09:45-10:30							Imaging (EVER)		
10:30-11:00	**Coffee Break**								
11:00-11:45	Wet AMD	Ant. Segment Imaging	Retina Misc.	Glaucoma Free Papers	Basic Science Free Papers	Dry Eye	Infections	Glaucoma Drug Delivery	Drug Development Free Papers
11:45-12:30			Retina Free Papers	Neuroprotection	Toxicology				
12:30-13:30	**Lunch Session**		**Novartis Lunch Session**			**Santen Lunch Session**			
13:30-14:00									
14:00-14:45	Macular Edema	Wound Healing	Retinal Vein Occlusion	Drug Delivery	Allergy	Cross Linking	Biologicals- The Path For The Future	Glaucoma MIGS	
14:45-15:30									
15:30-16:00	**Coffee Break**								
16:00-16:45	Macular Edema	Gene Therapy (I)	Imaging	Drug Delivery	Adapting New Steroids in Clinical Reality	Contact Lens	AC Tap	Neuropathies Advances	
16:45-17:30									
Evening	Get Together								

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Scientific Program

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Contents

Dear Colleague,

It is our great pleasure to welcome you to Berlin, Germany for the 12th ISOPT clinical meeting.
This year meeting will focus on drugs and devices as part of the ophthalmologist tool box dealing with ailments of the eye. Ophthalmology had been traditionally a surgical field. Over the last decades a slow, but significant revolution took place with the introduction of new drugs and utilizing invasive modes of delivery to the eye. In addition new devices and drug/device combinations are being launched and change the way we practice ophthalmology.

The vision of ISOPT Clinical had evolved since 1995 centering on:
• Increased knowledge and awareness of drug use in ophthalmology.
• Reflecting innovations and their application in the daily practice.
• Bridging the present to the future.
We hope to achieve this via:
• Discussion of treatment algorithms in major ophthalmic indications
• Implement data from clinical studies to daily practice
• Facilitate innovation – connecting innovators with clinicians
• Encourage meetings of young innovators with the pharma industry
ISOPT Clinical offers a relevant and updated scientific program in a relaxed atmosphere leading to direct interactions of its delegates.

We look forward for Interaction with colleagues from many different countries to stimulate a creative exchange of ideas and be personally rewarding.

We thank you for your participation and wish you successful and constructive days here in Berlin.

S. Krupsky

Sara Krupsky MD
Chairperson

R. Neumann

Ron Neumann
MD Chairperson

Committees

Chairpersons
S. Krupsky, Israel
R. Neumann, Israel

Special Program Advisers
B.D. Kuppermann, USA
B. Katz, USA
P. Asbell, USA

Section & Session Chairpersons

Retina
B.D. Kuppermann, USA
J. Seddon, USA
J. Sahel, France
F. Behar Cohen, Switzerland

Imaging
G. Soubrane, France
V. Sadda, USA
L. Schmetterer, Austria

External Eye Diseases
P.A. Asbell, USA

Glaucoma
B. Katz, USA
M. B. Eydelman, USA
K. Singh, USA

Inflammation & Infection
R. Neumann, Israel
U. Pleyer, Germany
E. K. Akpek, USA
I. Barequet, Israel

Drug Delivery
D.D-S, Tang Liu, USA
R. Gurny, Switzerland

Toxicology
R.W. Fraunfelder, USA

Basic Science
A. Das, USA
C. Paterson, USA

Neuro-ophthalmology
H. Leiba, Israel

Neuroprotection
L. Levin, USA

Innovation
R. Neumann,Israel
B. Levy, USA

Invited Speakers

M. Ader, Germany
E. Akpek, USA
S. Androudi, Greece
P. Asbell, USA
P. Ashton, USA
A. Augustin, Germany
W. Ayliffe, UK
F. Bandello, Italy
I. S. Barequet, Israel
T. Barisani, Austria
N. Barney, USA
A. Bate, USA
F. Behar-Cohen, Switzerland
R. Beuerman, Singapur
F. Boscia, Italy
J. Brandt, USA
K. Brazzel, USA
M. Bolz, Austria
S. R. Boyd, Canada
J. D. Bullock, USA
J. Busik, USA
B. Butler, USA
A. Chauhan, USA
S P. Chee, Singapore
R. Chuck, USA
J. Ciolino, USA
G. Coscas, France
D. Dalkara, France
A. Denniston, UK
P. Dugel, USA
I. El-Zaoui, France
M. Eydelman, USA
R. Feldman, USA
B. Flowers, USA
L. Fontana, Italy
C. Francois, USA
F. Fraunfelder, USA
A. Garcia Layana, Spain
D. Gabriel, Switzerland
D. Ghezzi, Switzerland
J. Goldberg, USA
N. Goldenberg -Cohen
M. Goldstein, Israel
M. Grant, USA
J. Groot-Mijnes, The Netherlands
Y. Guex-Crosier, Switzerland
F. Grus, Germany
A. Grzybowsk, Poland
P. Hamrah, USA
P. Harasymowycz, Canada
A. Harris, USA
R.V. Herrero, Spain
D. Heuer, USA
D. Hinton, USA
J. Reidy, USA
B. Jeng, USA
J. Jonas, Germany
M. Kasper, Germany
M. S.J. Katz, USA
B. Katz, USA
H. Kaufman, USA
U. B. Kompella, USA
R. P. Kowalski, USA
R. Kowluru, USA
C. Kostic, Switzerland
M. Kramer, Israel
B. D. Kuppermann, USA
H. Leiba, Israel
A. Leonardi, Italy
T. Leveillard, France
L. A. Levin, Canada
B. Levy, USA
W. H. Lee, USA
A. Ljubimov, USA
N. Lois, Ireland
I. Mantel, France
A. Matet, Switzerland
N. Medow, USA
O. Moghimi, USA
S. Mohr, USA
R. Neumann, Israel
G. Noronha, USA
G. D. Novack, USA
F. Obermayr, Austria
A. Ohira, Japan
E. Ongini, USA
M. Paques, France
C. Parsa, USA
S. Patel, USA
J. Penn, USA
L.E. Pillunat, Germany
C.S. Phaik, Singapur
U. Pleyer, Germany
M. J. Rafii,USA
CA Rasmussen, USA
Stefan Reber,
M. R. Rodriguez, Switzerland
H. Reitsamer, Austria
P. Roberts, Austria
E. Romanowski, USA
B. Roska, Switzerland
SV R. Sadda, USA
J.A. Sahel, France
V. Santer, Switzerland
P. Sieving, USA
L. Schmetterer , Austria
S. Schmitz-Valckenberg, Austria
J. M. Seddon, USA
M. Seiler, USA
R. M Shanks, USA
K. Shindler, USA
J. Shultz, USA
D. Silverman, USA
K. Singh, USA
J. Slakter, USA
A. Sodhi, USA
G. Soubrane, France
G. L. Spaeth, USA
J. Sparrow, USA
O. Stachs, Germany
B. V. Stanzel, Germany
G. Staurenghi, Italy
E. Stefánsson, Iceland
C. Struble, USA
N. Stübiger, Germany
F. Thieltges, Germany
M. Thormann, USA
E. Timm, USA
A. Timmers, USA
R. Toyos, USA
O. Ucakhan-Gunduz, USA
P. Udaondo, Spain
S. Uretsky, France
M. Vezina, Canada
N. Waheed, USA
K. Weber, Switzerland
M. Zierhut, Germany

General Information

Venue
Marriot Hotel, Inge-Beisheim-Platz 1
10785 Berlin, Germany
Tel: +49 (30) 22 000 0
Fax: +49 (30) 22 000 1000

Language
English is the official language of the Symposium.

Registration and Hospitality Desk
Thursday, July 909:00 – 17:30
Friday, July 1008:00 – 17:30
Saturday, July 1108:00 – 17:30
Sunday, July 12 08:00 – 12:30

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 WIFI will be available throughout the symposium in the session halls and exhibition area.

Certificate of Attendance
A certificate of attendance will be available at the registration desk from Saturday, July 11, noon time.

Attendance of ISOPT Clinical provides 20 CME credits (ECMEC) Exhibition Opening Hours
All participants are invited to view the exhibition. Exhibition opening hours are as follows:
Thursday, July 909:00 – 17:30
Friday, July 1008:00 – 17:30
Saturday, July 1108:00 – 17:30

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 provided computers.

Macintosh Users – please be advised that **the use of Mac computers is not possible**.
Mac users will be requested to convert their presentation to Office
If you wish to use your own laptop in the preview room, make sure to bring an adaptor to Windows/Office.

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

ISOPT Symposium Secretariat
Windman Events LTD.
Tel: +49 891 4367059
Fax: +49 180 510129029
Address: Borsigstr. 9, 10115 Berlin, Germany
Email: Office@ISOPTclinical.com

Reception & Refreshments

Welcome Reception

17:30 – Thursday, 09 June

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

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Lunch Sessions

Lunch boxes will be provided during the sponsored lunch sessions:

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Santen GmbH
Erika-Mann-Str. 21
80636 München
Germany
Tel. +49 89 848 078 0
Fax +49 89 848 078 60
mail@santen.de
www.santen.de

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Postfach 4002 Basel, Switzerland
+41-061-613248556

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Bayer HealthCare Pharmaceuticals
Bayer Pharma AG
Müllerstraße 170-178, 13353 Berlin, Germany
Tel: + 49 30 468-1111
Fax: +49 30 468 15305
www.healthcare.bayer.com

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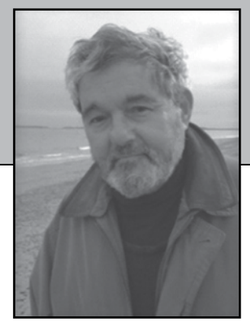
Toxikon Europe N.V.
Romeinsestraat 12
3001 Leuven, Belgium
Tel.: +32.16.400484
Fax.: +32.16.401304
info@toxikon.be

Toxikon is an international CRO with ISO, GMP and GLP accreditations. We contract and partner with pharma, biotech and medical device industries to deliver exceptional product development services from concept to final product. We provide ocular drug development services starting with the validation of Proof-of-Concept using animal disease models for Dry Eyes, Uveitis, Glaucoma, PVR and NV/AMD. Subsequently Toxikon can support you through the preclinical development road in order to qualify your compound to enter the clinic and beyond. Including full analytical services for CMC and bio-analytical work. At Toxikon, we take time to design and customize your project.

The ISOPT Retina section is devoted to

Prof. Ephraim Friedman

1930-2011



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Morning Sessions – Hall A

09:00-10:30	*Dry AMD* **Chair: Johanna M. Seddon**, Tufts University School of Medicine, USA	**Hall A**
09:00	**Fundus Autofluorescence: Quantitation and Interpretations** Janet Sparrow, USA	
09:08	**Regression of Drusen as a Marker for Disease Progression** Philipp Roberts, Austria	
09:16	**European perspective of the Nutritional Supplements in AMD Prevention** Alfredo Garcia Layana, Spain	
09:24	**Discussion**	
09:30	**Therapeutic Strategies in Geographic Atrophy**	
09:38	**Steffen Schmitz-Valckenberg, Germany**	
	Stem Cell Therapy for Dry AMD Wen-Hsiang Lee, USA	
09:46	**Targeting the Immune System in Dry AMD** Shelley Boyd, Canada	
09:54	**Discussion**	
10:00	**Imaging Early and Advanced Atrophic AMD** Philipp Roberts, Austria	
10:08	**OCT angiography in Non-exudative Macular Degeneration** Omid Moghimi, USA	
10:16	**Development of Risk Prediction Models for Macular Degeneration Incorporating 10 Common and Rare Genetic Variants 2006-2015: Genotype-Phenotype Correlations** Johanna M. Seddon, USA	
10:24	**Discussion**	
10:30-11:00	***Coffee Break***	**Exhibition Hall**
11:00-12:30	*Wet AMD* Chair: **Baruch D. Kuppermann**, USA	**Hall A**
11:00	**Encapsulated Cell Technology** Baruch Kuppermann, USA	
11:09	**Update on the Results of the Phase 2 Study of Squalamine Lactate Ophthalmic Solution 0.2% (OHR-102) in Neovascular Age-related Macular Degeneration (AMD)** Jason Slakter, USA	
	Synopsis of Comparison Studies: CATT, IVAN, MANTA, GEAFAL	
11:18	Francesco Boscia, Italy	
	Fovista Combination Therapy for Neovascular AMD	
11:27	Samir Patel, USA	
	Anti-PDGF Pretreatment in AMD - Results of a Pilot Study Evaluating VEGF/PDGF	
11:36	**Crosstalk** Pravin Dugel, USA	
	Regeneron Combination Therapy for nvAMD	
11:45	Rishi Singh, USA	
	Small Fragment Fab for Wet AMD	
11:54	Pravin Dugel, USA	
	New Drugs in Development for Wet AMD	
12:03	Jason Slakter, USA	
	LUMINOUS Study	
12:21	Albert Augustin, Germany	
12:30-13:30	***Lunch Break***	**Hall A**

Thursday, July 9, 2015

Morning Sessions – Hall B

09:00-10:30	**All Steroids Are Equal But Some Are More Equal Than Others** Chair: **Francine Behar Cohen**, Switzerland	**Hall B**
	Differentiating Steroids	
09:0	**Routes and Dose Make the Difference** Baruch Kuppermann, USA	
09:12	**Drugs Make the Difference** Francine Behar-Cohen, Switzerland	
	Steroid and IOP Raise	
09:24	**Corticoid Complications** Yan Guex-Crosier, Switzerland	
	Steroids Effects on Macular Edema	
09:36	**Equal to anti-VEGF** Albert Augustin, Germany	
09:48	**Different from anti-VEGF** Irmela Mantel, Switzerland	
	Retinal Neurotoprotective / Neurotoxicity of steroids	
10:00	**Steroids are Toxic for the Retina** Ikram Elzaoui, France	
10:12	**Steroids are Neuroprotective for the Retina** Stefan Reber, Germany	
10:24	**Round table discussion and conclusion**	
11:00-12:30	**Anterior Segment Imaging and In-Office Testing** Chairs: **Penny Asbell**, USA & **Pedram Hamrah**, USA	**Hall B**
11:00	**Ophthalmological Imaging with Ultrahigh Field Magnetic Resonance Tomography: Technical Innovations and Frontier Applications** Oliver Stachs, Germany	
11:10	**Clinical Indications for in Vivo Confocal Microscopy** Pedram Hamrah, USA	
11:20	**OCT for Surface Eye Tumors** Frederick Fraunfelder, USA	
11:30	**Imaging for Dry Eye Disease Metrics** Penny Asbell, USA	
11:40	**Large Scale Mosaicking the Subbasal Nerve Plexus of the Cornea** Oliver Stachs, Germany	
11:50	**Clinical Indications for Corneal En-Face OCT** Pedram Hamrah, USA	
12:00	**Q & A Panel**	
12:30-13:30	***Lunch Break***	**Hall A**

Thursday, July 9, 2015

Afternoon Sessions – Hall A

14:00-15:30	***Diabetic Macula Edema*** Chair: **Baruch D. Kuppermann**, USA	**Hall A**
14:00	**Protocol T** Rishi Singh, USA	
14:15	**Aerpio TIE-2 Inhibition** Pravin Dugel, USA	
14:30	**Bevordex** Baruch Kuppermann, USA	
14:45	**Steroid Implants for DME** Patricia Udaondo, Spain	
15:00	**Combination Therapy for Diabetic Macular Edema** Albert Augustin, Germany	
15:15	**Guidelines for the Use of Laser, Anti-VEGF, or Steroids in DME** Patricia Udaondo, Spain	
15:30-16:00	***Coffee Break***	**Exhibition Hall**
16:00-17:30	***Diabetic Macula Edema*** Chair: **Baruch D. Kuppermann**, USA	**Hall A**
16:00	**Comparison of Outcomes from DME Trials** Baruch Kuppermann, USA	
16:20	**Drugs in the Pipeline for DME** Rishi Singh, USA	
16:40	**Medicare Analysis of DME Treatment** Pravin Dugel, USA	
16:50	**Improving the conventional eyedrop:** **Topical treatment for retinal disease including diabetic macular edema** Einar Stefánsson, Iceland	
17:00	**The effect of topical 1.5% dexamethasone -cyclodextrin nanoparticle eye drops for diabetic macular edema** A. Ohira, Japan	
17:10	**Panel: Diabetic Macula Edema - Case Discussion** Rishi Singh, Ohio, USA, Patricia Udaondo, Spain, Baruch Kuppermann, USA, Albert Augustin, Germany, Francesco Boscia, Italy	

Thursday, July 9, 2015

Afternoon Sessions – Hall B

14:00-15:30	**Inflammation/Wound Healing** Chairs: **Penny Asbell**, USA & **Roger Beuerman**, Singapore	**Hall B**
14:00	**A Dexamethasone-eluting Contact Lens for Treatment of Ocular Inflammation** Joseph Ciolino, USA	
14:10	**Corneal Allograft Rejection** Bennie Jeng, USA	
14:20	**Surrogate Biomarkers for Inflammation in Dry Eye Disease to Asses Therapeutic Efficacy** Pedram Hamrah, USA	
14:30	**Wound Healing, Fibrosis More Exactly** Roger Beuerman, Singapore	
14:40	**Post op Inflammation After Intraocular Surgery and Discuss Our FDA Studies and Current Studies on Post op Drops** Rolando Toyos, USA	
14:50	**Corneal innervation, growth factors, and persistent epithelial defects: Current concepts and future directions** James Reidy, USA	
15:00	**Molecular Biomarkers and Personalized Medicine in Ocular Surface Disease** Roger Beuerman, Singapore	
15:10	**Surgical Treatment of Anterior Segment Inflammation** Aspek Essen, USA	
15:20	**Q & A panel** All speakers	
16:00-17:30	***Coffee Break***	**Exhibition Hall**
16:00-17:30	***Gene Therapy (i)*** Chair: **Francine Behar Cohen**, Switzerland and **Botond Roska**, Switzerland	**Hall B**
16:00	**Cell Transplantation for Retinal Repair: Clinical Experiences and Future** Boris Stanzel, Germany	
16:10	**Ciliary Muscle Electrotransfer for Ocular Gene Therapy: from the Bench to the Bedside** Francine Behar Cohen, Switzerland	
16:20	**Viral Vectors: Is Subretinal Injection a Real Option** Alexandre Matet, Switzerland	
16:30	**The New Challenge of Retinal Gene Therapy: Controlling Protein Dose** Corinne Kostic, Switzerland	
16:40	**Gene Therapy and Bioengineering for Retinal Diseases: What is the Future** Diego Ghezzi, Switzerland	
17:20	**Optogenetic: A cure for Blindness?** Botond Roska, Switzerland	

Friday, July 10, 2015

Morning Sessions – Hall A

09:00-09:45	***Dry AMD*** Chair: **Baruch D. Kuppermann**, USA	**Hall A**
09:00	**Pathophysiology of Dry AMD** Francesco Boscia, Italy	
09:12	**Treatment Pipeline for Dry AMD** Jason Slakter, USA	
09:32	**C3 Inhibition For Age-Related Macular Degeneration** Cedric Francois, USA	
09:45-10:30	***Gene Therapy*** Chair: **Jose-Alain Sahel**, France	**Hall A**
09:45	**Phase I/IIa Gene Therapy Trial of AAV8-RS1 by Intravitreal Delivery for X-Linked Retinoschisis** Paul Sieving, USA	
09:55	**Rod-derived Cone Viability Factor stimulates glucose metabolism of cone photoreceptors** Thierry Leveillard, France	
10:05	**Optogenetics for Vision Restoration** Deniz Dalkara, France	
10:15	**Gene Therapy for Leber Hereditary Optic Neuropathy** Jose-Alain Sahel, France	
10:30-11:00	***Coffee Break***	**Exhibition Hall**
09:45-10:30	***Retina – Miscellaneous*** Chair: **Baruch D. Kuppermann**, USA	**Hall A**
11:00	**Treatments for CSR** Francine Behar-Cohen, Switzerland	
11:15	**Update on Ocriplasmin for Vitreomacular Traction** Baruch Kuppermann, USA	
11:30	**Low Dose Atropine in Myopia** Andrezi Grzybowski, Poland	
11:45-12:30	**Retina Free papers** Chair: **A. Ohira**, Japan	**Hall A**
11:45	**Choroidal neovascularization in highly myopic elderly patients: A special form of choroidal neovascularization?** Maria Rosalba Ramoa Osorio, Spain	
12:00	**Ocular manifestations and choroidal thickness measured by Swept-Source OCT (SS-OCT) in patients with familial hypercholesterolemia (FH) treated with oral intensive statin therapy** Félix Alexander Manco Lavado, Spain	
12:15	**Objective perimetry based on chromatic multifocal pupillometer for treatment follow-up and diagnosis in patients with retinal and macular dystrophies** Ygal Rotenstreich, Israel	
12:30-13:30	***Lunch Session sponsored by Novartis***	**Hall A**

Friday, July 10, 2015

Morning Sessions – Hall B

08:00-09:00	**Glaucoma That the Rest of Us See** Chair: **Barrett Katz**, USA	**Hall B**
08:00	**A Cornea Perspective** Roy Chuck, USA	
08:15	**A Pediatric Ophthalmology Perspective** Norman Medow, USA	
08:30	**A Retina Perspective** Matthew S.J. Katz, USA	
08:45	**A Neuro Ophthalmology Perspective** Barrett Katz, USA	
09:00-10:30	**More Than Just Cupping: Disc Changes in Glaucoma** Chair: **Barrett Katz**, USA	**Hall B**
09:00	**Cup/disc ratios mislead; they are of little diagnostic value in contrast to the DDLS** George L. Spaeth, USA	
09:12	**Disc Changes Unique to Glaucoma** Robert Feldman, USA	
09:24	**Normal Tension Glaucoma - A Distinct Disease Entity?** Kuldev Singh, USA	
09:36	**Parapapillary Alpha, Beta, Gamma and Delta Zones in Glaucoma** Jost Jonas, Germany	
09:48	**NFL Density in Glaucoma - OCT Correlates** Hebert Reitsamer, Austria	
10:00	**Vascular Changes in Glaucoma** Alon Harris, USA	
10:12	**CSF Pressure and the Eye** Jost Jonas, Germany	
10:24	**Q&A Discussion**	
10:30-11:00	***Coffee Break***	**Exhibition Hall**
11:00-11:45	***Glaucoma Free Papers*** Chair: **Barrett Katz**, USA	**Hall B**
11:00	**New useful thoughts about old ideas; or "It is better to be certain than to guess"** George L. Spaeth, USA	
11:20	**Clinical Evaluation of the Eye-to-visual-pathway Integrity of Glaucomatous Neurodegeneration Using 1.5T MR Imaging** Kaya Nusret Engin, Turkey	
11:30	**Structure and Function in Normal Pressure Glaucoma** Lutz E. Pillunat, Germany	
11:45-12:30	**Neuroprotection** Chair: **Leonard A. Levin**, Canada	
11:45	**Anti-VEGF and steroids: neuroprotection or neurotoxicity?** Francine Behar Cohen, Switzerland	
12:00	**Phosphodiesterase-5 Inhibition: Optic Nerve Erection Without Neuroprotection** Nitza Goldenberg-Cohen, Israel	
12:15	**Adenosine's Neuroprotection: Can it be retained in an adenosine mimetic?** William McVicar	
12:30-13:30	***Lunch Session sponsored by Novartis***	**Hall A**

Friday, July 10, 2015

Morning Sessions – Hall C

08:00-09:00	***Inhibition of Diabetic Retinopathy*** Chair: **Arup Das**, USA	**Hall C**
08:00	**DNA Methylation: A New Player in the Blinding Disease of Diabetes** Renu Kowluru, USA	
08:15	**Targeting Caspase-1 in Diabetic Retinopathy** Susanne Mohr, USA	
08:30	**Stem Cell Therapy in Diabetic Eye Diseases** Alexander Ljubimov, USA	
08:45	**A Double Sword Action of miR-15a in Diabetic Retinopathy - Inhibition of VEGF and Sphingolipid Pathways** Julia Busik, USA	
09:00-10:30	**Panel: Uveitis Studies Endpoints** Chair: **Altastrair Denniston**, UK	**Hall C**
09:00	**The Story of Interferon, Evaluating Drug Effect Without the Engine of The Industry** Manfred Zierhut, Germany	
09:15	**NEI/FDA Clinical Study Design - Meeting Summary** Malvina Eydelman, USA	
09:25	**Regulatory Point of View (MHRA)** David Silverman, USA	
09:35	**Clinical Point of View - 'Endpoints in Uveitis: Past, Present and Future'** Alastrair Denniston, UK	
09:50	**Patient Point of View (The PEP that would most matter to patients)** Ron Neumann, Israel	
09:55	**Moving ahead – lessons from other medical fields** Gary Novack, USA	
10:10	**Panel: Moderated by** Alastrair Denniston, UK **Participating: All session presenters**	
10:30-11:00	***Coffee Break***	**Exhibition Hall**

Friday, July 10, 2015

Morning Sessions – Hall C

11:00-11:45	***Basic Science Free Paper*** Chair: **Arup Das**, USA	**Hall C**
11:00	**Targeting Receptor Interacting Protein-2 (RIP2) to Prevent Hyperglycemia-Mediated Inflammatory Signaling in Müller Cells** Derrick Feenstra, USA	
11:10	**Normalising eNOS function to facilitate repair of the ischaemic retina** Denise McDonald, Ireland	
12:20	**A novel target for therapy development in optic neuropathies – a second life for presenilins?** Peter Koulen, USA	
12:30	**Regulated expression of recombinant anti-VEGF single chain antibody fragments – towards personalized medicine in neovascular retinal disorders** Tobias Wimmer, Germany	
12:40	**KinostatTM prevents cataracts in diabetic dogs** Peter Kador, USA	
11:45-12:30	***Toxicology*** Chair: **Frederick Fraunfelder**, USA	**Hall C**
11:45	**ReNu-Related Fusarium Keratitis Event of 2004-2006** John Bullock, USA	
11:54	**How Much Preclinical Safety Data for a Clinical Study in Ophthalmology?** Gary Novak, USA	
12:03	**Toxicity with Glaucoma Drops** Penny Asbell, USA	
12:12	**Emerging Pharmacovigilance Methods and Approaches for Safety Surveillance in Real World Data** Andrew Bates, UK	
12:21	**Vaccine Associated Uveitis** Frederick Fraunfelder, USA	
12:30-13:30	***Lunch Session sponsored by Novartis***	**Hall A**

Afternoon Sessions – Hall A

14:00-15:30	***Retinal Vein Occlusion*** Chair: **Baruch D. Kuppermann,** USA	**Hall A**
14:00	**BRIGHTER and CRYSTAL Studies** Francesco Boscia, Italy	
14:15	**VIBRANT Trial** Patricia Udaondo, Spain	
14:30	**Steroids for RVO** Albert Augustin, Germany	
14:45	**Laser for RVO (mechanism)** Einar Stefansson, Iceland	
15:00	**Panel: RVO - Case Discussion** Francesco Boscia, Italy , Patricia Udaondo, Spain, Albert Augustin, Germany, Einar Stefansson, Iceland	
15:30-16:00	***Coffee Break***	**Exhibition Hall**
16:00-17:30	***Lessons Taught by Imaging about Atrophy in Retinal Disease*** Chairs: **Gisèle Soubrane** , France & **SriniVas R. Sadda**, USA	**Hall A**
16:00	**Adaptive Optics** Michel Paques, France	
16:15	**Lessons learnt about retinal pigment epithelial atrophy by the use of fundus autofluorescence imaging** Noemie Lois, UK	
16:30	**En Face OCT of Geographic Atrophy** Srinivas Vas R. Sadda, USA	
16:45	**OCT angiography versus Traditional Multimodal Imaging in Exudatibe AMD** Gabriel Coscas, France	
17:00	**Color and Multicolor Imaging** Giovanni Staurenghi, Italy	
17:15	**Q & A**	

Friday, July 10, 2015

Afternoon Sessions – Hall B

14:00-15:30	***Drug Delivery - Practical Considerations*** Chairs: **Diane Tang-Liu**, USA & **Robert Gurny**, Switzerland	**Hall B**
14:00	**A Vision of Future of Glaucoma Care: Combination of Device and Drug Products** Adrian Timmers, USA	
14:15	**Ocular Anti-Neovascularization Models: Advantages and Limitations Relating to Drug Delivery, Model Duration and Translatability** Mark Vezina, Canada	
14:30	**Improvements in Technologies to Maintain Sustained Levels of Ophthalmic Drugs in the Eye: PRINT Particles and Novel Bioconjugates** Craig Struble, USA	
14:45	**Enhanced Ocular Drug Delivery with Mucus-penetrating Nanoparticles** Kim Brazzel, USA	
15:15	**Using Suprachoroidal Administration as an Approach to Treat Noninfectious Uveitis – from Concept through Clinical Data** Glenn Noronha, USA	
	Ocular Safety and Tolerability: from Bench to Bedside **Roundtable Discussion**	
15:30-16:00	***Coffee Break***	**Exhibition Hall**
16:00-17:30	***Drug Delivery - Innovation*** Chairs: **Diane Tang-Liu**, USA & **Robert Gurny**, Switzerland	**Hall B**
16:00	**Protein Self-assemblies for Enhanced Stability, Activity, and Delivery** Uday B. Kompella, USA	
16:15	**Novel Formulations of Cyclosporin for Improved Delivery to Eye** Doris Gabriel, Switzerland	
16:30	**Therapeutic Effect of mTor-inhibition in Autoimmune Uveitis in Mice and Man?** Maren Kasper, Germany	
16:45	**Improved Ocular Tolerance and Bioavailability of Latanoprost** Robert Gurny, Switzerland	
17:00	**Visualization and quantification of intra-corneal triamcinolone acetonide biodistribution following topical iontophoresis: a new approach to treat corneal graft rejection** Verena Santer, Switzerland	
17:15	**Biodegradable Microparticles for the Delivery of Ocular Therapeutics** Rocci Herrero-Vanrell, Spain	

Friday, July 10, 2015

Afternoon Sessions – Hall B

14:00-15:30	***Drug Delivery - Practical Considerations*** Chairs: **Diane Tang-Liu**, USA & **Robert Gurny**, Switzerland	**Hall B**
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Friday, July 10, 2015

Afternoon Sessions – Hall C

14:00-15:30	**Ocular Allergy** Chair: **Essen Akpek**, USA	**Hall C**
14:00	**Introduction to Allergic Conjunctivitis** Essen Akpek, USA	
14:15	**Current and Emerging Treatments of Atopic Keratoconjunctivitis** Bennie Jeng, USA	
14:30	**Use of Biologics in Treatment of Allergic Eye Disease** Neal Barney, USA	
14:45	**Vernal Kertoconjunctivitis; Global Impact** Andrea Leoardi, Italy	
15:00	**New Treatments for Seasonal Allergic Conjunctivitis** Penny Asbell, USA	
15:15	**Case Discussion** Essen Akpek, USA, Bennie Jeng, USA, Neal Barney, USA, Penny Asbell, USA	
15:30-16:00	***Coffee Break***	**Exhibition Hall**
16:00-17:30	**Adapting new steroid preparations in ocular inflammation** Chair: **Will Ayliff,** UK	**Hall C**
16:00	**Iluveien** Albert Augustin, Germany	
16:15	**Durezol – Selecting Steroids Eye Drops for My Post Cataract Patient** Penny Asbell, USA	
16:30	**Sustained release dexamethasone (Ozurdex) for uveitis** Will Ayliffe, UK	
16:45	**Choosing the Steroid Product Most Appropriate to My Patient** **Moderator**: Will Ayliffe, UK **Panel:** Francine Behar-Cohen, Switzerland, Sofia Androudi, Greece, Penny Asbell, USA, Albert Augustin, Germany	

Morning Sessions – Hall A

08:00-10:30	***Innovations in Ophthalmology*** Chairs: **Ron Neumann**, Israel & **Brian Levy**, USA	**Hall A**
08:00	**Jde-003, A Novel, Topical, Cross-Linked Hyaluronic Acid (Ha) Gel, Promotes Regeneration Of Damaged Corneal Cells Following Various Types Of Ocular Corneal Trauma** MaryJane Rafii, USA	
08:10	**Novel spleen Tyrosine Kinase (SYK) inhibitor for the treatment of fungal keratitis** Michael Thormann, USA	
08:20	**Electrophysiological Testing of Visual Neural Function: Use in Glaucoma** Vance Zemon, USA	
08:30	**A novel therapeutic non-steroidal drug for inflammatory eye diseases** Franz Obermayr, Austria	
08:40	**CLT-28643 significantly improves the surgical outcome of glaucoma surgery in pre-clinical models.** Mario Fsadni, UK	
08:50	**A novel microdosing system of applying eye drops** Barry Butler, USA	
09:00	**Nitric Oxide (NO) an Emerging Target for IOP Lowering** Ennio Ongini, USA	
09:10	**Efficient and Effective Drug Delivery Systems: The Mobius Experience** Ed Timm, USA	
09:20	**Delivering Drugs and Biologics to the Retina** Paul Ashton, USA	
09:30	**The Valuation Process: How much is my product worth?** Barry Butler, USA	
09:40	**FDA's role in Supporting Innovation of Ophthalmic Devices** Malvina Eydelman, USA	
09:55	**Discussion: All Speakers**	
10:30-11:00	***Coffee Break***	**Exhibition Hall**
11:00-12:30	***Dry Eye Disease Treatment*** Chairs: **Penny Asbell**, USA & **Bennie Jeng,** USA	**Hall A**
11:00	**Why Aren't There More New Pharmacotherapies for Dry Eye?** Gary D. Novack, USA	
11:20	**Autologous Serum for OSD** Bennie Jeng, USA	
11:30	**New Therapies for DED** Michael Goldstein, USA	
11:40	**Intense Pulse Light Treatment for Dry Eye Disease due to Meibomian Gland Dysfunction, a 3-year retrospective study** Rolando Toyos, USA	
11:50	**Biomarkers in Tear Fluid** Franz Grus, Germany	
12:00	**Diagnosis of Inflammatory Dry Eye using Inflammadry** Herbert Kaufman, USA	
12:10	**Effects of Punctal Occlusion on Dry Eye Clinical Signs and Symptoms, and Tear Cytokine Levels Using Direct Measurement and Generalized Linear Modeling** Roger Beuerman, Singapore	
12:20	**Hybrid formulations for the treatment of glaucoma and dry eye** Rocci Herrero-Vanrell, Spain Q & A	
12:30-13:30	***Lunch Session sponsored by Santen***	**Hall A**

Saturday, July 11, 2015

Morning Sessions – Hall B

08:00-09:00	**Therapy for Antiangiogensis** Chair: **Arup Das**, USA	**Hall B**
08:00	**Inhibition of Subretinal Fibrosis in Choroidal Neovascularization** David Hinton, USA	
08:10	**Potential Therapeutic Impact of NFAT Inhibitors in Diabetic Retinopathy** John Penn, USA	
08:20	**Novel HIF-regulated Therapeutic Targets and Diagnostic Markers in Diabetic Eye Diseases** Akrit Sodhi, USA	
08:30	**Apelin Receptor antagonist for Retinal Angiogenesis** Maria Grant, USA	
09:00-09:45	***Stem cells Therapy*** Chair: **Chris Paterson**, USA & **Magdalene Seiler,** USA	
09:45	**Visual Restoration by Retinal Progenitor Sheet Transplants** Magdalene Seiler, USA	
09:55	**Photoreceptor transplantation into pre-clinical models of retinal degeneration** Marius Ader, Germany	
10:05	**Pluripotent Stem Cell Derived and Cell Carrier Supported RPE Replacement in Large-Eyed Preclinical Animal Models** Fabian Thieltges, Germany	
09:45-10:30	***Imaging EVER*** Chair: **Leopold Schmetterer,** Austria	
09:45	**Retinal Oxygen Extraction in Humans** Leopold Schmetterer, Austria	
09:55	**AO Imaging of Retinal Vessels: Blood Pressure, Retinal Vein Occlusions, Vasculitis and More** Michel Paques, France	
10:05	**Vascular Imaging with the Retinal Function Imager (RFI)** Nicole Stübiger, Germany	
10:15	**Diabetic macular edema: Bridging the gap between imaging and therapy** Matthias Bolz, Austria	
10:30-11:00	***Coffee Break***	**Exhibition Hall**

Morning Sessions – Hall B

11:00-12:30	***Ocular Infections*** Chair: **Irina S. Barequet**, Israel	**Hall B**
11:00	**Antibiotic Resistance- Surveillance Studies** Penny Asbell, USA	
11:10	**Bacterial Inhibition of Corneal Wound Healing** Robert M. Shanks, USA	
11:20	**The Resurgence of Penicillin-Susceptible Staphylococci Aureus from Infectious Keratitis** Regis P. Kowalski, USA	
11:30	**Cross-Linking in Infectious Keratitis** Irina S. Barequet, Israel	
11:40	**Fusarium and Non-Fusarium Fungal Corneal Infections During the Worldwide ReNu-Related Fusarium Keratitis Event of 2004-2006** John D. Bullock, USA	
11:50	**The Evaluation of Topical SPL, a Novel Dendrimer Antiviral, Against Adenovirus in NZW Rabbit Ocular Models** Eric Romanowski, USA	
12:00	**Different practice patterns in endophthalmitis prophylaxis in different parts of the world** Andrzei Grzybowski, Poland	
12:10	**Panel discussion:** Moderated by: **I Barequet** Participants: P. Asbell, USA, R. M. Shanks, USA, R.P. Kowalski, USA, J. D. Bullock, USA E. Romanowski, USA A. Grzybowski, Poland	
12:30-13:30	***Lunch Session sponsored by Santen***	**Hall A**

Morning Sessions – Hall C

08:00-09:00	***Neuro-Ophtalmology*** Chair: **Hanna Leiba**, Israel	**Hall C**
08:00	**Visual Loss Caused by Cobalt Neurotoxicity from Hip Implants** Konrad Weber, Switzerland	
08:10	**New horizons in optic pathways gliomas treatment** Nitza Goldenberg-Cohen, Israel	
08:20	**Pharmacologic treatments for nystagmus: what might one expect?** Cameron Parsa, France	
08:30	**New horizons in thyroid ophthalmopathy treatment** Hanna Leiba, Israel	
08:40	**The OCT as a window to the brain** Andrzei Grzybowsk, Poland	
08:50	**Q & A**	
09:00-10:30	***Therapeutic advances in Glaucoma*** Chair: Barrett Katz, USA	**Hall C**
09:00	**Glaucoma surgery: where are we?** Jeffery Shultz, USA	
09:13	**Why aren't there more pharmacotherapies for glaucoma?** Gary Novack, USA	
09:26	**ROCK inhibitors: ready for prime time** Brian Levy, USA	
09:39	**Glaucoma Drug Delivery: Concepts** Anuj Chauhan, USA	
09:52	**Glaucoma Drug Delivery: Update** Carol Rasmussen, USA	
10:05	**Latanoprost-eluting contact lens** Josesph Ciolino, USA	
10:18	**Q & A**	
10:30-11:00	***Coffee Break***	**Exhibition Hall**
11:00-12:30	**Novel Drug Delivery Approaches for Glaucomatous Disease** Chairs: **Malvina Eydelman**, USA & **Kuldev Singh**, USA	**Hall C**
11:00	**Introduction: Co-chairs Malvina Eydelman and Kuldev Singh**	
11:02	**Noncompliance with Glaucoma Therapy: The Magnitude of the Problem** George Spaeth, USA	
11:12	**FDA's regulation of Glaucoma Drug Delivery Products** Malvina Eydelman, USA	
11:22	**Injectable Intraocular Drug Delivery for IOP Lowering: Opportunities and Challenges** Dale Heuer, USA	
11:32	**Glaucoma Stents as Vehicles for Drug Delivery** Paul Harasymowycz, Canada	
11:42	**Punctal Plugs as Reservoirs for Glaucoma Drug Delivery** Brian Flowers, USA	
11:52	**Non Punctal Extraocular Drug Delivery in Glaucoma Patients** James Brandt, USA	
12:02	**Glaucoma Drug Delivery: The Importance of Surveillance** Kuldev Singh, USA	
12:12	**Q&A All Faculty**	
12:30-13:30	***Lunch Session sponsored by Santen***	**Hall A**

Afternoon Sessions – Hall A

14:00-15:30	***Cornea Cross-Linking (CXL)/New Innovations*** Chairs: **Penny Asbell**, USA	**Hall A**
14:00	**Efficacy and safety of accelerated cross link for keratoconus** Luigi Fontana, Italy	
14:10	**Corneal cross linking and the Boston Kpro** Joseph Ciolino, USA	
14:20	**Pediatric Corneal CXL** Omur Ucakhan-Gunduz, Turkey	
14:40	**Evaluating Progression in Keratoconus to Assess Cross Linking Efficacy** Penny Asbell, USA	
14:50	**Corneal collagen cross-linking: Past, present, and future** James Reidy, USA	
15:00	**Drops for Presbyopia** Almamoun Abdelkader, USA **Information on RVL-1201 and the pharmacologic treatment of ptosis** Barry Butler, USA	
15:10	**Q&A**	
10:30-11:00	***Coffee Break***	**Exhibition Hall**
16:00-17:30	***Symposium on Contact Lenses*** Chairs: **Penny Asbell**, USA & **Omur Ucakhan-Gunduz**, Turkey	**Hall A**
16:00	**Improving CL Safety** Malvina Eydelman, USA	
16:15	**Contact Lens Discomfort - Causes and Treatment** Omur Ucakhan-Gunduz, USA	
16:30	**Neurobiology of Contact Lens Discomfort** Pedram Hamrah, USA	
16:45	**Is there a role for MGD in contact lens drop out?** Penny Asbell, USA	
17:00	**Myopia progression** Omur Ucakhan-Gunduz, Turkey	
17:10	**Topical steroids protects the lacrimal functional unit of dry eye patients from desiccating stress** Jose Pinto-Fraga, Spain	
17:20	**Q & A**	

Saturday, July 11, 2015

Afternoon Sessions – Hall B

14:00-15:30	***Biologically designed drugs: present and future*** Chairs: **Uwe Pleyer,** Germany	**Hall B**
14:00	**IL- 17 inhibitors** Sofia Androudi, Greece	
14:15	**TNF inhibitors** Christoph Deuter, Germany	
14:30	**IL-1 antagonists for the treatment of uveitis** Michal Kramer, Israel	
14:45	**The horizons of biologically designed drugs for ocular inflammation** Uwe Pleyer, Germany	
15:00	**A panel discussion : Immediate and long term benefit/risk, The after effect – stopping therapy schemes, Pediatric populations and other special populations, The topical vs. systemic treatment paradigms, Biological step ladder approach for the non-responding patient** Moderated by: Uwe Pleyer, Germany Participating: Christoph Deuter, Germany, Michal Kramer, Israel, Sofia Androudi, Greece	
15:30-16:00	***Coffee Break***	**Exhibition Hall**
16:00-17:15	***Employing AC tap for anterior uveitis – practical applications*** Chair: **Talin Barisani**, Austria	**Hall B**
16:00	**Indications for ocular tapping in anterior viral uveitis** Soon Phaik Chee, Singapore	
16:15	**Available PCR primers, the definition of positive and negative errors, pros and cons: PCR vs. Goldmann-Witmer technique** Jolanda de Groot-Mijnes, Netherlands	
16:30	**Adapting therapy to PCR diagnosis** Talin Barisani, Austria	
16:45	**Panel: Future directions in AC TAP in practical clinical evaluation of uveitis patients** Moderated by: Talin Barisani, Austria Participants: Soon Phaik Chee, Singapore, Jolanda de Groot-Mijnes, Netherlands, Michal Kramer, Israel	

Saturday, July 11, 2015

Afternoon Sessions – Hall C

14:00-15:30	***Innovation For Safe and Effective Minimally Invasive Glaucoma Surgery*** Chairs: **Malvina Eydelman**, USA & **Kuldev Singh,** USA	**Hall C**
14:00	**Defining the Patient Population For Implantable MIGS Devices** Kuldev Singh, USA	
14:10	**Cataract Surgery as IOP Lowering Procedure** James Brandt, USA	
14:20	**Implantable MIGS Devices: Canal Based** Paul Harasymowycz, Canada	
14:30	**Implantable MIGS Devices: Suprachoroidal and Other Spaces** Brian Flowers, USA	
14:40	**Safety Endpoints and Patient Related Outcomes for MIGS Devices** George Spaeth, USA	
14:50	**Effectiveness Endpoints for MIGS Devices** Dale Heuer, USA	
15:00	**FDA Draft MIGS Guidelines** Malvina Eydelman, USA	
15:10	**Q&A**	
10:30-11:00	***Coffee Break***	**Exhibition Hall**
16:00-16:45	***Therapeutic advances in other optic neuropathies*** Chairs: **Barrett Katz**, USA	**Hall B**
16:00	**Neuroprotection – are we making any progress?** Leonard Levin, Canada	
16:10	**Neuroregeneration in non-glaucomatous optic neuropathies** Jeffrey Goldberg, USA	
16:20	**A Recombinant AAV2/2 Carrying the Wild-Type ND4 Gene for the Treatment of LHON: Preliminary Results of a First-In-Man Study and Upcoming Pivotal Efficacy Trials** Scott Uretsky, France	
16:30	**Neuroprotection in optic neuritis** Kenneth Shindler, USA	
16:40	**Q & A**	

Sunday, July 12, 2015

Morning Sessions – Hall B

08:00-09:00	***Infection Free Papers*** Chairs: **Eric Romanowski**, USA & **Regis P. Kowalski,** USA	**Hall B**
08:00	**The In Vitro Evaluation of the Virucidal Efficacy of Povidone-Iodine against Multiple Ocular Adenoviral Types** Eric Romanowski, USA	
08:10	**In vitro activity of toyocamycin and novel thioinozine derivative as potential drugs against amphizoic amoebae - the causative agents of Acanthamoeba keratitis** Lidia Chomicz, Poland	
08:20	**Corneal Cross-Linking as an Alternative Treatment in Refractory Acanthmoeba Keratitis** Justyna Izdebska, Poland	
08:30	**The In Vitro and In Vivo Antibacterial Evaluation of Brilacidin** Regis P. Kowalski, USA	
08:40	**cytomegalovirus retinitis in hiv-negative patients, retrispective interventional case series and practivcal approach to patients management** Vicktoria Vishnevskia-Dai, Israel	
08:50	**Eye pain and secondary headache in in the course of infection caused by Demodex** Maciej Oseka, Poland	
09:00-10:30	***Retina Free Papers*** Chairs: **Francesco Bandello**, Italy & **Ygal Rotenstreich**, Israel	**Hall B**
09:30	**A minimally invasive adjustable blunt injector for posterior segment delivery of drugs and cell therapy** Ygal Rotenstreich, Israel	
09:40	**TAK1 and PI3K inhibition decreases oxidative stress in RPE cells** Mordechai Goldberg, Israel	
09:50	**Evaluation of the safety of repeated subthreshold micropulse yellow laser photocoagulation in diabetic macular edema treatment** Elena Pedanova, Russia	
10:00	**Treatment selection after screening by Clearpath DS-120 lens fluorescence biomicroscope in diabetic patients** Francesco Bandello, Italy	
10:10	**Can AMD be prevented? The possible role of hydroxichloroquine in preventing AMD.** Joseph Pikkel, Israel	
10:20	**Effect of Chromogranin A-Derived Vasostatin-1 on Laser-Induced Choroidal Neovascularization in the Mouse** Francesco Bandello, Italy	
10:30-11:00	***Coffee Break***	**Exhibition Hall**

Sunday, July 12, 2015

Morning Sessions – Hall B

11:00-12:00	***Drug Development Free Papers*** Chairs: **Diane Tang-Liu,** USA & **Robert Gurney,** Switzerland	**Hall B**
11:00	**Special requirements for unpreserved multi-dose ophthalmic formulations** Degenhard Marx, Germany	
11:10	**Enhanced corneal permeation of coumarin-6 using nanoliposomes containing dipotassium glycyrrhizinate: in vitro mechanism and in vivo permeation evaluation** Xianggen WU, China	
11:20	**Essential Polyunsaturated Fatty Acid-Phloroglucinol conjugates protect RPE and Neural Retina against All-trans-Retinal-induced Damages** Aurelie Cubizolle, France	
11:30	**Nanoparticle cross-linked collagen shields for ocular drug delivery** Ilva Rupenthal, New Zealand	
11:40	**Fluorescein uptake in the anterior ocular segment to test a new topical drug delivery device for ocular medication** Rene Wubbels, Netherlands	
11:50	**A Novel Ex Vivo Model to Evaluate the Role of Müller Cells in Retinal Drug Delivery** Karen Peynshaert, Belgium	

E-Posters

DON ILHAM
Short-term response to intravitreal anti-VEGF treatment and the choroidal thickness in polypoidal choroidal vasculopathy
Jaromir Wasyluk
Evaluating the influence of trehaloze / hyaluronate solution on tear film osmolarity and ocular surface parameters in glaucoma patients on chronic topical therapy with BAK-preserved prostaglandines
MOON JEONG CHOI
Diffuse Unilateral Subacute Neuroretinitis: Case Report in Korea
chulgu kim
Comparison of 6-month Treatment Outcomes of Retinal Angiomatous Proliferation Between Ranibizumab and Aflibercept
María Sebastián Morelló
Use of antioxidants in the treatment of retinitis pigmentosa: Absorption of glutathione (GSH) through ocular membranes
Barbara Rajtar
The in vitro evaluation of antiviral activity of polyhexsanide against adenovirus type 5.
JOON MO KIM
The Effect of Anthocyanoside and Ginkgo Biloba Extract on Normal-Tension Glaucoma According to Presence of Diabetes
Shawkat Michel
Optical Coherence Tomography revolutionized early diagnosis and management of neovascular (wet) age related macular degeneration (AMD.
Ana Belén Haro Alvarez
Efficacy and safety of treatment with intravitreal Lucentis® in patients with advanced form of wet age-related macular degeneration in east area of Valladolid. Clinical practice.
Daniela Monti
Hot-melt extrusion technique (HME) to develop intravitreal inserts
Xian Zhang
the effect of a novel compound sq-603 in eiu and preliminary study of its mechanism
sophie seguin-greenstein
Afliberbept improves vision in eyes with severe vision loss due to wet age related macular degeneration
Naoual Dahmana
Development of micellar formulations of spironolactone for the topical treatment of eye diseases
Anna Ambroziak
EVALUATION OF CATIONIC NANOEMULSION TREATMENT FOR DRY EYE SYNDROME WITH ODDISEY ALGORITHM.
Eunjin Sohn
Extract of Polygonum cuspidatum attenuates diabetic retinopathy via inhibition of high-mobility group box-1(HMGB1) expression in streptozotocin-induced diabetic rats
ANETA HILL-BATOR
The eye wipes with polyhexanide (Hexaclean) in preoperative prophylaxis of cataract surgery.
yunmi lee
ANTI-GLYCATION AND ANTI-ANGIOGENIC ACTIVITIES OF 5'-METHOXYBIPHENYL-3,4,3'-TRIOL, A NOVEL PHYTOCHEMICAL COMPONENT OF OSTEOMELES SCHWERINAE
Izabela Chudzicka-Strugala
Effectiveness and safety of lipogel containg essential oils from Spanish Sage and Aloe Vera in chronic blepharitis caused by Demodex spp.

12th ISOPT *Clinical*

The International Symposium on
Ocular Pharmacology and Therapeutics

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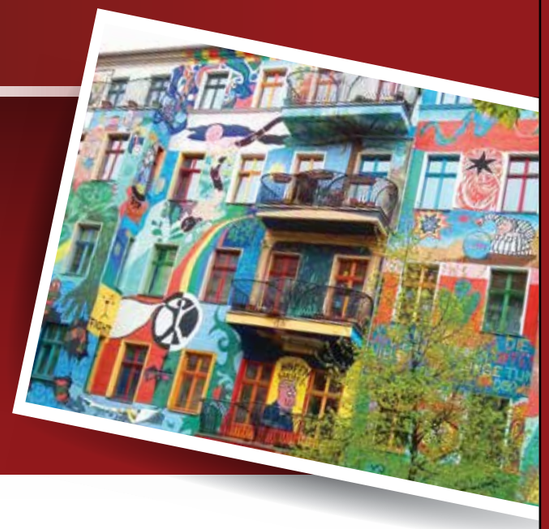

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Friday, July 10, 2015

Lunch Sessions – Hall A

12:30-13:30	***Molecular networks and retinal growth factors – advancing the science of care*** ***Novartis Sponsored Session***	**Hall A**

Welcome and introduction
Eric Souied , France
Growth factor dynamics in the eye
Eric Souied , France
The role of pericytes and PDGF in the eye
Antonia Joussen (Germany)
Targeted combination therapy – the next step for nAMD care?
Michael Larsen (Denmark)
Questions
Closing remarks Eric Souied, France

Saturday, July 11, 2015

Lunch Sessions – Hall A

Hall A

12:30-13:30	***Ikervis®: Changing paradigms of treating severe keratitis in dry eye disease*** ***Santen Sponsored Session***

12:30	**Rationale for anti-inflammatory treatment in severe dry eye** Elisabeth Messmer, Germany
12:50	**Improving delivery of active substances to the ocular surface with cationic emulsions** Simon Benita, Israel
13:10	**Ikervis® – a new therapeutic option for the treatment of severe keratitis in dry eye** Andrea Leonardi, Italy

12th ISOPT Clinical

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Abstracts

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Abstracts

Fundus autofluorescence: Quantitation and Interpretations

Janet Sparrow

Ophthalmology, Columbia University Medical Center, USA

Short-wavelength fundus autofluorescence (SW-AF) originates from fluorophores that are deposited in retinal pigment epithelial (RPE) cells as lipofuscin. These fluorophores exhibit

spectral features consistent with SW-AF. The compounds of RPE lipofuscin that have been identified are bisretinoid molecules that form in photoreceptor cells due to reactions of vitamin A aldehyde.

Interest in a role for RPE lipofuscin in AMD stems from its age-related increase, an accumulation that is more pronounced in central retina, a propensity for adverse effects on cells and demonstrated links to drusen. Nevertheless, it is also understood that contributions to AMD pathogenesis from RPE lipofuscin would operate within the context of background genetic risk.

SW-AF imaging is commonly used to monitor the healthy of RPE with areas of high AF indicating increased lipofuscin levels and areas of low or absent AF indicating RPE loss. However interpretations of SW-AF signal can be complex. For instance impaired photoreceptor may generate increased levels of bisretinoid fluorophores thus amplifying SW-AF signal. Methods recently developed to quantify SW-AF using images acquired with a confocal laser scanning ophthalmoscope (cSLO) and an internal fluorescent reference, may help to clarify the role of lipofuscin. On the other hand, since RPE lipofuscin undergoes photodegradation, SW-AF intensities measured at any time likely reflect only a portion of the total amount of fluorescent material that has been deposited in RPE.

Regression of drusen as a marker for disease progression in age-related macular degeneration

Philipp Roberts[1], Ferdinand Schlanitz[1], Bernhard Baumann[2], Michael Pircher[2], Christoph K Hitzenberger[2], Michael Pircher2, Christoph K Hitzenberger[2], Ursula Schmidt-Erfurth[1]

Ophthalmology, Medical University of Vienna, Austria Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Austria

Purpose: To quantify the change of drusen volume during disease progression from early to advanced age-related macular degeneration (AMD) and identify its prognostic value. Methods: Participants with early and intermediate AMD were consecutively included in a prospective observational study. All eyes underwent continuous follow-up examinations every six months over a minimum of three years using a standardized protocol including spectral-domain optical coherence tomography (SD-OCT) and polarization-sensitive OCT (PS-OCT). Drusen volume was measured by PS-OCT using an automated algorithm exploiting the RPE-specific property to depolarize light. SD-OCT (Spectralis) data were segmented manually by expert graders in a reading center setting.
Results: 109 participants with AREDS categories 2 and 3 were included in the study. Fifty eyes were followed consecutively for at least three years. Gradings from 32,000 individual B-scans were analyzed for drusen volume, showing an initial mean drusen volume of 0.17mm^3. The increase in drusen volume was similar among all eyes, and a long-term drusen volume development could be reconstructed, with the function volume = 0.005 + 0.007x + 0.0002x2 + 0.00009x3 with x = years and a R2 = 0.955. Spontaneous drusen regression was observed in 18 of 50 eyes at least once during the study period, three of which developed neovascular AMD and four geographic atrophy subsequent to regression. Mean drusen volume was significantly higher in eyes undergoing regression than in those with no regression.
Conclusion: Drusen demonstrate a cubistic increase in volume over time. Spontaneous drusen regression occurs at increased volumes and appears to precede conversion to advanced neovascular and atrophic AMD.

The European perspective of the nutritional supplements in AMD prevention

Alfredo Garcia Layana

Ophthalmology, Clinica Universidad de Navarra, Spain
CUN, Fundacion Instituto Sanitario de Navarra, Spain
RETICS OFTARED, Instituto de Salud Carlos III, Spain
SERV, Vitreo-Retinal Spanish Society, Spain

European legislation relating to food supplements calls for maximum amounts of addition (Recommended Dietary Allowances) to protect consumer's safety. These doses exceed those used in the two AREDS studies. Nevertheless, micronutrition has already become part of the day-to-day management of AMD for a considerable proportion of European ophthalmologists.. In this context, European use of micronutrients in AMD prevention has many weakness, unresolved questions and difficult to extrapolate AREDS2 results. The control group in AREDS2 received high dose supplements already shown to be effective in the prevention of AMD progression, and more than 10% added DHA/EPA supplements to their diet. These two factors might be responsible for a 'ceiling effect' wherein AREDS2 that could make it more difficult to demonstrate a real effect of DHA/EPA. Given the findings in some European interventional studies in this area, it is necessary to urge caution in closing the chapter on omega-3, but rather suggest building on these findings with more detailed exploration of its role with different formulations and populations. Health claims regarding the role of DHA and EPA in the maintenance of vision have recently received approval from the European Food Safety Authority. There is not enough data about the effect of DHA/EPA combined with the RDA of vitamins and minerals, or the addition of other micronutrients with biological plausibility effects on AMD prevention such as resveratrol, vitamin B or vitamin. A European clinical trial about the micronutrition effects of these substances in AMD is mandatory.

Abstracts

Therapeutic strategies in geographic atrophy

Steffen Schmitz-Valckenberg,
Frank G. Holz, Monika Fleckenstein
Ophthalmology, University of Bonn, Germany

Purpose: Geographic atrophy (GA) secondary to age-related macular degeneration (AMD) is the next challenge following the breakthrough in the treatment of neovascular AMD. This paper gives an overview of various interventional pharmacologic approaches.

Methods: GA is characterized by the development and continuous enlargement of atrophic patches (mean rate between 1.2 to 1.8 mm2/year) that are spatially confined to absolute scotomata. The slow progression of the disease and the low sensitivity of central visual acuity measurements compared to progressive visual disabilities require innovative concepts for the assessment of therapeutic efficacy. The primary goal in treating GA is still to identify the underlying cause.

Results: Clinical endpoints include reduction in drusen burden, slowing the enlargement rate of GA lesion area, and slowing or eliminating the progression to advanced AMD. Different pathways that are currently evaluated include the preservation of retinal pigment epithelium (RPE) cells and photoreceptors, prevention of oxidative damage, reduction in the accumulation of retinal toxins, and alleviation of inflammatory damage. Particularly regulators of the complement systems such as Eculizumab, LFG316, ARC-1905 or Lampalizumab have been recently in focus. While photoreceptor and RPE loss may be the initial event, intervention at any individual molecular pathway may not be sufficient to completely halt the progression to GA.

Conclusions: The complement system is currently one major target for pharmaceutical interventions to slow down GA progression. Until efficacy and safety is demonstrated in large-scale clinical trials for any therapeutic strategy, visual rehabilitation remains essential.

Stem Cell Therapy for Dry AMD

Wen-Hsiang Lee

Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, USA

Purpose: Geographic atrophy is a non-neovascular form of advanced age-related macular degeneration (AMD) characterized by loss of photoreceptors and retinal pigment epithelium (RPE) associated with severe central visual loss and visual impairment. Currently there is no treatment for atrophic form of AMD. Stem cells can potentially differentiate into RPE cells, and stem cell therapy is a potential treatment strategy for atrophic AMD.
Methods: Systematic review of literatures and scientific presentations on mechanisms and types of stem cells and current stem cell studies for atrophic AMD. Types of stem cells used and methods of delivery were compared, and the pros and cons, special considerations, and potential complications of stem cell therapy were reviewed.

Results: Current clinical studies or clinical trials on stem cells for atrophic AMD include induced pleuripotent stem cells, human embryonic stem cells, human neural stem cells, and human umbilical tissue-derived stem cells. Preliminary results from these studies showed good safety profile. While preliminary data from one study showed potential visual improvement, results from other studies are still pending.
Conclusions: Clinical studies using various types of stem cells for treatment of atrophic AMD are currently ongoing. Although long-term results are still needed to determine the treatment efficacy, preliminary data show stem cells to be a potential new therapeutic strategy for atrophic AMD.

TARGETING THE INNATE IMMUNE RESPONSE IN LATE DRY AGE RELATED MACULAR DEGENERATION

Shelley R. Boyd
Dept of Ophthalmology & Vision Sciences, University of Toronto, Canada
BioMedical Engineering, McMaster University, Canada
President & Chief Scientific Officer, Translatum Medicus inc (TMi), Canada

Purpose: AMD is the leading cause of irreversible blindness in the developed world, yet no treatments exist to reduce the onset or expansion of geographic atrophy (GA). The purpose of our work was to (1) clarify the role of macrophage activity in a clinically-relevant model of dry AMD, and (2) evaluate the effects of the immunomodulatory compound TMi-018.

Results: Using a novel model of aggressive dry AMD with GA that uniquely phenocopies disease, we identified a progressive shift in the cytokine and mRNA networks that define the M1/M2 spectrum of macrophage polarization. By tipping the cytokine profile in favour of M2, TMi-018 dose-dependently reduces the size of patchy retinal pigment epithelium (RPE) loss and its expansion. With a novel mechanism of action, we show that TMi-018 alters mRNA transcription of key components of the M1/M2 transcriptome.

Conclusions: We suggest that modulation of the M1/M macrophage profile is a useful therapeutic approach to reduce both the onset and expansion of GA.

Abstracts

Imaging early and advanced atrophic AMD

Philipp Roberts[1], Ferdinand Schlanitz[1], Christopher Schuetze[1], Bernhard Baumann[2], Michael Pircher[2], Christoph K. Hitzenberger[2], Ursula Schmidt-Erfurth[1]
[1]*Department of Ophthalmology, Medical University of Vienna, Austria*
[2]*Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Austria*

Purpose: To identify characteristic findings in early and advanced atrophic age-related macular degeneration (AMD) using multimodal imaging.

Methods: More than 200 patients with different stages of AMD (AREDS 2-4) were prospectively included in an observational longitudinal imaging study. Participants were examined every 3 months including spectral-domain optical coherence tomography, infrared imaging, fundus autofluorescence and polarization-sensitive OCT (PS-OCT). Drusen load and area of geographic atrophy (GA) were automatically segmented by PS-OCT imaging. Typical findings in the different imaging systems were compared.

Results: In eyes with drusen, the level of RPE alteration was significantly related to drusen size, shape, internal reflectivity and homogeneity of the drusen. Spontaneous drusen regression was observed in 18 of 50 eyes at least once during the study period. In this group, three eyes developed choroidal neovascularisation and four GA subsequent to volume regression. Mean drusen volume was significantly higher in eyes undergoing regression than in those without regression. In fellow eyes of patients with unilateral CNV, monthly increase in drusen load, automatically measured by PS-OCT, was higher in eyes developing CNV than in non-progressing eyes. In eyes with GA, PS-OCT demonstrated high reproducibility of GA lesion size determination. There was no statistically significant difference in GA-progression between AF and PS-OCT in eyes with GA during follow-up.

Conclusion: Multimodal imaging in early AMD facilitates the detection of risk factors for the conversion to advanced AMD. Automated segmentation of drusen and geographic atrophy by three-dimensional PS-OCT imaging offers objective and reproducible endpoints for interventional studies.

OCT angiography of the choroidal vasculature in non-exudative macular degeneration

Nadia Waheed, Talisa deCarlo, Mehreen Adhi, Omid Moghimi, Adam Chin, Jay Duker
Ophthalmology, Tufts University Medical Center, New England Eye Center, USA

PURPOSE: To investigate spectral domain optical coherence tomography (SD-OCT) angiography to visualize vascular changes in patients with non-exudative age-related macular degeneration (AMD).
DESIGN: Observational, prospective, cross-sectional study.

PARTICIPANTS: A total of 20 eyes from normal subjects and 20 eyes from patients with non-exudative AMD were included in our study. Of the 20 eyes with non-exudative AMD, 12 eyes had AMD without geographic atrophy (GA) and 8 eyes had AMD with GA.

METHODS: A commercially available SD-OCT system (Optovue XR Avanti) was used to perform volumetric optical coherence tomography angiography (OCTA) of the retinal and choriocapillaris (CC) vasculatures in normal subjects and in patients with non-exudative AMD.

MAIN OUTCOME MEASURES: Qualitative comparison of retinal and CC vasculatures in normal subjects versus those in patients with the clinical diagnosis of non-exudative AMD.

RESULTS: In all 8 eyes with GA, OCTA showed CC atrophy within the region of GA, which extended beyond the margins of the GA. AMD patients without GA exhibited CC alterations of varying severity. Drusen were identified both above regions of CC alteration and above regions of normal CC. However, there was significant signal attenuation seen below some areas of drusen that confounded the results of choriocapillaris alteration under drusen.

CONCLUSIONS: The ability of OCTA to noninvasively visualize alterations in the retinal and CC vasculatures makes it a promising tool for assessing AMD as well as for elucidating disease pathogenesis and progression. However, caution must be taken in interpreting the results of the OCTA given significant shadowing artifact

Development of Risk Prediction Models for Macular Degeneration Incorporating 10 Common and Rare Genetic Variants 2006-2015: Genotype-Phenotype Correlations

Johanna M. Seddon
Ophthalmology, Tufts Medical Center, USA

Purpose: To determine predictors of advanced age-related macular degeneration (AMD), develop a new predictive model and an online application, and assess genotype-phenotype associations.

Methods: Among 2951 subjects with a mean follow-up time of 8.8 years, 834 progressed to geographic atrophy or neovascular AMD. Survival analysis was used to assess genetic, demographic, environmental, and macular covariates independently associated with progression. Analyses also included attributable risk (AR), area under the curve statistics (AUCs), reclassification odds ratios (ORs), and split-sample validation. The clinical phenotype for the rare variant CFH R1210C, the strongest risk factor for AMD to date, was assessed.

Results: Ten genetic loci were independently associated with progression:rare variants CFH R1210C and rare variant C3 K155Q (hazard ratio: 1.7, 95% confidence interval: 1.2-2.5, p=0.002), and common variants in CFH, ARMS2/HTRA1, CFB, C3, C2, COL8A1 and RAD51B. The AMD rare variant in the C9 gene was related to progression in the univariate model. Eighty percent of incident AMD was attributable to genetic factors. The AUC for progression to advanced AMD over 10 years was 91.1% based on the composite risk model; split-sample

validation AUC was 90.7%. Subjects were categorized into a more accurate risk category if genetic information was included (OR: 3.2, p <0.0001). The composite risk score addded information beyond the baseline macular phenotypes.The online risk calculator is available at www.seddonamdriskscore.org. The CFH R1210C variant was associated with earlier onset of AMD and extensive macular and extra-macular drusen and advanced disease.

Conclusion: The on-line comprehensive model will be useful for identifying high risk patients, selecting therapies and designing clinical trials. Rare variants are associated with earlier disease and characteristic phenotypes.

Update on the Results of the Phase 2 Study of Squalamine Lactate Ophthalmic Solution 0.2% (OHR-102) in Neovascular Age-related Macular Degeneration (AMD)

Jason Slakter
Ophthalmology, NYU School of Medicine, USA

Purpose: To determine if topical OHR-102 administered BID in combination with Ranibizumab (RBZ) PRN can safely improve visual outcomes and reduce treatment frequency of RBZ compared to RBZ PRN monotherapy in patients with neovascular AMD.

Methods: Phase 2, prospective, randomized, double-masked, placebo-controlled, multicenter study in treatment naïve patients with CNV due to AMD measuring 12 disc areas and any lesion composition, and BCVA of 20/40 to 20/320. Diabetics without diabetic retinopathy were included. All patients received RBZ at baseline and randomized 1:1 to topical OHR-102 BID or vehicle solution BID. Patients were followed monthly for 9 months. RBZ retreatment was performed under strict OCT criteria.

Results: 142 patients were enrolled, with 128 completing the nine month study period. Mean baseline BCVA was 59 letters (~20/63 Snellen). In the intent-to-treat (ITT-LOCF) population with classic containing CNV (OHR-102 n=38, RBZ monotherapy n=32), 42% of the OHR-102 group achieved ≥3 line gain at nine months, compared to 28% in the RBZ monotherapy group. Less of a benefit was seen in the overall population (classic containing and occult only CNV lesions). Mean gains in visual acuity were +10.5 letters for OHR-102 combination arm and +5.4 letters with RBZ monotherapy, a benefit of +5.1 letters. The mean number of injections between the arms was not meaningfully different. OHR-102 was generally well tolerated, with only two treatment related discontinuations.

Conclusion: The positive visual effects of topical OHR-102 in combination with RBZ PRN on in classic containing CNV support the planned Phase III development program.

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

Francesco Boscia, D'Amico Ricci Giuseppe Dott. Giuseppe
D'Amico Ricci, Ermete Giancipoli, Giulia Airaghi
Ophthalmology, Azienda Ospedaliera Universitaria Sassari, Italy

An overview of controlled clinical trials comparing head to head ranibuzmab to bevacizumab.
The first major study to compare bevacizumab and ranibizumabwas the Comparison of AMD Treatments Trials (CATT), 2- year noninferiority study. There were 4 treatment groups, with each drug being dosed either monthly or PRN.
Both 1-year and 2-year results demonstrated that the 2 drugs were fairly similar in efficacy, particularly when dosed monthly throughout the 24-month study.
The Inhibit VEGF in Age-related Choroidal Neovascularization (IVAN) study, conducted in the United Kingdom, was the first international version of CATT with the treatment groups defined in the same way as CATT.
The IVAN results confirmed the CATT results in both years. Bevacizumab was not found to be noninferior to ranibizumab.
The Groupe d'Evaluation Français Avastin versus Lucentis (GEFAL) study - which was conducted in France and followed the study design of both CATT and IVAN - confirmed through the first year similar findings that these 2 larger studies have shown.
The MANTA results show that bevacizumab is equivalent to ranibizumab for visual acuity at all time points over 1 year, in patients aged more than 50 years with treatment naive nAMD.
There is no significant difference of decrease of retinal thickness or number of adverse events.
Both studies CATT and IVAN showed that the intermittent approach (CATT PRN and IVAN discontinuous) was significantly inferior when compared to monthly treatment. All four comparative clinical trials (CATT, IVAN, MANTA, GEFAL) demonstrated a statistically significant difference in the risk of systemic SAE by drug, with a potential disadvantage to bevacizumab.

New Drugs in Development for Wet AMD

Jason Slakter
Ophthalmology, NYU, USA

Purpose: To identify new therapeutic approaches to the management of exudative AMD.

Methods: A review of current clinical investigative programs targeting choroidal neovascularization secondary to AMD.

Results: New drugs in development for CNV can be classified into three main categories: 1) Increased duration of effect to reduce treatment burden with similar or improved visual efficacy (e.g. anti-VEGF DARPIN, ESBA 1008, sFLT1 Gene Therapy); 2) Combination treatment along with anti-VEGF to improve visual function (e.g. Fovista anti-PDGF, OHR-102 anti VEGF/PDGF/bFGF, REGN2176-3 anti-VEGF/PDGF, Sphingomab anti-S1P, X-82 anti VEGF/PDGF), and 3) Alternative delivery approaches including topical, oral and gene

therapy delivery techniques (e.g. Topical OHR-102, Topical Pan-90806, Topical Regorafenib, Oral X-82, Gene therapy sFLT1).

Conclusions: What the future holds for the treatment of CNV in AMD is likely a combination of the agents currently in clinical trials as well as others in earlier stages of development. It is probable that we will utilize agents that control various steps in the angiogenic cascade as well as those which may act outside the VEGF pathways to control neovascular proliferation. Damage from fibrosis and underlying atrophic degeneration of the RPE will require additional lines of research to resolve.

LUMINOUS Study

Albert Augustin
Department of Ophthalmology, Klinikum Karlsruhe, Germany

The Luminous study is a long term real-world examination of both, safety and effectiveness of Ranibizumab. In this investigation Ranibizumab was used for a variety of retinal diseases with AMD being the major disease entity. This study aims to investigate how Ranibizumab is used in actual practice (real world experience). The patients were treated according to local protocols within the respective Ranibizumab licence. The age range is wider than in the clinical trials. The study includes multiple countries, and is ethnically diverse. Patients in the study included those who had been receiving Ranibizumab as well as newly diagnosed patients who had never received any treatment before. Ranibizumab demonstrated favourable 1-year safety profile for wet AMD which was consistent with previous reported trial data. Additional data from a larger patient population are needed to better describe the long-term safety profile of Ranibizumab in routine clinical practice and further evaluate risk for infrequent but serious events in real-life settings.

Steroid and IOP raise - Corticoid complications

Yan Guex-Crosier
Jules Gonin Eye Hospital, uveitis clinic, Fondation Asile des Aveugles, University of Lausanne, Switzerland

Since their discovery in the 1950s, corticosteroids have been widely used in the treatment of inflammation and particularly the management of auto-immune diseases. More than 50% of blindness could be prevented by the use of corticosteroids in Juvenile Idiopathic Arthritis. Corticosteroids achieve rapid control of ocular inflammation. The dose can be modulated to control the disease, b its use is not indicated for long term.

To avoid severe systemic or ocular side effects, clinicians must be aware of pros and cons of each specific molecule depending also on the route of administration. Topical steroid drops are preferred in anterior uveitis. Peri-ocular or intraocular corticosteroid injections are used to achieve efficacy in the posterior segment. Beside systemic complications, ocular complications are mainly ocular hypertension in up to 30% of patients and cataract. Combination of local and systemic therapies, as well as switching to an immune-modulator is probably the key of success.

Macular edema : Steroids are Equal to anti-VEGF

Albert Augustin
Department of Ophthalmology, Klinikum Karlsruhe, Germany

Macular edema is the final common pathway of numerous retinal diseases, and ocular disorders associated with this condition are, when considered together, a major cause of blindness in the Western world. In a physiological setting, the blood-retinal barrier (BRB), which is largely formed by the retinal pigment epithelium and the retinal capillary endothelial cells, blocks the passage of fluid and potentially harmful blood-borne molecules into the retina. When this barrier is broken, water and proteins can enter the retinal extra- and intracellular space, with fluid accumulation leading to edema. Frequently, BRB leakage occurs at the macula, causing ME and vision loss.

The biochemical/physiological basis for the barrier are tight junctions between endothelial cells (inner barrier) and tight junctions between the apices of RPE-cells (outer barrier). Those tight junctions can be altered by numerous mechanism which leads to fluid movement to the tissue (edema development). A temporary closure can be achieved by anti-VEGF drugs which are known to act faster than steroids. However, because of a short halflife these effects are also short and relapses occur frequently. Steroids act not as fast as anti-VEGF drugs but may lead to a more durable effect. Thus, looking at a longer period of time steroids are at least equal to anti-VEGF. Evidence from current literature will be presented.

ALL STEROIDS ARE EQUAL BUT SOME ARE MORE EQUAL THAN OTHERS

Ikram EL-ZAOUI, Ikram EL-ZAOUI[1,2], Francine BEHAR-COHEN[1,2]
[1]Team 17, physiopathology of ocular diseases to clinical developments, France
2Centre de Recherche des Cordeliers, 2Pierre et Marie Curie University, France

Glucocorticosteroids (GCs) are widely used in the treatment of many pathologies, including ophthalmological diseases. Notably, high doses of GC are injected intra-ocularly or systemically to treat macular oedema, neovascularization and numerous general inflammatory states. Amongst the widely recognized side effects of GCs, retinal injuries have been well documented.

A series of experimental and clinical studies have shownthatthe therapeutically used doses of GCs are toxic for retina and their effect was dependent of both chemical structure of GC and cell type. Detailed pre-clinical data will be presentedand cell
death mechanisms involved will be discussed.

Abstracts

Ophthalmological imaging with ultrahigh field magnetic resonance tomography: technical innovations and frontier applications

Oliver Stachs
Ophthalmology, University of Rostock, Germany

This review documents technical progress in ophthalmic magnetic resonance imaging at ultrahigh fields (UHF-MRI; B(0)≥7.0 T). The review surveys frontier applications of UHF-MRI tailored for high spatial resolution in vivo imaging of the eye, orbit and optic nerve. Early examples of clinical ophthalmic UHF-MRI including the assessment of melanoma of the choroid membrane and the characterisation of intraocular masses are demonstrated. A concluding section ventures a glance beyond the horizon and explores research promises along with future directions of ophthalmic UHF-MRI.

Clinical Indications for In Vivo Confocal Microscopy

Pedram Hamrah
Cornea Service and Boston Image Reading Center, New England Eye
Center and Tufts Medical Center, Department of Ophthalmology, Tufts University, USA

In vivo confocal microscopy (IVCM) is minimally invasive and high-resolution technology that allows for the assessment of the cornea and the ocular surface at a cellular level. It provides images at a quasi-histological level, delineating corneal epithelial cells, the Bowman's layer, immune and inflammatory cells, stromal keratocytes, corneal nerves, and the corneal endothelium in healthy eyes. This review summarizes current and promising clinical indications for the use of IVCM.
Applications for diagnosis and management of ocular surface diseases will be discussed, where IVCM can aid in the understanding of the pathophysiology of disease. In addition, this review will focus on the management of infectious keratitis, including Acanthamoeba and fungal keratitis. Further, IVCM allows for the study of corneal nerves, and its utility in diagnosis and management of neurotrophic keratopathy and corneal neuralgia will be addressed. We discuss how, by providing both qualitative and quantitative assessment, IVCM can be used to demonstrate early subclinical disease, grade layer-by-layer severity, and allow monitoring of disease severity by cellular alterations. Imaging-guided stratification of patients may also be possible in conjunction with clinical examination methods. Visualization of subclinical changes and stratification of patients in vivo, allows objective image-guided evaluation of tailored treatment response based on cellular morphological alterations.

OCT for surface eye tumors

Frederick Fraunfelder
Ophthalmology, University of Missouri, USA

Purpose: To analyze OCT imaging of surface eye tumors and demonstrate clinically useful evidence for this diagnostic tool in caring for eye cancer patients.
Methods: Literature review and case reports.
Results: Hyperreflective nuclei, dysplastic cells, tumor volume, and growth over time are useful parameters to observe with OCT
Conclusion: OCT imaging can be an effective tool to diagnose and follow surface eye malignancies.

Large scale mosaicking the subbasal nerve plexus of the cornea

Oliver Stachs
Ophthalmology, University of Rostock, Germany

The high resolution of corneal confocal microscopy (CCM) allows in vivo imaging of the corneal sub-basal nerve plexus (SNP). The field of view of a conventional single CCM image (0.16 mm^2) is not sufficient for the reliable morphometric characterisation of the SNP. Therefore we are developing a highly automated mosaicking technique for large-area imaging of the SNP using CCM image sequences. Using a first prototype system and an appropriate fixation target trajectory, a mean growth of the covered SNP area of 0.18 mm^2/s could be achieved. Using the presented technology, large-area images of the SNP can be generated. The technology is characterized by a high degree of automation and short examination times.

Clinical Indications for Corneal En Face OCT

Pedram Hamrah
Cornea Service and Boston Image Reading Center, New England Eye
Center and Tufts Medical Center, Department of Ophthalmology, Tufts University, USA

Optical coherence tomography (OCT) has revolutionized the clinical practice of ophthalmology. It is a noninvasive imaging technique that provides high-resolution, cross-sectional images of tissues. More recently, with volume-rendering procedures, "En Face" images can be reconstructed, which complement and identify microstructural information not available with standard anterior segment (AS)-OCT.
En Face AS-OCT images provide clinicians with a better understanding of a specific area of interest in the cornea, similar to in vivo confocal microscopy. This review discusses the clinical applications of the En Face AS-OCT in the diagnosis and management of corneal and anterior segment diseases. Applications for ocular surface disease, meibomian gland dysfunction, conjunctival lesions, infectious keratitis, corneal scarring, corneal edema, corneal neovascularization, anterior uveitis, corneal transplantation, keratoprosthesis and corneal trauma will be discussed. The emergence of En Face imaging will aid clinicians in medical and surgical management of corneal and anterior segment diseases beyond cross-sectional AS-OCT imaging.

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 lasercoagulation as a primary treatment for diabetic macular edema. Macular grid lasercoagulation after intravitreal triamcinolone for diffuse diabetic macular edema is another possible combination therapy for DME. Several authors demonstrated that lasercoagulation following IVTA is more effective than IVTA monotherapy for diffuse DME. Combination therapy required fewer additional treatments and resulted in a lower recurrence rate than IVTA monotherapy.
Several authors evaluated the effectiveness of pars plana vitrectomy (PPV) with removal of the internal limiting membrane (ILM). The strategy offers promising results. However, a longer follow-up is needed to assess the effects of this treatment. The results of the major most recent trials will be presented.

Improving the conventional eyedrop: Topical treatment for retinal disease including diabetic macular edema

Einar Stefansson
Ophthalmology, Univ. Iceland, Iceland

Conventional eye drops are washed off the eye within minutes and generally deliver only 3-5% of the drug into the eye. Lipophilic drug molecules which can penetrate the layers of the eye wall are generally poorly soluble in aqueous eye drops and can only be formulated in relatively low concentrations. As a consequence conventional eye drops deliver relatively small amounts of drugs into the eye, which do not reach the posterior segment in biologically active concentrations.
Cyclodextrin nanoparticle eye drops
Cyclodextrin nanoparticles improve these limitations of conventional eye drops.
Cyclodextrins can dissolve large concentrations of lipophilic molecules in an aqueous solution. The naonoparticles adhere to the ocular surface for at least 6 hours compared to a few minutes with conventional eye drops. Sustained release and high drug concentration improve bioavailability and relatively large amounts of drug enter the eye and reach the choroid, retina and vitreous. One application of 1.5% dexamethasone cyclodextrin nanoparticle eye drops provides 60 ng/g of dexamethasone in the rabbit retina.
Clinical studies
To date 37 patients have received dexamethasone cyclodextrin nanoparticles eye drops for diabetic macular edema, DME. About 30% of these patients have improved visual acuity by 15 ETDRS letters or more and central macular thickness has decreased significantly. Similarly in intermediate and posterior uveitis with cystoid macular edema, improvement in retina thickness, vitreous haze and visual acuity have been seen. Cyclodextrin nanoparticle eye drops provide sustained release and high drug concentration eye drops. They deliver large amounts of drugs into the eye and relatively less into the systemic circulation. In clinical studies they effectively treat retinal diseases including diabetic and uveitis macular edema.

The effect of topical 1.5% dexamethasone γ-cyclodextrin nanoparticle eye drops for diabetic macular edema

Akihiro Ohira, Katsunori Hara[1,2], Gauti Johannesson[3], Thorsteinn Loftsson[4], Einar Stefansson[5]
[1]*Ophthalmology, Shimane University, Japan*
[2]*Ophthalmology, Shimane University School of Medicine, Japan*
[3]*Department of Clinical Science, Ophthalmology, Umea University,*
[4]*Faculty of Pharmaceutical Sciences, University of Iceland, Iceland Sweden*
[5]*Department of Ophthalmology, Faculty of Medicine, National University Hospital, University of Iceland, Iceland*

Purpose: To examine the effect of topical 1.5% dexamethasone γ-cyclodextrin nanoparticle eye drops for diabetic macular edema (DME) and compare to posterior subtenon injection of triamcinolone acetonide.
Methods: In a prospective randomized controlled trial 26 eyes of 26 consecutive patients with chronic DME were randomized to a) topical treatment with dexamethasone nanoparticle eye drops x3/day for one month, x2/day the next month and finally x1/day the third month or b) one posterior subtenon injection of 20mg triamcinolone acetonide. Study visits included best-corrected visual acuity, intraocular pressure (IOP), spectral domain optical coherent tomography and blood samples at baseline and at 4,8,12 and 16 weeks.
Results: The logMAR visual acuity improved significantly with dexamethasone nanoparticle eye drops from 0.4930.37 (mean3SD) to 0.3930.31 and 0.3830.31 at 4 and 8 weeks respectively. One third of the eye drop group improved more than 0.3 logMAR units. For triamcinolone, logMAR changed significantly from 0.3930.28 at baseline to 0.3030.28 at 4 weeks and 0.3130.34 at 12 weeks. There was a modest increase in IOP at all time points with dexamethasone nanoparticle eye drops while no increase was seen with triamcinolone. Serum cortisol was affected by both treatments.
Conclusion: Topical dexamethasone γ-cyclodextrin nanoparticle eye drops significantly improve visual acuity and decrease macular thickness in patients with DME. The effect is similar to that from subtenon triamcinolone as well as to reports on intravitreal steroid implants (Ozurdex®) and triamcinolone intravitreal injections.

Abstracts

Corneal Allograft Rejection

Bennie Jeng
Ophthalmology and Visual Sciences, University of Maryland School of Medicine, USA

The mechanism of corneal allograft rejection is complex.
The normal cornea is immune privileged, but this privilege can be lost by inflammation and neovascularization. Standard management of corneal graft rejection has not changed much in recent times. Prompt recognition by patients through education is paramount.
Treatment involves corticosteroids: topical, subconjunctival, subtenon, oral, and even intravenous. Intravitreal injection of steroids, as well as the use of cytotoxic agents has also been proposed for use in treating allograft rejection. Prevention of corneal graft rejection involves the identification of "high-risk" situations. Calcineurin inhibitors, antimetabolites, and even monoclonal antibodies are routinely used in these situations. Other drugs and modalities are also currently being studied for use in prophylaxing against allograft rejection in "high-risk" eyes.

Surrogate Biomarkers for Inflammation in Dry eye disease for Assessment of Therapeutic Efficacy

Pedram Hamrah[1,3], Yureeda Qazi[1], Ahmad Kheirkhah[1], Thomas Dohlman[2], Reza Dana[2]
[1]*Ocular Surface Imaging Center, Cornea Service, Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, USA*
[2]*Cornea Service, Ophthalmology, Massachusetts Eye and Ear*
[3]*Cornea Service, New England Eye Center and Tufts Medical Center, Department of Ophthalmology, Tufts University, USA Infirmary, Harvard Medical School, USA*

Purpose: To quantify changes in corneal dendritic cell (DC) density using in vivo confocal microscopy (IVCM) before and after anti-inflammatory therapy in evaporative dry eye (EDE), and to compare these changes to symptoms and clinical signs.

Methods: A phase IV, randomized, vehicle-controlled, double-masked, single-center clinical trial was conducted with 54 subjects clinically diagnosed with EDE that received either steroid alone, steroid with antibiotic, or artificial tears alone for 4 weeks with bilateral quantification of central corneal DC densities on IVCM pre- and post-treatment. Sixty-two healthy reference controls were included for comparison. Symptoms were measured by Ocular Surface Disease Index (OSDI) questionnaire. Clinical improvement was assessed by corneal fluorescein staining (CFS) and tear break-up time (TBUT).

Results: Corneal DCs increased by over five-fold in EDE (P0.0001) with no differences between the treatment groups at baseline (P=0.59). Following treatment, DC density reduced in both the steroid-containing treatment groups (P0.01), but not AT (P=0.44) demonstrating specificity of response. DC density correlated positively with both CFS (R=0.48, P0.0001) and OSDI scores (R= 0.37, P0.0001), and inversely with TBUT (R=-0.25, P0.01).
Conclusions: Corneal DCs, an indicator of tissue immune response, are increased in EDE. Quantification of DC density in vivo allows detection of changes in the corneal immune response following anti-inflammatory therapy in dry eye, providing a responsive endpoint. Given the modest but highly significant correlation of corneal DC density to both symptoms and clinical signs, this in vivo imaging parameter may therefore serve as a surrogate biomarker of therapeutic efficacy in clinical trials.

Corneal innervation, growth factors, and persistent epithelial defects: Current concepts and future directions.

James Reidy
Ophthalmology, The State University of New York at Buffalo, USA

The ocular surface has a high density of sensory nerve fibers that originate within the trigeminal ganglion. One of the main functions of these nerve fibers is to provide sensory feedback that regulates lacrimal secretion. The nerves terminate within the corneal epithelium where they help regulate cellular function by means of growth factor secretion. Damage or destruction of these sensory fibers may result in corneal ulceration and delayed epithelil healing. Failure to re-epithelialize oftens leads to corneal melting, secondary infection, and eventual perforation. Replacement or augmentation of growth factors can improve epithelial healing and help restore the ocular surface. Currently, autologous serum provides the only means to suppliment deficient growth factors. We will review endogenous human growth factors that play a role in corneal wound healing and discuss potential future development of therapeutic agents.

The new challege of retinal gene therapy: Controlling proteine dose

Corinne Kostic
Jules-Gonin Eye Hospital, University of Lausanne, Switzerland

Ocular diseases are promising candidates for gene therapy thanks to the identification of a growing number of genes causing visual impairment as well as to the particularity of the eye as an accessible organ easy to monitor. The existence of many animal models for inherited ocular diseases also accelerated the application of gene transfer into the eye. The main illustration of this phenomenon is the clinical trials for RPE65-affected patients that are proposed now using AAV vectors. After evidence of the absence of severe adverse effects following AAV-RPE65 injection in the subretinal space of patients, younger affected patients were treated to determine if such approach can improve vision. Despite a transient amelioration of visual sensitivity there is no stop of the retinal degeneration. Optimization of RPE65 gene replacement strategy is thus now required.
A possible explanation for this limited success is the inadequate dose of the therapeutic protein delivered in the epithelium. A review of the data available from the literature as well as from our own studies will be covered to examine this hypothesis.

Gene therapy and bioengineering for retinal diseases: what is the future?

Diego Ghezzi
Medtronic Chair in Neuroengineering,
Center for Neuroprosthetics,
Ecole Polytechnique Federale de Lausanne, Switzerland

Sight restoration after retinal degeneration still represents an unmet goal. Since therapeutic strategies increasingly require interdisciplinary competencies, photoreceptor degeneration is attracting several research areas, including: life science, material science, engineering, and clinical science. Gene therapy, optogenetics, and neural prostheses are just few examples of research fields benefiting from multidisciplinary research. This talk will provide a broad description of the current approaches applied to the restoration of sight from the bio- and neuro-engineering point of view, with particular emphasis on gene correction and therapy. Moreover, I will highlight future directions involving engineering science in this exciting path towards sight restoration.

Treatment Pipeline for Dry AMD

Jason Slakter
Ophthalmology, NYU School of Medicine, USA

Purpose: To identify new therapeutic approaches to the management of dry AMD.
Methods: A review of current clinical investigative programs targeting reduction in progression of geographic atrophy and/or improvement in visual function due to non-exudative AMD.
Results: New treatments targeting control of geographic atrophy include: 1) Visual cycle modulators (Emixustat hydrochloride), 2) Complement inhibitors (Lampalizumab/Factor D inhibitor; APL-2/C3 Inhibitor), 3) Amyloid Beta blockers (GSK933776, RN6G), 4) Neuroprotectants (Brimonidine tartrate, CNTF), 5) Gene therapy (CD59 glycoprotein). New treatments for restoration of vision include: 1) Stem cells (Human central nervous stem cells/HuCNS-SC, Human embryonic stem cells/hESC), 2) Human umbilical tissue-derived cells/hUTD cells, 3) Electronic subretinal implants.
Conclusions: What the future holds for the treatment of dry AMD depends on the stage of development of disease. Treatments will initially be directed to controlling damage from geographic atrophy and then restoring the visual loss associated with the disease. Ultimately new treatments will be needed to prevent the development of atrophy and control the initial stages of AMD.

C3 Inhibition For Age-Related Macular Degeneration

Cedric Francois
CEO, Apellis Pharmaceuticals, USA

Purpose. Age-related macular degeneration (AMD) remains the leading cause of blindness in developed countries. Complement activation and genetic variations play

a central role in AMD pathogenesis. APL-2 is a Complement C3 inhibitor that inhibits all activation and effector pathways of the complement system. A phase II clinical trial is on-going to determine whether APL-2, when injected monthly or every two months, can slow or halt the progression of Geographic Atrophy, the advanced form of dry AMD. The study was designed to evaluate the efficacy of C3 inhibition to that of Factor D inhibition, as seen in the MAHALO study.
Method. This is a multicenter, randomized, single-masked, sham-injection controlled clinical trial to evaluate the safety, tolerability, and evidence of activity of APL-2 10mg. Patients are randomized to receive APL-2 (or sham) monthly or every-other-month. FAF and SD-OCT images are obtained at multiple time points over 18 months for measurement of GA areas.
Conclusion. Based on its mechanism of action, APL-2 is expected to have a similar efficacy profile as that seen for lampalizumab in the MAHALO study. Of particular interest will be to evaluate whether patients negative for the CFI SNP, which did not seem to respond to lampalizumab treatment, are responsive to treatment with APL-2. This result would provide mechanistic support to the role of the classical pathway of complement activation in that group of patients. Also of interest will be to evaluate the efficacy of APL-2 when administered every two months versus monthly.

Phase I/IIa Gene Therapy Trial of AAV8-RS1 by Intravitreal Delivery for X-Linked Retinoschisis

Paul Sieving[1], Paul Sieving, Vijayasarathy Camasamudram[2], Yong Zeng[2], Vijayasarathy Camasamudram, Dario Marangoni[2], Zhijian Wu[1], Lisa Wei[1], Ronald Bush[2]
[1]*National Eye Institute, NIH, USA*
[2]*NIDCD, NIH, USA*

We initiated a human gene therapy clinical trial (NCT02317887) for X-linked retinoschisis (XLRS) from mutations in RS1, an extracellular matrix protein. XLRS causes splitting through the neural retinal layers and intraretinal cysts. We have demonstrated prominent synaptic dysfunction that causes the "electronegative ERG response" in XLRS. Providing the AAV8-RS1 vector (2.5e9 vector genomes (vg)/eye) by intravitreal injection to the mature Rs1-KO mouse retina repairs the schisis cavities and reverses the synaptic functional defect. The photoreceptor-depolarizing bipolar cell (DBC) synapse initially develops normally in Rs1-KO mice, but later the post-synaptic signaling molecules are not maintained at the synapse, and TRPM1 channels are mislocalized. Following AAV8-RS1 gene transfer, TRPM1 and the signaling molecules return to their proper location at dendritic tips, and the DBC membrane resting potential is restored, along the ERG b-wave recovers. Our clinical trial utilizes the same vector and will probe reversal of pathology and synaptic plasticity in XLRS patients. This is a prospective, dose-escalation, single-center study conducted at the National Eye Institute. One eye of each participant receives the RS1 gene vector given by intravitreal injection. Beyond safety, the doses are scaled to probe efficacy. Invoking synaptic plasticity for therapeutic repair would be a desirable treatment strategy for a number of neurological conditions. These findings in Rs1-KO mice provide insight into the molecular pathology of XLRS disease and demonstrate remarkable plasticity of a critical synapse in the visual system. Reversal of synaptic pathology by an AAV8-RS1 gene construct demonstrates novel possible therapeutic avenues other diseases involving synaptic pathology.

Rod-derived Cone Viability Factor stimulates glucose metabolism of cone photoreceptors

Thierry Leveillard
Genetics, Institut de la Vision, UMR-S 968, France

Rod-derived Cone Viability Factor (RdCVF) is an inactive thioredoxin secreted by rod photoreceptors that protects cones. RdCVF is an alternative splice product of the NXNL1 gene which also encodes for an active thioredoxin involved in the defense of the retina against photo-oxidative damage. Because the secondary loss of cones in retinitis pigmentosa is leading to blindness, the administration of RdCVF is a promising therapy independent of the causative gene for this untreatable neurodegenerative disease.

We have identified the mechanism of action of RdCVF on cones. RdCVF binds to basigin-1 (BSG1) a transmembrane protein that is expressed specifically by photoreceptors. Basigin-1 is an alternative splice product of the basigin gene with a third immunoglobin domain as compared to the more broadly expressed basigin-2 protein. Basigin-1 associates at the surface on the cones with the glucose transporter GLUT1. RdCVF interaction with the BSG1/GLUT1 complex increases glucose entry into cones and promotes cone survival by stimulation of aerobic glycolysis. This constitutes a novel mechanism of neuroprotection.

In patients suffering from retinitis pigmentosa, cone outer segments are shortened with the progression of the disease, although cones seem to survive even in advanced cases of retinitis pigmentosa. The mechanism of action revealed here implies that administration of RdCVF in patients suffering from retinitis pigmentosa could not only stabilize central vision but also ameliorate cone vision by stimulating cone outer segments re-growth.

Optogenetics for vision restoration

Deniz Dalkara[1], Jose Alain Sahel[1], Serge Picaud[1], Jens Duebel[1], Olivier Marre[1], Emilie Mace[2], Melissa Desrosiers[1], Elisabeth Dubus[1], Elena Brazhnikova[1], Celine Jaillard[1], Romain Caplette[1], Antoine Chaffiol[1]
[1]*INSERM, UPMC, Institut de la Vision, France*
[2]*FMI, FMI, Switzerland*

Converting inner retinal neurons to photosensitive cells by expressing genetically encoded light channels offers a novel approach for treating blindness caused by retinal degenerative diseases. A number of studies reported the safety and feasibility of restoring light sensitivity to photoreceptor-deficient retinas in rodents by expressing channelrhodopsin-2 (ChR2). Studies in rodents have shown that the intravitreal injection of Adeno-associated virus (AAV) can mediate robust expression of ChR2 in the inner retinal neurons. However, there have been a limited number of detailed studies of AAV-mediated transgene expression in inner retinal neurons in nonhuman primates through intravitreal injection. Though intravitreal injections present benefits from the surgical standpoint, they lead to transduction of a limited zone in the primates and evidence suggests they are more likely to lead to immune response. Therefore the evaluation of the AAV-mediated microbial opsin delivery in the retina of nonhuman primates through intravitreal administration would be an important step in developing ChR2-based gene therapy in humans. We examined the efficacy, safety and functionality of the AAV-mediated expression a ChR2 variant using AAV in the retina of macaques. The preliminary results of this translational study will be discussed from the point of view of light intensity requirements, immunological safety and efficacy.

Choroidal neovascularization in highly myopic elderly patients: A special form of choroidal neovascularization?

Maria Rosalba Ramoa Osorio[1,2], Felix Alexander Manco Lavado[1,2], Ana Belen Haro Alvarez[1], Maria Isabel Lopez Galvez[1,2], Ignacio Alonso de la Fuente[1,2]
[1]*Ophthalmology, Hospital Clinico Universitario de Valladolid, Spain*
[2]*Ophthalmology, IOBA, Spain*

Purpose: To evaluate the safety and efficacy of intravitreal bevacizumab (IVB) in the treatment of high myopic choroidal neovascularization (CNV) in patients over 60 years of age.
Methods: We retrospectively reviewed ophthalmic medical records of all myopic eyes with CNV treated with IVB as first-line with a pro-re-nata (PRN) regimen and 12 months of follow-up. Only patients over 60 years of age and with a complete baseline ophthalmologic examination, including best-corrected visual acuity (BCVA), fundus examination, fluorescein angiography and optical coherence tomography were included in the study. An initial injection of IVB (1.25mg/0.05mL) was administered, and extra doses of IVB were used when persistent or additional retinal exudation was observed. Patient`s general clinical records were reviewed for systemic adverse events related to drug therapy.

Abstracts

Results: 21 eyes of 21 patients were included, 15 women (71.43%) and 6 men (28.57%) with a mean age of 66.2735.47 and 68.1734.14 years, respectively. Only 3 patients (14.29%) gained more than or equal to 10 letters of visual acuity at twelve months. 13 patients (61.9%) maintain visual acuity, and 5 patients (23,81%) lost at least 5 letters. The mean number of injections was 2.4831.4 during the follow-up period. Regarding safety, two patients suffered angor pectoris during treatment (at 7 and 30 days after the injection). Both patients were at high risk for cardiovascular events.
Conclusion: IVB is useful in myopic CNV, but functional outcomes in patients older than 60 years are poor and visual gains are rare. Further studies are needed in this population.

Ocular manifestations and choroidal thickness measured by Swept-Source OCT (SS-OCT) in patients with familial hypercholesterolemia (FH) treated with oral intensive statin therapy.

Félix Alexander Manco Lavado[1,3],
Maria Rosalba Ramoa Osorio[1,3], Gonzalo Diaz Soto[2],
Maria Isabel Lopez Galvez[1,3], Lucia Manzanas Leal[1,3]
[1]*Ophthalmology, Hospital Clinico Universitario de Valladolid, Spain*
[2]*Endocrinology, Hospital Clinico Universitario de Valladolid, Spain*
[3]*Ophthalmology, IOBA, Spain*

Purpose: High levels of cholesterol have been related to macular degeneration. In animal models hypercholesterolemia damages the neurosensory retina and induces an increase in thickness of the choroid and sclera. The purpose of this study is to evaluate the anatomical findings in FH patients treated with oral intensive statin therapy using SS-OCT.
Methods: We designed a descriptive, cross-sectional and comparative study of 18 FH patients treated with statins versus 18 healthy controls. All patients underwent a complete ophthalmic examination. Primary outcomes were the presence of typical ocular manifestations of FH, and the quantitative and qualitative changes in retina and choroid on SS-OCT in FH patients compared to controls.
Results: Mean age of FH patients was 54.0311.9 years-old, 50% were male. Mean LDL-c level at diagnosis was 260.6347.6mg/dl, but 133.7334.0mg/dl twenty-years after treatment. Mean best-corrected visual acuity was 0.0130.04 logMAR, corneal arcus was found in 61.1%, xanthelasmas in 11.1% and one patient showed vascular narrowing in the fundus. Neither lipemia retinalis nor cholesterol crystals were found. There were no qualitative changes in the retina analysed by SS-OCT. Mean subfoveal choroidal thickness (CT) was 265.17396.71Qm, nasal-CT 210.90388.70Qm and temporal-CT 208.20390.43Qm. In control group, the mean age was 42.3311.9 years
and the mean LDL-c level was 110.6345.2mg/dl. Choroidal and retinal thickness was within the normal range. No differences were found between both groups.
Conclusions: The intensive statin therapy prevents and reduces the ocular damage of hypercholesterolemia. The choroidal and retinal thickness in treated FH patients measured by SS-OCT is within the normal range.

Objective perimetry based on chromatic multifocal pupillometer for treatment follow-up and diagnosis in patients with retinal and macular dystrophies

Ygal Rotenstreich[1,2], **Ygal Rotenstreich**, Ron Chibel,
Ron Chibel[1,2], Soad Hajyahia[1], Soad Hajyahia, Daniel Ben-Ner[1],
Mohamad Omar Mhajna[1], Michael Belkin[1,2], Ifat Sher[1,2]
[1]*Goldschleger Eye Institute, Sheba Medical Center, Israel*
[2]*Sackler Faculty of Medicine, Tel Aviv University, Israel*

Purpose: Objective non-invasive perimetry and diagnosis in healthy subjects and patients with macular and retinal degeneration using an infrared chromatic multifocal pupillometry.
METHODS: A multifocal chromatic pupillometer was used to record pupillary responses (PR) to red and blue light stimuli (peak 485 nm and 640 nm, respectively) presented by 76 LEDs at different points of the 18 degree visual field (VF). PR amplitude, constriction velocity (CV) and the time of maximal constriction velocity (TMCV) were measured in 17 retinitis pigmentosa (RP) patients, 5 Vitelliform Macular Dystrophy patients and 26 age-matched controls. Pupillometer results were compared with subjective Humphrey 24-2 and Goldmann perimetry.
RESULTS: RP patients demonstrated significantly longer TMCV and reduced amplitude and CV in majority of locations. The variability in TMCV recorded at different VF locations was significantly higher in RP patients compared with controls in response to the red stimulus (p0.0001). Tight correlation was observed between severity of VF loss determined by the chromatic Goldmann and the variability of TMCV (R=0.77). Macular dystrophy patients demonstrated significantly lower amplitude and CV in response to the red stimulus and nearly normal PR to the blue stimulus in majority of VF locations. High consistency was observed in PR recorded in serial testing (P0.001, R=0.74 for red and P0.001, R=0.683 for blue, n=870).
CONCLUSIONS: This study demonstrates the feasibility of using the multifocal chromatic pupillometer for objective non-invasive differential diagnosis, assessment of VF defects and phenotype characterization.

Cornea Perspective

Roy Chuck
Ophthalmology, Albert Einstein College of Medicine, Montefiore Medical Center, USA

We will review the process of development of topical anti-glaucoma drug delivery from the perspective of a cornea clinician-scientist. Specifically, we will briefly detail "Development of a Novel Nanoparticle for Intraocular Nitric Oxide Delivery for Glaucoma Treatment." Issues to be discussed include: encapsulation of an unstable drug; chemical modifications needed to penetrate cornea, conjunctiva and sclera; experimental systems to measure drug penetration; and planning transition from in vitro/ex vivo to animal modeling.

Abstracts

Pediatric Ophthalmology Perspective

Norman Medow
Department of Ophthalmology, Montefiore Hospital Medical Center, USA

Children are not just small adults ! They present with special problems that require special solutions.....Children with glaucoma are no exception.
This presentation will explore the differences in the eyes of children with glaucoma that require using different medications,and surgical proceedures than do adults and often times result in different outcomes !!...
The reasons for these differences will be discussed, analyzed and evaluated.

Retina Perspective

Matthew S.J. Katz
Ophthalmology, National Retina Institute, USA

Retinal diseases share many risk factors with the glaucoma. Thus, it is not unusual to see patients suffering from both a retinopathy and a glaucomatous optic neuropathy. Open and easy communication between the glaucoma specialist and the vitreoretinal surgeon serves both well. Patients suffering myriad retinopathies frequently develop glaucoma; conversely, glaucoma and its surgical complications often necessitate the intervention of the retina surgeon.

Primary open angle glaucoma occurs in association with myopia. Glaucoma specialists need to be cognizant of axial lengths of their patients;' eyes pre-operatively, and vigiliant for complications - retinal tears or detachments as well as choroidal neovascularization – post-operatively. Pigment dispersion glaucoma has been associated both with an increased incidence of lattice degeneration and its sequela, frank retinal detachment.

Pseudo-exfoliation syndrome too is associated with two conditions that may necessitate the intervention of a vitreoretinal surgeon; ectopia lentis and IOL dislocation. Indeed, the necessary intervention of the vitreoretinal surgeon in and of itself may lead to or exacerbate glaucoma.

Topical, periocular, and intravitreal steroids remain useful tools in the treatment of macular edema in association with venous occlusion, diabetes, age-related macular degeneration, and epiretinal membrane; yet steroids unmask or exacerbate glaucomatous optic neuropathy. The two-year incidence of secondary ocular hypertension was found to be 45%. Likewise after intravitreal fluocinolone implant, up to 75% of patients required ocular antihypertensive therapy.

Given the frequent concordance of glaucoma and retinal disease, the retina surgeon and the glaucoma specialist need to be thinking about and planning for mitigating interventions to protect eachothers' sphere of influence. The time to do this is before surgery, not after.

Neuro-Ophthalmology Perspective

Barrett Katz
Office of Clinical Trials, Montefiore Medical Center, Albert Einstein College of Medicine, USA

For many years, the clinical world respected the axiom of Neuro-Ophthalmology that ***the optic nerve was ours***; the only caveat to this were objections from the Glaucoma world. Over the past decades, the glaucomas have been recognized to be but another family of optic neuropathies with much in common with all optic nerve diseases. While pressure related optic neuropathies share some common features with other optic neuropathies, they also have unique markers. ***The hallmark of all optic neuropathies is that they are characterized by the company they keep. Their most intimate company is how they affect the appearance of the optic disc.*** The Neuro-Ophthalmologist is in the unique position to see the forest and the trees, and recognize subtleties within the glaucomas that resonate with other optic neuropathies.

What are some of those unexpected observations?

- Glaucoma commonly causes relative afferent pupillary defects;
- Compression within the anterior visual pathways can unfold into glaucomatous excavation;
- While dyschromatopsia is a hallmark of optic nerve disease, it is a late marker for glaucoma;
- Patients with thyroid orbitopathy commonly have elevated IOPs but rarely suffer glaucmatous damage or field loss;
- Pallor of the disc is a marker for glaucomatous optic neuropathy, but that pallor does not extend to or include the neuro-retina rim;
- Peripapillary attenuation of retinal vascular flow is much more common in AION than any other adult optic neuropathy;
- NFL / arcuate defects which respect the vertical meridian are a marker for retro-chiasmal disease;
- High intracranial pressure may be somewhat protective for the development of glaucoma;
- Having glaucoma does not immunize the patient from having an intracranial process.

Cup/disc ratios mislead; they are of little diagnostic value in contrast to the DDLS

George L. Spaeth
Ophthalmology, Wills Eye Hospital, USA

Most ophthalmologists continue to use cup/disc ratios to describe the optic nerve and especially in glaucoma. However, they correlate poorly with actual glaucomatous damage, because they do not consider either the rim configuration, disc configuration, or disc size. An absent rim in a disc with a c/d of 0.5 is always pathologic and always associated with a visual field defect. In contrast, a c/d of 0.5 with a rim/disc ratio of 0.5 in all rim areas is never associated with field loss. Furthermore, a c/d of 0.9 can be normal in a large disc, whereas a c/d of 0.3 in a small disc is almost certainly abnormal.

This presentation will desribe in detail the Disc Damage Likelihood Scale (DDLS) as a clinically useful, inexpensive, relevant, and valid method of characterizing the optic disc.

Abstracts

Disc changes in glaucoma

Robert Feldman
Ruiz Department of Ophthalmology and Visual Science, The University of Texas Medical School at Houston, USA
Glaucoma Service, Robert Cizik Eye Clinic, USA

Optic nerve evaluation is critical in diagnosing and managing glaucoma and other optic neuropathies. It is unequivocally important in outcome measures in long-term clinical trials for glaucoma therapies. Various examiner and imaging techniques have been used to evaluate the optic nerve, and their utilities in various clinical and trial settings will be discussed.

Normal tension glaucoma - a distinct disease entity?

Kuldev Singh, Kuldev Singh
Ophthalmology, Stanford University, USA

Von Graefe initially proposed that glaucomatous optic nerve damage could occur in eyes without high intraocular pressure (IOP) approximately 150 years ago which led to such severe criticism that he recanted his views. Schnabel, a half century later, supported von Graefe's initial position that optic nerve susceptibility to intraocular pressure varies considerably between patients. There remains an ongoing debate in our profession regarding whether or not Normal Tension Glaucoma should be considered a different disease entity than Primary Open Angle Glaucoma. We have come a long way since the myth of 21 mm Hg when glaucoma was considered primarily a disease of IOP with a single level defining the disease and determining the success and failure of therapy. While we may use different therapies for patients depending upon the level of IOP, conclusive evidence supporting Normal Tension Glaucoma as a unique disease entity remains absent.

Peripapillary attenuation of vascular flow: Aspects of parapapillary gamma and delta zones

Jost Jonas
Medical faculty Mannheim, University Heidelberg, Department of Ophthalmology,, Germany

New anatomical findings of the parappaillary region including the description of parapapillary beta zone (presence of Bruch´s membrane, no retinal pigment epithelium), gamma zone (no Bruch´s membrane) and delta zone (extended peripapillary scleral flange in aaialy highly myopic eyes) will be presented including their association with glaucoma and axial myopia

New useful thoughts about old ideas; or "It is better to be certain than to guess"

George L. Spaeth, George Spaeth
Glaucoma Department, Wills Eye Hospital, USA

1) Means and standard deviations are not reliable indicators of clinical significance. Pay attention to what is ALWAYS certainly pathologic, such as a notched disc; risk calculators are poor guides to which individuals need treatment. A finding that is not in the range of ALWAYS pathologic is usually of unknown value. 2) Cup/disc ratios are not valid descriptors of nerve damage and are poorf diagnostic guides. They do not take into account disc size or cup eccentricity (rim width), and they correlate poorly with field loss. There is no c/d ratio which is ALWAYS certainly diagnostic of glaucoma. Learn the Disc Damage Likelihood Scale (DDLS); it is a valid, relevant indicator of stage of optic nerve damage, which must be known with certainty for treatment to be appropriate.3) Bias is insidious and powerful. Learn to recognize personal, institutional and professional biases such as the incorrect belief that "Objective" findings are more valuable than "Subjective" findings, and the incorrect advice to look at the field before examining the disc. 4)"Hypotony" is often a misleading word. The threshhold intraocular pressure below which problems occur can not be accurately predicted. Just as what level of elevated IOP will cause field loss in an individual can not be certainly predicted, so also the pressure below which the level of pressure will cause problems can not be accurately predicted with certainty. 5) The evidence that trabeculectomy itself causes cataracts is unconvincing. Postoperative cataract usually results from surgical trauma, or use of topical corticosteroids for more than 4 weeks.

al Evaluation of the Eye-to-visual-pathway Integrity of Glaucomatous Neurodegeneration Using 1.5T MR Imaging

Kaya Nusret Engin[1], Nurten Turan Guner[3], Sibel Toreyen Bayramoglu[3], Ulviye Yigit[2], Onur Ozyurt[4], Muhittin Taskapili[5], Ahmet Agachan[2], Penbe Cagatay[6]
[1]*Ophthalmology, Umraniye Education Research Hospital, Turkey*
[2]*Ophthalmology, Bakirkoy Education Research Hospital, Turkey*
[3]*Radiology, Bakirkoy Education Research Hospital, Turkey*
[4]*Biomedical Engineering, Bosphorus University, Turkey*
[5]*Ophthalmology, Beyoglu Goz Hospital, Turkey*
[6]*Biostatistics and Medical Informatics, Istanbul University, Turkey*

Purpose: Accumulating data imply that glaucoma may actually represent a neurodegenerative disorder affecting the entire visual system. We evaluated retrobulbar glaucomatous damage with favorable techniques for 1.5T diffusion-tensor magnetic resonance (DT MR) imaging and we compared those techniques with clinical data in a large case series.
Methods: This Cross-sectional study included 130 eyes of 65 patients with primary open angle glaucoma. Patients with no known ocular or systemic concomitant disorders, neurological diseases, previous glaucoma surgeries, or antioxidant usage were selected. Optical coherences tomography and central visual field results of the subjects were recorded. Glaucoma analysis with optical coherences tomography (OCT) and standard automated perimetry (SAP) results of the subjects were recorded.
DT MR analysis of optic nerves and radiations were performed, computing fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity ($\lambda 1$) and radial diffusivity ($\lambda\perp$). Correlation between the DT MR and clinical eye parameters of glaucomatous neurodegeneration were statistically evaluated.
Results: The correlations between diffusion parameters and age were highly significant. Optic nerve- fractional anisotropy and ipsilateral optic radiation-$\lambda 1$ were significantly correlated with corneal thickness. Statistically significant correlations were found between ganglion cell complex and apparent diffusion coefficient, $\lambda 1$, $\lambda\perp$ of optic nerves.
Conclusions: Eye-brain connection in glaucoma can be evaluated with routine clinical instruments. Our study also revealed a limited correlation of retrobulbar glaucomatous neurodegeneration with ophthalmic damage. A better understanding of retrobulbar damage will enable us to develop more efficient strategies and a more accurate understanding of glaucoma.

Vascular changes in glaucoma

Alon Harris
Ophthalmology, Glick Eye Institute, USA

The past twenty years have witnessed the acceptance of non-intraocular pressure physiological processes contributing to glaucomatous optic neuropathy. Foremost among other contributory factors is an impaired ocular circulation. For decades glaucoma has been associated with vascular diseases such as systemic hyper/hypo-tension, diabetes and migraine and dozens of prospective studies have found low ocular blood flow in glaucoma patients. Many large population based studies have reported low ocular perfusion pressures to be a risk factor for prevalence, incidence and progression of glaucoma. The contribution of ischemic damage in glaucoma may be local, confined within the retina and anterior optic nerve, or may represent only one aspect of a more generalized ischemic process. The exact relationship of blood flow disturbances to glaucoma progression remains insufficiently described; however pilot evidence has began to show a predictive association is present in some individuals. Certain groups of individuals may be at elevated risk for glaucoma due to vascular insults including patients of African descent and patients with diabetes. Other important considerations include the dynamic interaction between intraocular and intracranial pressures and their affects on ocular structure and circulation. This presentation will explore the past, present and future direction of ocular blood flow research in glaucoma management and facilitate discussion on the link between ocular blood flow deficits and optic neuropathy. Advances in dynamic mathematical modeling have recently allowed for the exploration of glaucoma risk factor interconnectivity; providing further insight into glaucoma pathophysiology and eventually may allow for individualized screening and improved treatment options.

CSF pressure and the Eye

Jost Jonas
Medical faculty Mannheim, University Heidelberg, Ophthalmology, Germany

The optic nerve head forms the interface between the intraocular compartment and the retrobulbar compartment. The former is characterized by what we term intraocular pressure (IOP) and the latter by orbital cerebrospinal fluid pressure (CSFP). The trans-lamina cribrosa pressure difference (TLCPD) is defined as the difference between the pressures in the two compartments. Any change in one of them can be associated with a disturbance of homeostasis of the optic nerve head, such as papilledema or glaucomatous optic neuropathy. In particular, glaucomatous optic neuropathy may be due to either an elevated IOP and/or an abnormally low orbital CSFP, or due to a change in the time-dependent relationship between the pulse-synchronous changes in IOP and orbital CSFP. Based on the triangular relationships between IOP, CSFP and blood pressure, glaucoma may be described as an imbalance between these three pressure parameters, eventually leading to an increased TLCPD. Because the retinal and choroidal venous blood drains through the CSFP space, elevated CSFP may be associated with dilated retinal veins, increased incidence of retinal vein occlusions, higher prevalence and severity of diabetic retinopathy, and thicker choroid.

Phosphodiesterase-5 Inhibition: Optic Nerve Erection Without Neuroprotection

Nitza Goldenberg-Cohen
Pediatric Ophthalmology Unit, Sackler School of Medicine, chneider Childrens Medical Center of Israel and Tel Aviv University, Israel

Purpose: To investigate the possible neuroprotective effect of PED5i (sildenafil) injected prior to optic nerve crush (ONC) and immediately following induction of stroke in mice. The MCAO filament model in mice facilitates the investigation of possible neuroprotective effect of the treatment.
Methods: In the ONC group, mice received intravitreal (IVT) or intraperitoneally (IP) injection of sildenafil, or saline. Quantitative real-time PCR was used to quantify optic nerve ischemic-related gene expression.
MCAO induction was followed by single IP injection of sildenafil or saline. Brain edema, penumbra and total infarct area were visualized by 2,3,5-triphenyltetrazolium chloride staining on coronal brain sections.
Results: Both IVT and IP injections of sildenafil caused retinal vessel dilatation. At 21
days following ONC, RGCs loss was similar in sildenafil and untreated group, but molecular studies revealed a significant, 7.5-fold elevation of SOD in the IVT 1d group, and an 11-fold rise in BAX on day 3 in the IP group. Total stroke volume was 19.20 3 6.38mm3, mean penumbra 4.5 3 2.03 and hemispheric asymmetry 106.5% in saline treated, and 18.42 3 5.41, 5.73 2.02 and 109.9% in the sildenafil treated group, respectively. No neuroprotection was seen, but brain edema significantly increased

in the sildenafil groups compared with untreated mice.
Conclusions: Injection PDE5i increased choroidal perfusion in the eye, and might have neuroprotective effect in ONC. However, in experiments conducted without ONC, PDE5i induced optic nerve stroke. In the brain, a single IP injection immediately after MCAO-induction showed increased brain edema of the injured hemisphere without neuroprotection.

DNA Methylation: A New Player in the Blinding Disease of Diabetes

Renu Kowluru
Ophthalmology, Wayne State University, USA

Diabetes is fast becoming a global epidemic with nearly one in ten people expected to have the disease by 2035. With increasing rate of diabetes, the prevalence of its major sight-threatening complication, diabetic retinopathy, is also increasing considerably. Diabetic environment alters the expressions of many genes in the retina. Emerging evidence has shown that stable and heritable covalent modifications, caused by the environment of a cell, can also alter gene expression without altering the base sequence of the DNA. These 'epigenetic' modifications are reversible, and are considered to have pathogenic role(s) in complex eye diseases such as corneal dystrophy, cataract, glaucoma, and age-related macular degeneration. We have shown that diabetes alters DNA methylation of nuclear- and mitochondrial DNA-encoded genes in the retina. This talk will focus on elucidating the role of DNA methylation in the pathogenesis of diabetic retinopathy, especially in maintaining mitochondrial homeostasis. Better understanding of the role of DNA methylation in diabetic retinopathy should provide novel therapeutic targets for this debilitating disease, which is feared the most by diabetic patients.

Targeting Caspase-1 in Diabetic Retinopathy

Susanne Mohr, Derrick Feenstra
Physiology, Michigan State University, USA

Purpose: Diabetes-induced chronic tissue inflammation leads to death of retinal cells, such as Müller cells, and diabetic retinopathy. Caspase-1 seems to be a mediator of this retinal inflammation. However, the importance of caspase-1 activation for the development of diabetic retinopathy has never been evaluated. How caspase-1 is controlled and regulated under hyperglycemic conditions is also unknown to date. Interleukin-10 (IL-10) is an anti-inflammatory cytokine with the potential to regulate caspase-1 signaling. Therefore, the focus of this project was to identify the importance of caspase-1 for the development of diabetic retinopathy and to determine the effect of IL-10 on targeting hyperglycemia-induced caspase-1 activation.Methods: Wild type C57Bl6 mice and Cas-1-/- mice were made diabetic. Müller cell loss and formation of acellular capillaries were determined. Human Müller cells (hMC) were treated with normal (5mM) or high glucose (25mM) media in the presence or absence of IL-10 for up to 96 hours. Caspase-1 activity, IL-10 mRNA, and cell death were measured.
Results: Cas-1-/- mice were protected against diabetes-induced Müller cell loss and diabetic retinopathy. In vitro results show that high glucose downregulated IL-10 mRNA levels by 60% in Müller cells. IL-10 treatment (10ng/ml) significantly reduced hyperglycemia-induced cell death by 67.135.5% and caspase-1 activity from 50.7335.1 to 41.7131.2 pmol AFC/mg/min (normal: 38.5131.4 pmol AFC/mg/min) suggesting that IL-10 exerts its protective effect by preventing caspase-1 activation.
Conclusion: Caspase-1 activation is crucial for the development of diabetic retinopathy. Therefore, drugs that target caspase-1 like IL-10 might present a new strategy to prevent diabetic retinopathy.

Stem Cell Therapy in Diabetic Eye Diseases

Alexander Ljubimov, Mehrnoosh Saghizadeh, Andrei Kramerov
Biomedical Sciences, Regenerative Medicine Institute, Cedars-Sinai Medical Center, USA

Significant degenerative changes that could be potentially corrected by stem cell therapies have been observed during nonproliferative stages of diabetic retinopathy (DR). These alterations include vascular hyperpermeability, capillary closure, pericyte dropout and neural dysfunction. Adult stem cells (vascular progenitor cells or adipose stem cells), and induced pluripotent stem cells from cord blood have been used with success to counteract these pathologies. The injected stem cells were able to engraft into damaged vessels in pericyte or endothelial positions in models of DR and ischemia-reperfusion with functional amelioration of vasculature and electroretinograms in diabetic models. Another approach with clinical potential for autologous progenitor cell therapy is to normalize dysfunctional diabetic bone marrow and residing endothelial progenitors using various means including NO donors, PPAR-d and -g agonists, or inhibition of TGF-b. A DR-associated neuropathy could also be reduced by stem cells, either naïve (e.g., paracrine-acting adipose stem cells) or secreting neuroprotecting factors, such as ciliary neurotrophic factor or brain-derived neurotrophic factor. Recent advances in stem cell therapies for DR-associated microangiopathy may translate into clinical trials in the near future. Additionally, limbal cell therapy may prove beneficial for diabetic corneal disease (diabetic keratopathy) with pronounced epithelial stem cell dysfunction.

A double sword action of miR-15a in Diabetic Retinopathy - inhibition of VEGF and sphingolipid pathways

Julia Busik
Physiology, Michigan State University, USA

Diabetic retinopathy is a sight threatening disease with few therapeutic options. A number of hyperglycemia- and dyslipidemia-activated pathways promoting the increase of pro-inflammatory cytokines, pro-inflammatory lipids and pro-angiogenic factors leading to retinal endothelial cell dysfunction have been identified. Dysregulation of these pathways is hypothesized to involve microRNAs (miRNAs). These small non-coding RNAs anneal imperfectly to target genes and simultaneously control translation and transcription. Several miRNA classes have been shown to contribute to diabetic retinopathy. We have identified miR-15a as a key regulator of both pro-inflammatory and pro-angiogenic pathways. miR-15a accomplishes these tasks through direct binding and inhibition of the central enzyme in the sphingolipid pathway, acid sphingomyelinase (ASM), and inhibition of VEGF-A. We have demonstrated that miR-15a is downregulated in human retinal endothelial cells (HREC) isolated from diabetic donors and in diabetic mouse retina. Moreover, upregulation of miR-15a using miR-15a mimic prevented hyperglycemia and cytokine-induced ASM upregulation and VEGF production in HREC, retinal pigment epithelial and Muller cells. Manipulation of miR-15a to simultaneously control sphingolipid metabolism and pro-angiogenic pathways through direct regulation of ASM and VEGF-A production in the diabetic retina could provide a unique and effective "combination therapy" approach that will add to the pharmacological armamentarium of drug therapies for diabetic retinopathy.

The story of Interferon: showing drug effect without industry support

Manfred Zierhut
Centre of Ophthalmology, University of Tuebingen, Germany

The presentaton will report about the use of interferon alpha and how experience has optimized our results. After a successfull use in Behcet´s Disease (BD) without ocular involvement we adapted this drug to ocular BD. In the first step the dosage had to be adapted, later to optimize the reduction of the drug, with the result that this drug is now one of the very few biologicals which allows to stop treatment without immediate rebound of the inflammation. We then started a non-industry-sponsored study because the Industry never was interested to get another indication. Seeing the results in BD we also studied the influence on cystoid macular edema in non-BD situations. That created its own challenges. In addition to indications and schedules the management of co-medication and avoidence of side effects was a major challenge, resulting now in a highly effective treatment schedule with manageable side effects.

Regulatory point of view (MHRA)

David Silverman
MHRA, MHRA, UK

Regulatory approval of innovative therapies in the EU in uveitis, a therapy area where there are no published guidelines and few licensed products, is a challenge both for industry and the regulators. The presentation will cover some of the basics of the regulatory approval process for new medicines in the EU, the regulatory perspective on the choice of endpoints, the procedure for obtaining scientific advice in the EU, and details of specific schemes that may apply to innovative medicines in areas of unmet need.

Clinical Studies: Patient Point of View

Ron Neumann, MD. Medical Consultant Inflammatroy Eye Diseases for Maccabi Health Care Services, and Ophthalmology Therapeutic Area Head Global Clinical Development, Teva Pharmaceutical Industries Ltd.

Clinical studies create artificial laboratory conditions intended to increase the chance to observe differences between the study and the control groups. Typically, patients prefer to be included in the study group. They often join clinical studies as a result of their dissatisfaction with current therapy on one hand and their desire to be treated with cutting-edge medications, on the other. Universally, patients wish to gain "something" from their participation in the study. This "something" may represent better visual functions (not necessarily visual acuity), improved ocular symptoms or a general feeling of well-being. Those parameters may not be reflected in the regulatory path of approval but may be critical to the value of the product once it is approved. A classic example is "signs & symptoms" in dry eye disease. The regulator asks for statistical improvement in both signs and symptoms whereas patients' direct concern would be amelioration of their symptoms, reduced dependency on artificial tears etc. This short presentation focuses on the patient point of view in the discussion of clinical studies design claiming that sophisticated statistics is only part of the picture. This angle is commonly hidden in the background] of clinical studies design. Finally, studies should be designed to improve patient quality of life via reduction of their symptoms, improvement of their signs such that they can experience better sense of health, and benefit true medical value.

Moving ahead – lessons from other medical fields

Gary Novack
R&D, PharmaLogic Development, Inc., USA

We all know that ophthalmology is unique in its development of novel therapeutics. The ability to delivery drugs locally as well as to non-invasively visualize neural tissue allows more rapid development of therapeutics compared to systemic medications. Our colleagues in drug development in systemic medicine make frequent use of pharmacokinetic in both healthy volunteers and patients. They can then evaluate the relationship between drug concentration and drug activity (pharmacokinetic/pharmacodynamic relationship, PK/PD). They also can evaluate the wealth of genomic data – either on how drugs are metabolized and transported, or the more challenging efficacy and safety response to drugs. Unfortunately, the limited ability to sample drug concentration at target tissue limits our clinical ocular pharmacokinetics. This then limits our ability to conducted PK/PD relationships, and finally to genomic interactions. We will discuss possible ways to move ophthalmology forward.
Novack GD. Pipeline: Thoughts generated by the Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics. Ocul Surf 2004;2(3):212-214.
Novack GD. Pipeline: Personalized Medicine and the Ocular Surface. Ocul Surf 2010:8(3):157-160.

Abstracts

Targeting Receptor Interacting Protein-2 (RIP2) to Prevent Hyperglycemia-Mediated Inflammatory Signaling in Müller Cells

Derrick Feenstra, Susanne Mohr
Physiology, Michigan State University, USA

Purpose: Activation of the pro-inflammatory caspase-1/Interleukin-1β (IL-1β) pathway plays an important role in the development of diabetic retinopathy. In order to develop therapies targeting this pathway a better understanding of the mechanisms leading to caspase-1 activation under diabetic conditions is necessary. Receptor Interacting Protein-2 (RIP2) is a known activator of caspase-1 in other systems, and this study tests the hypothesis that caspase-1 is activated by (RIP2) under hyperglycemic conditions and by IL-1β signaling.
Methods: Primary human Müller cells (hMC), were isolated and cultured from retinas of non-diabetic donors. hMCs (1x106 cells) were treated with normal (5 mM) or high (25 mM) glucose for 48 hours or treated with recombinant IL-1β (2ng/ml) for 24 hours in the presence or absence of siRNA against RIP2. Caspase-1 activity and IL-1β release was measured.
Results: Caspase-1 activity was significantly increased by 5333.0% (p0.05) in Müller cells treated with high glucose compared to those treated with normal glucose. siRNA against RIP2 decreased high glucose-induced caspase-1 activity from 16.830.3 to 11.930.7 pmol AFC/mg/min (p0.05). Accordingly, high glucose-induced IL-1β release was significantly attenuated from 6.230.3 to 1.430.9 pg/ml/mg (normal: 2.030.4 pg/ml/mg) in cells treated with siRNA against RIP2. IL-1β treatment led to increased caspase-1 activity (67.637.0%; p0.05). siRNA against RIP2 abrogated IL-1β-induced caspase-1 activity by 6231.5% (p0.05).
Conclusion: Our results demonstrate that RIP2 indeed mediates hyperglycemia-induced caspase-1 activation in Müller and thus, might be responsible for the onset of retinal inflammation seen in diabetic retinopathy. Therefore, RIP2 represents a valid therapeutic target to treat diabetic retinopathy.

Normalising eNOS function to facilitate repair of the ischaemic retina

Denise McDonald
Centre for Experimental Medicine, Queen's University Belfast, UK

In ischaemic retinopathies, an abnormal response to growth factor stimulation leads to the misdirection of reparative angiogenesis away from the hypoxic retina leading to sight-threatening intravitreal neovascularisation (NV). Therapeutic strategies which could reverse this trend would be extremely beneficial. Endothelial nitric oxide synthase (eNOS)-derived NO plays an important role in promoting vascular growth and survival, a function which is dependent upon the cofactor, tetrahydrobiopterin (BH4). Previously, we have shown that oxidative stress depletes retinal BH4 levels, reduces NO production and exacerbates vascular closure, the prelude to ischaemic injury. Thus, here we investigated if supplementing BH4 levels can protect the retina from oxidative insult and normalise vascular growth.

Endothelial specific eNOSGFP transgenic mice at postnatal day 7 were subjected to 2-5 days, and retinal microvascular endothelial cells (RMEC) to 24h hyperoxia to induce oxidative damage. Supplementation was achieved with sepiapterin and elevated BH4 levels confirmed by HPLC, NO production was measured by nitrite and NOS activity and nitrotyrosine (NT) by western blotting. Proliferation was determined by BrdU labelling and lectin staining of retinal flat mounts was used to
determine the extent of vessel closure before and after treatment.

Hyperoxia exposure in vitro and in vivo deleted BH4 levels, diminished NO production, elevated free radical production and negatively impacted EC proliferative ability. These effects were corrected by BH4 supplementation which improved NO production, enhanced EC proliferation and increased vessel coverage in eNOSGFP animals. Thus, BH4 supplementation reverses oxidative stress-induced endothelial damage and preserves vascular integrity in the neonatal retina.

A novel target for therapy development in optic neuropathies – a second life for presenilins?

Peter Koulen
Vision Research Center, Department of Ophthalmology, and Department of Basic Medical Science, University of Missouri - Kansas City, School of Medicine, USA

Loss of visual function in optic neuropathies is characterized by the degeneration of retinal ganglion cells (RGCs). Cell death of RGCs is preceded by cellular calcium dyshomeostasis and toxicity caused by chronically elevated intracellular calcium concentrations. Control of calcium signaling pathways has become the target of related therapy development efforts. Others and we recently described a new role for presenilin proteins. In addition to their function in amyloid precursor protein processing, presenilins control the intracellular calcium concentration by regulating the activity of intracellular calcium release channels. The present study tested the hypothesis that modulation of the presenilin protein concentration leads to RGC protection.
The viability of murine RGCs was measured in response to chronic L-glutamate-mediated toxicity using immunocytochemistry assays. After altering the concentration of presenilins in RGCs changes in intracellular calcium ion signaling were measured using electrophysiology, calcium imaging and pharmacological control of intracellular calcium channel activity.
Both presenilin 1 and 2 are expressed by RGCs. Knockdown of presenilin 1 significantly increased viability of both isolated cultured RGCs and of organotypic cultures. This was paralleled by significantly attenuated calcium release from
intracellular stores. Overexpression of presenilin 1 elicited potentiated calcium release from intracellular stores and decreased viability of RGCs. Modulation of presenilin 2 generated similar responses.
Presenilins control calcium release from intracellular stores and thereby affect cellular viability as a function of cellular calcium dyshomeostasis following injury or resulting from disease processes. These mechanisms of action therefore represent novel
potential targets for therapeutic intervention and drug development in optic neuropathies.

Abstracts

Regulated expression of recombinant anti-VEGF single chain antibody fragments – towards personalized medicine in neovascular retinal disorders

Tobias Wimmer, Birgit Lorenz, Knut Stieger
Department of Ophthalmology, Justus-Liebig-University Giessen, Germany

Purpose: Most retinal neovascular disorders are associated with up-regulation of the vascular endothelial growth factor (VEGF) expression. Currently, disorders like age-related macular degeneration, diabetic retinopathy and retinal vein occlusion are treated with repeated injections of anti-VEGF molecules like Bevacizumab, Ranibizumab, or Aflibercept. Repeated injections of anti-VEGF molecules can be connected to severe side effects and represent a financial burden to the patients. The aim of this project is to develop an alternative strategy i.e. controlled expression of anti-VEGF molecules within the retina.
Methods: The open reading frames of ranibizumab were cloned into an expression plasmid separated by an internal ribosomal entry site (IRES) (Ra01). The construct was mutated to generate ranibizumab single chain variable fragments (Ra02-Ra05). Expression was verified by Western blotting. Biological activity, VEGF binding properties and the doxycycline depend induction of anti-VEGF expression was tested. An AAV2/5 vector was generated containing the optimal variant Ra02.
Results: Ra variants 01-05 were detected in cell culture medium. While VEGF binding affinity was significantly lower compared to Lucentis®, the inhibition of cell migration was comparable and the maximum inhibition of Ra01 and Ra02 was reached at lower doses. The expression of Ra02 was shown to be controllable with the TetOn-system® as plasmid and AAV vector construct.
Conclusion: Anti-VEGF molecules related to ranibizumab can be produced in eukaryotic cells after AAV mediated gene transfer in a controlled manner in vitro and display comparable biological activity as Lucentis®. These results are the basis for a gene-based therapy in human VEGF overexpressing mice, a model for human neovascular disorders.

KinostatTM prevents cataracts in diabetic dogs

Peter Kador[1,2], Milton Wyman[1], Manley Paulos[1], the Kinostat Trial Study Group[3]
[1]*Research, Therapeutic Vision, Inc., USA*
[2]*College of Pharmacy, University of Nebraska Medical Center, USA*
[3]*11 Eye Centers, Veterinary Ophthalmologists, USA*

Purpose: A majority of dogs develop blinding bilateral cataracts within 6 months after diagnosis of diabetes mellitus (DM). Here, we present an interim analysis of a randomized masked placebo controlled clinical trial (1/3 placebo) of the topical aldose reductase inhibitor KinostatTM that is being conducted at 11 centers across the United States.
Methods: 135 dogs are being evaluated by board certified veterinary ophthalmologists at the time of enrollment and then at 1, 2, 3, 6 and 9 months. The dog's owners administer the topical formulations TID. Dogs not developing cortical cataracts during the 9-month period are then given KinostatTM with ophthalmic evaluations required at 6-month intervals.
Results: Newly diabetic dogs of all sizes, breeds, and sex with only equatorial vacuoles of less than 360o present and no other ocular disease were recruited. The results, to date, confirm the initial proof of concept study (Vet. Ophthlamol. 13:363-8, 2010) that daily administration of KinostatTM to diabetic dogs significantly prevents cataract formation for up to 6-years. A required toxicology study found that daily application of KinostatTM at doses of up to 5x the recommended doses did not induce any direct local or systemic toxic effects in any of the tissues examined.
Conclusion: KinostatTM is the first drug to prevent the clinical development of diabetic cataracts and reduce the need for cataract surgery. Because KinostatTM meets an unmet medical need, the FDA has granted KinostatTM a fast-track Minimum Use in a Major Animal Species designation.

Mathematical Model of Alexidine Absorption by High Density Polyethylene Plastic Bottles and the Worldwide ReNu-Related Fusarium Keratitis Event of 2004-2006

John D. Bullock, Ronald E. Warwar, Harry J. Khamis
Community Health, Wright State University, USA

BACKGROUND: In May 2006, Bausch & Lomb was cited by the Food and Drug Administration for improper storage/transport temperatures of ReNu with MoistureLoc (RML) multi-purpose contact lens solution. The Centers for Disease Control and Prevention suggested disinfection failure as the cause of this event [JAMA 2007;298:2867-2868]. RML contained the antimicrobial alexidine, 4.5 parts per million (PPM). In our previous studies: heating (56oC) RML in its unique bottle resulted in its decreased ability to inhibit Fusarium organisms [Arch Ophthalmol 2011;129:133-136]; and, Fourier transform infrared (FTIR) spectroscopy showed that alexidine absorbed into the wall of the RML polyethylene bottle [N Engl J Med 2014;370:88-89]. The purposes of the present study were to measure alexidine concentrations over time and correlate them with our previous FTIR spectroscopic and microbiological studies.
METHODS: Triplicate alexidine levels (initially, 4.5 PPM) were measured by liquid chromatography/mass spectroscopy in heated (56oC)/unheated ReNu bottles stored for six hours to four weeks. Using a Gauss-Newton iterative least squares nonlinear regression estimation procedure (Statistical Analysis System [SAS]), alexidine loss, L, was fit to an exponential saturation curve, L = S(1-e-kt), where S is the alexidine saturation level, k is a function of storage temperature, and t is time.
RESULTS: The ratio of heated:unheated alexidine loss, calculated by integrating the exponential functions, was 3.0, equivalent to that previously determined by FTIR spectroscopy (3.1). Over 95% of the alexidine was lost from the heated solution at one week. When the alexidine concentration decreases to < 0.8 PPM, the solution fails to inhibit Fusarium organisms.
CONCLUSIONS: These studies signify that temperature-enhanced alexidine-polyethylene interaction was the pharmaceutical failure mechanism of the Fusarium keratitis event of 2004-2006.

Abstracts

How much preclinical safety data for a clinical study in ophthalmology?

Gary Novack, Gary Novack[1,2], Elizabeth Moyer[3]
[1]R&D, PharmaLogic Development, Inc., USA
[2]*Ophthalmology and Pharmacology, University of California, Davis, USA*
[3]*R&D, M/P Biomedical, USA*

Develop of novel therapeutics involved basic research on normal and pathological physiology, synthesizing or finding molecules with activity in these systems, and then developing products for clinically evaluation of safety and efficacy. That development involves characterization of the drug substance, formulation of a stable drug product, and the conduct of nonclinical safety studies. These safety studies involve in vitro and in vivo genotoxicity, single- and multiple-dose exposure toxicology, including toxicokinetics and evaluation by various routes and species at doses which represent multiples of anticipated human dosing/ exposure. Key to efficient development, especially in determining cost and timing, is the safety package in order to evaluate novel therapies in humans. The author will present current concepts on nonclinical safety as it relates to the clinical development plan for ophthalmic products.

Emerging Pharmacovigilance methods and approaches for safety surveillance in real world data

Andrew Bate, Pfizer, USA

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Spontaneous reporting systems identify emerging issues post-approval and epidemiological studies in observational databases of electronic medical records and transactional insurance claims databases for hypothesis testing of potential adverse effects.

BRIGHTER and CRYSTAL studies for RVO

Francesco Boscia, Ermete Giancipoli, D' Amico Ricci Giuseppe "Dott. Giuseppe D'Amico Ricci", Pintore Pierpaolo
Ophthalmology, Azienda Ospedaliera Universitaria Sassari, Italy

BRIGHTER and CRYSTAL are two ongoing 24-month (M) studies assessing the long-term efficacy and safety of a stabilization criteria-driven pro re nata ranibizumab 0.5 mg (RBZ) dosing regimen in patients with branch and central RVO (BRVO and CRVO).
BRIGHTER study will generate comparative data for 0.5-mg ranibizumab using pro re nata dosing administered with or without adjunctive laser treatment versus laser photocoagulation (the current standard of care) up to Month 6 and will provide efficacy and safety data for 0.5-mg ranibizumab using pro re nata dosing, administered with or without adjunctive laser treatment, over 24 months in patients with visual impairment due to ME secondary to BRVO.
In CRYSTAL Trial a total of 356 patients with visual impairment due to macular edema secondary to CRVO were enrolled in the study from 78 sites in Europe, Australia and Canada. The mean age at baseline was 65.5 years and 64% of the patients were male. The study started in February 2012 and the last patient first visit (LPFV), occurred in April 2013 signifying that by April/May 2014 patients should have completed treatment period 1 (12-months) and reached the primary endpoint which will be subject to analysis and outcome results disclosure.
The two clinical trials will provide new insides on the long-term safety and efficacy of different treatment regimens with Ranibizumab, in patients with BRVO / CRVO elated macular edema.

Steroids for RVO

Albert Augustin
Department of Ophthalmology, Klinikum Karlsruhe, Germany

Some years ago, the possibility of applying long-lasting steroids, such as triamcinolone and subsequently the dexamethasone implant Ozurdex, directly in the eye, without the systemic side effects observed after their oral or intravenous administration, aroused great enthusiasm among ophthalmologists. This new treatment strategy changed our approach in the management of macular edema from RVO. Retinal vein occlusion is considered a multifactorial disease with a complex pathogenesis that often reflects systemic vascular and hemodynamic disorders. It is generally agreed that the RVO management should target the angiogenic factors as well as the inflammatory compounds of this etiologic complex. The inflammatory reactions put in motion by retinal ischemia and subsequent macular edema in RVO are closely associated to the angiogenic manifestation of the pathology and include various interrelated processes such as vasodilatation, leukostasis, diapedesis, increased vascular permeability and inflammatory proteins secretion. These factors promote hyperpermeability of blood vessel wall, contributing to the breakdown of blood retinal barrier, and subsequently leading to macular edema. Thus, the rationale of using steroids that are well-known for their potent anti-inflammatory action in RVO is based on their ability, among others, to block IL-1 mRNA synthesis and ICAM-1 mediated leukocyte adhesion to vessel walls, and to inhibit VEGF expression. Steroids delivered into the vitreous have the advantage of directly targeting the edematous macula and leaking retinal blood vessels, with a stronger and more efficient action against the disease processes and without inducing systemic side effects. There are various drug formulations, delivery methods, and treatment doses protocols. In our presentation we will show both, the efficacy and safety of the most commonly used intravitreal steroids in current practice.

Abstracts

Mechanism of laser treatment and pathophysiology of retinal vein occlusion.

Einar Stefansson
Ophthalmology, Univ. Iceland, Iceland

Pathophysiology:
Retinal vein occlusion increases resistance and decreases blood flow, which leads to hypoxia as demonstrated with invasive PO2 measurements and non invasive retinal oximetry imaging. Tissue hypoxia activates hypoxia inducible factor, HIF which stimulates production of vascular endothelial growth factors, VEGF and other cytokines. VEGF stimulates neovascularization and increases permeability of blood vessels so that plasma proteins leak into the tissue leading to tissue edema according to Starling´s law.
Venus obstruction increases intraluminal blood pressure in the microvasculature, which increases hydrostatic pressure difference between vessels and tissue. Water flows down this pressure gradient into the tissue contributing to edema. Starling´s law describes the two main forces that control edema formation, hydrostatic and osmotic pressure differences between vessel and tissues. The latter are influenced by serum macromolecules leaking through vessel wall.
Treatment mechanisms:
Treatment for retinal vein occlusion consists of intravitreal anti VEGF drugs and steroids and laser treatment. Laser application coagulates RPE cells and adjacent photoreceptors, decreasing the oxygen consumption of the retina. Oxygen coming from the choroid can now diffuse into the inner retina and relief hypoxia. This has been demonstrated in experimental animals.
Reduced hypoxia decreases VEGF formation and thereby the stimulus for neovascularization and edema formation. Decreased hypoxia constricts retinal arterioles, which decreases hydrostatic pressure in the microcirculation and the hydrostatic component of edema formation.
Laser treatment and anti VEGF drugs influence the same general mechanism of pathophysiology in retinal vein occlusions, based on ischemia, hypoxia, VEGF and Starling´s law.

Lessons learnt about retinal pigment epithelial atrophy by the use of fundus autofluorescence imaging

Noemie Lois, Vikki McBain
Queen's University, Queen's University, UK

Fundus autofluorescence (AF) and near-infrared autofluorescence (NIA) have been used for many years to assess clinically, in a non-invasive manner, the status of the retinal pigment epithelium (RPE). Their value in the evaluation of patients with posterior segment disorders has expanded; both are currently used in ophthalmic clinics throughout the world for the assessment of patients with degenerative, inflammatory and neoplastic disorders. This talk will provide an overview on how AF and NIA have contributed to the characterisation of atrophy in retinal diseases, from lessons learnt using these imaging technologies about risk stratification, early diagnosis, disease progression and treatment effects, to the understanding of the pathogenic mechanisms of this condition.

En Face OCT of Geographic Atrophy

Srinivas Sadda
Doheny Eye Institute, University of California, USA

Advances in OCT technology, including the development of higher scanning speeds and swept source acquisition techniques, have facilitated the use of en face OCT for various retinal diseases. En face OCT is particularly suited for the evaluation of geographic atrophy (GA) as the lesion or pathology tends to be relatively planar. En Face OCT facilitates the identification and accurate segmentation of the borders of the GA lesion as increased transmission of light to the choroid in areas of RPE loss causes areas of atrophy to appear bright in the en face OCT choroidal slab image. Commercial automated segmentation algorithms are already available to quantify and monitor the progression of GA lesions using en face OCT. En face OCT has also provided new insights into the pathogenesis of atrophy, and in particular, has revealed the radial orientation of outer retinal tubulations (ORTs) at the border of these lesions. GA lesions with ORTs seem to grow considerably slower than lesions without ORTs (1.85 mm2/year vs 2.67 mm2/year). En face OCT can also be obtained at other layers of interest that are affected by the atrophic process such as the photoreceptors. En face slabs through the outer segments can demonstrate a "penumbra" of hyporeflectivity around the GA lesion. These areas of hyporeflectivity are thought to foreshadow areas of future atrophy growth and may provide a potential biomarker to identify more rapidly progressing lesions.

OCT-Angiography versus Traditional Multimodal Imaging in Exudative AMD

Gabriel Coscas[1], Marco Lupidi[2], Florence Coscas[1]
[1]*Department of Ophthalmology, Creteil University Hospital, France*
[2]*Department of Biomedical and Surgical Sciences, Eye Clinic, S.Maria Della Misericordia Hospital, University of Perugia, Italy*

The OCT-Angiography (OCT-A) is a new promising method, which allows visualizing both the retinal and choroidal vascular layers and the neovascularization in the macular region.
OCT-A generates a high contrast between circulating cells and static tissues, making visible, in 3D, choroidal and retinal vessels without dye injection. The specific advantage of OCT-A on Fluorescein Angiography is that it provides 3-dimensional deep functional information on blood flow in the vessels and, particularly, in case of neo-vessels.
Fluorescein angiography maintains several advantages such as: evaluating the walls of finest vessels and capillaries, their permeability, recognizing diffusion phenomena, analyzing the circulatory dynamics and obtaining images of the entire posterior pole or up to the periphery. All this fine semiology of dye angiography remains precious, irreplaceable for some doubtful diagnosis and often useful for the initial diagnosis! However, the dye angiography only provides two-dimensional images, which superimpose all retinal and choroidal vascular layers.
The OCT-Angiography, on the contrary, can be easily performed, without dye injection, and allowing the patient benefit based on frequent controls and a guided regimen. OCT-A provides functional and morphological information, because simultaneously acquired with the

conventional OCT.The interpretation of OCT-A obviously requires some learning time, but several "activity criteria" of new vessels, are already under study and statistical validation.
This new evolution and this remarkable imaging progress, will thus allow fast and easy diagnosis.
Therapeutic decisions are suggested without any delay during the post treatment follow-up, which may become more frequent, effective and well tolerated.

A vision of future of glaucoma care: combination of device and drug products.

Adrian M. Timmers, Lichun Zhong, Laxman Desai
Ocular Sciences, Toxikon Corporation, USA

Purpose: The first approach to treatment of glaucoma are topical applications of IOP lowering drugs. Long-term efficacy is impacted by several factors. Ocular absorption is subject to fluctuation because of blinking, tear concentration and nasolacrimal drainage. Ocular drug concentrations oscillate, highest after application with subsequent decrease. Treatment success depends on patient behavior (compliance) and potential drug washout when multiple drugs are prescribed. Glaucoma treatment could benefit greatly from alternative methods of drug application.
Methods. Based on literature review and experiences with a variety of products, the path to design of device-drug combination requires consideration of a plethora of factors: identification of a device (polymer, bio-degradable) for sustained release; location(s) of the drug-device and release kinetics of the API. Furthermore, efficacious drug concentration, maximal tolerated doses, sustainability of efficacy need to be assessed. Here we will discuss examples of studies with microfibers with a prostaglandin prodrug in normotensive animals.
Results. Drug release/fiber degradation kinetics tested in rabbits show similar release kinetics with intravitreal and subconjunctival administration. These kinetics are similar to drug release in phosphate buffer. The drug-device combination was well tolerated in rabbits. Comparison of topical drug application to the drug-device injected subconjunctival in normotensive dogs reveal similar efficacy in IOP reduction. A single application of the drug-device produced long-term IOP lowering albeit with a delayed onset compared to topical application.
Conclusions. Micro-fibers infused with IOP lowering drugs deliver effective and long-term IOP reduction. Future: is the duration of IOP reduction impacted by drug-device delivery? Can devices be modified for use with fixed combination glaucoma drugs?

Ocular Anti-Neovascularization Models: Advantages and Limitations Relating to Drug Delivery, Model Duration and Translatability

Mark Vezina
Ocular and Neuroscience, Charles River, Canada

This presentation will cover animal models of neovascularization with an emphasis on laser-induced choroidal neovascularization (CNV) in rodents and non-rodents. Advantages and limitations of the model in the context of model variability and duration, drug delivery and translatability will be discussed.

Improvements in Technologies to Maintain Sustained Levels of Ophthalmic Drugs in the Eye: PRINT Particles and Novel Bioconjugates

Craig Struble[1], Ben Yerxa[2], Tomas Navratil[2], Andres Garcia[2], Rozemarijn Verhoeven[2], Yuhua Hu[3], Tim Lam[3], Wayne To[3], Stephen A. Charles[3], Victor Perlroth[3]
[1]*Department of Drug Metabolism, Covance Laboratories, USA*
[2]*Research and Development, Envisia Therapeutics, USA*
[3]*Research and Development, Oligasis, USA*

There are unmet needs in treatments for ocular diseases to improve current delivery modalities to the eye. Therapies are subject to limitations that could prevent a patient from achieving the full therapeutic benefit, including frequent dosing, limited efficacy, and poor patient compliance. New approaches are needed to provide ophthalmic drugs with enhanced retention in the eye along with good tolerability.
In this presentation two different technological approaches will be discussed; preclinical data will be presented. One, using the PRINT® Technology developed by Envisia Therapeutics, is a proprietary system capable of engineering highly precise microparticle and nanoparticle systems. PRINT® Technology offers the unique ability to rationally design precise particles of virtually any size, shape and chemistry, including small molecule active pharmaceutical ingredients (API), biologic APIs, and polymeric drug delivery systems (e.g. extended-release formulations). Envisia has created particulate delivery systems that offer therapies with enhanced retention, sustained delivery ranging from days to multiple months, and excellent safety and tolerability.
A second approach, pioneered by Oligasis, employs a novel product platform using a bioconjugate of a bioactive compound and a branched hydrophilic phosphorylcholine (PC)-based biopolymer. The biopolymer is synthesized from a custom initiator and repeating units of a PC-based monomer. In preclinical in vivo tests, bioconjugates were (i) well tolerated both intraocularly and systemically, and (ii) demonstrated ocular half-lives 5-times longer than the current standard of care for chronic ocular diseases. PC-based biopolymer conjugates are a promising new class of therapeutic agents with a unique combination of versatility, tolerability, and extended ocular half-life.

Abstracts

Enhanced ocular drug delivery with mucus-penetrating nanoparticles

Kim Brazzel
R&D, Kala Pharmaceuticals, USA

The Mucus Penetrating Particles (MPP) platform is a proprietary drug delivery technology used to enhance delivery of drugs through mucus-protected tissues via surface modified nanoparticles. The MPP technology allows drugs to rapidly penetrate through and uniformly distribute across mucus barriers to enable enhanced penetration of drugs into target tissues of the eye. Enhanced ocular pharmacokinetics of MPP-based eye drops have been demonstrated with multiple drugs in various animal models.
The lead MPP candidate KPI-121 is a novel nanoparticle formulation of loteprednol etabonate utilizing the MPP technology to enhance penetration into target tissues of the eye. KPI-121 has been studied in multiple clinical trials, including 1% and 0.25% formulations for the treatment of post-surgical ocular inflammation and pain and a 0.25% formulation for dry eye and meibomian gland disease. Positive top-line results from a Phase 3 clinical trial of KPI-121 for the treatment of inflammation and pain in patients who had undergone cataract surgery were recently announced. In this trial KPI-121 achieved all primary efficacy endpoints and was generally well tolerated, with no significant treatment-related safety findings observed during the course of the trial. Results from a Phase 2 clinical trial of KPI-121 in patients with dry eye disease were also recently reported. KPI-121 achieved statistical significance for the primary sign endpoint of bulbar conjunctival hyperemia, and promising trends were observed for key symptom endpoints.
A novel, small molecule receptor tyrosine kinase inhibitor program for potential topical treatment of retinal disease utilizing the MPP platform is also undergoing preclinical investigation.

Using suprachoroidal administration as an approach to treat noninfectious uveitis – from concept through clinical data

Glenn Noronha
R&D, Clearside Biomedical, Inc, USA

We are a clinical stage company developing first-in-class drugs to treat unmet blinding eye diseases where the pathologies dominantly manifest in the retina and the choroid. We have a unique method of administering drugs to the suprachoroidal space (SCS) using a proprietary microinjector. We chose to target uveitis, a collection of inflammatory conditions affecting the eye, because of the posterior eye tissues affected and the potential for treatment using suprachoroidal administration.
In an acute pig model of uveitis, at the 0.2 mg dose, suprachoroidal injection of triamcinolone acetonide (TA) was more effective than intravitreal (IVT) injection, and as effective as a 2 mg IVT dose, demonstrating that a 10-fold lower dose administered to the SCS was sufficient. In pharmacokinetic studies in rabbits, distribution of the drug over a 90-day period following single suprachoroidal administration showed that TA was 12X more available in the choroid and outer retina compared to the distribution following intravitreal injection, with minimal amounts of drug in the anterior chamber and vitreous compared to levels following IVT injection.
Both the potential for efficacy with lower dose, as well as the unique posterior localization of drug suggesting that we could provide a safer and more effective uveitis therapy through SCS administration were encouraging. In a Phase 1/ 2 clinical study, we dosed 8 subjects with intermediate, posterior or pan uveitis with a single 4 mg TA suprachoroidal injection and followed them for 6 months. Safety and efficacy information from this clinical study will also be presented.

Novel formulations of Cyclosporine A (CsA) for improved delivery to the eye

Doris Gabriel[1], Maren Kasper[2], Herve Courthion[3], Marta Rodriguez Aller[1], Arnd Heiligenhaus[2], Robert Gurny[1,3]
[1]*Department of Pharmaceutical Sciences, University of Geneva, Switzerland*
[2]*Department of Ophthalmology and Ophtha-Lab, St. Franziskus Hospital, Germany*
[3]*Apidel R&D, Apidel SA, Switzerland*

Pegylated hexyl-poly-lactic acid (mPEGhexPLA) polymer based nanocarriers have been shown to safely and efficiently deliver CsA payloads into anterior structures of the eye [1, 2]. In the present study we assessed CsA distribution and therapeutic efficacy after repeated topical administration in an experimental autoimmune uveoretinitis model (EAU). CsA nanocarrier or placebo formulations were applied five times daily to the right eyes of treated animals, from day 12 to day 21 post immunization. CsA levels of corneal, retinal and choroidal tissue samples were quantified at the end of the treatment by UPLC-MS/MS: elevated CsA levels were found in corneas of treated right eyes, versus non-treated left eyes. Furthermore, animals receiving the CsA nanocarrier formulation had significantly higher CsA serum levels compared to animals treated with PBS. Increased CsA levels were also found in cervical and inguinal lymph nodes of CsA nanocarrier treated animals. On a therapeutic level, a significant reduction in EAU score was observed for CsA nanocarrier treated right eyes, as well as for non-treated left eyes of the corresponding animals. These results, together with the tissue distribution data point to the fact that therapeutic effects may be mediated by a systemic drug action after five daily administrations of CsA nanocarrier eye-drops.

References
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2] Di Tommaso C et al. Eur J Pharm Biopharm 2012 June 81(2):257-64

Therapeutic effect of mTor-inhibition in autoimmune uveitis in mice and man

Maren Kasper[1], Dirk Bauer[1], Lena Wildschuetz[1,2], Dirk Bauer, Lena Wildschuetz, Arnd Heiligenhaus[1,2], Arnd Heiligenhaus

[1]*Ophtha-Lab, Department of Ophthalmology at St. Franziskus Hospital, Germany*
[2]*Department of Ophthalmology, University of Duisburg-Essen, Germany*

Uveitis comprises a diverse group of inflammatory diseases involving the vascular tissues in the eye. Endogenous intermediate and posterior uveitis, frequently take a chronic course, which may be associated with a high risk of visual loss and impaired quality of life. Endogenous uveitis is presumed to be a T-cell-mediated autoimmune disease. Various components of the immune system during initiation and perpetuation of inflammation are involved. Beside corticosteroids, cyclosporine A currently represents the mainstay of therapy as an approved drug for the treatment of endogenous uveitis. As another treatment option, we analyzed the efficacy of systemic m-Tor inhibiton by using everolimus in mice and man. Our data show good efficacy on the uveitic course in mice and man, and the promotion of peripheral tolerance.
In order to diminish possible systemic adverse events, the effect of topically adminstered everolimus micellar nanocarriers (mPEGhexPLA (methoxy-poly-ethylene-glycol hexyl substituted poly-lactic acid) was studied. This formulation led to a milder course of experimental autoimmune uveitis (EAU). Meanwhile, the regional and systemic immune responses were modulated.

Visualization and quantification of intra-corneal triamcinolone acetonide biodistribution following topical iontophoresis: a new approach to treat corneal graft rejection

Verena Santer, Sergio del Rio-Sancho, Yogeshvar N. Kalia
School of Pharmaceutical Sciences, University of Geneva, Switzerland

Background: Immuno-rejection is the major cause of corneal graft failure. Hourly administration of corticosteroid eye-drops can decrease rejection rates but efficacy is modest and patient compliance an issue. The aim of this study was to evaluate the effect of iontophoresis on the intra-corneal delivery of novel water-soluble, biolabile triamcinolone acetonide (TA) prodrugs. Short duration iontophoresis may improve ocular bioavailability and efficacy, constituting a “single-shot” treatment option.
Methods: Amino-acid ester prodrugs of TA were synthesized, characterized and their solubility and stability investigated. HPLC-UV and UHPLC-MS/MS methods were validated. Anodal iontophoresis (2.3mM TA-Arg solution; 10min, 3mA/cm2) was performed using fresh isolated porcine cornea. Intra-corneal delivery of TA was quantified “layer-by-layer” in 40Qm thick corneal lamellae to a depth of 1000Qm. TA distribution in corneal epithelium and stroma was visualized by optical coherence tomography (OCT).
Results: Anodal iontophoresis of TA-Arg increased corneal deposition of TA by 17-fold as compared to passive delivery (468.25359.70 and 27.1530.47 nmolTA/cm2, respectively). OCT images from corneas following iontophoresis of TA-Arg showed a 3-fold increase in brightness compared to passive controls – providing striking visual confirmation of the enhanced delivery. OCT image luminosity profiles and the measured amounts of TA in the lamellae provided qualitative and quantitative confirmation of extensive TA penetration to 480Qm after iontophoresis for 10 min. Post-iontophoretic passive diffusion for 1h resulted in a statistically significant deeper penetration of TA into corneal stroma.
Conclusions: Iontophoresis of TA prodrugs might represent an alternative to conventional topical corticosteroid therapy for the treatment or prevention of corneal allograft rejection.

New latanoprost formulation for improved ocular tolerance

Marta Rodriguez-Aller, Davy Guillarme, Jean-Luc Veuthey, Robert Gurny
School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Switzerland

Latanoprost is a poorly water-soluble prostaglandin F2α analog used as a first-line agent for glaucoma treatment. It is an ester prodrug challenging to be formulated as an eye drop due to its poor water solubility and the presence of an ester bond. The active form of latanoprost is its acid that stimulates FP and EP receptors leading to a decrease in intraocular pressure but also to hyperemia. Hyperemia was identified as the major issue related to topical ocular administration of prostaglandin analogs, being reported in 45% of the patients and responsible for the noncompliance of 37% of them (Zimmerman et al. J Ocul Pharmacol Ther, 2009).
One approach to simultaneously address pharmaceutical and clinical limitations is to use cyclodextrins (CDs) which are known to form water-soluble complexes with latanoprost. First, a panel of CDs was screened to select the best CD for latanoprost formulation. Second, the ocular tolerance of the best latanoprost-CD formulation was compared to the one of a commercially available latanoprost eyedrop based on clinical and microscopical evaluation of ocular irritation using a rabbit model. These in vivo experiments demonstrated that the new latanoprost-CD formulation presented an improved ocular tolerance compared to commercially available eyedrops (Rodriguez-Aller et al. Eur J Pharm Biopharm, 2015).
Thus, the new latanoprost-CD formulation was demonstrated to successfully address the current stability, solubility, and tolerance issues of conventional latanoprost formulations.

Abstracts

Visualization and quantification of intra-corneal triamcinolone acetonide biodistribution following topical iontophoresis: a new approach to treat corneal graft rejection

Verena Santer, Sergio del Rio-Sancho, Yogeshvar N. Kalia
School of Pharmaceutical Sciences, University of Geneva, Switzerland

Background: Immuno-rejection is the major cause of corneal graft failure. Hourly administration of corticosteroid eye-drops can decrease rejection rates but efficacy is modest and patient compliance an issue. The aim of this study was to evaluate the effect of iontophoresis on the intra-corneal delivery of novel water-soluble, biolabile triamcinolone acetonide (TA) prodrugs. Short duration iontophoresis may improve ocular bioavailability and efficacy, constituting a “single-shot” treatment option.
Methods: Amino-acid ester prodrugs of TA were synthesized, characterized and their solubility and stability investigated. HPLC-UV and UHPLC-MS/MS methods were validated. Anodal iontophoresis (2.3mM TA-Arg solution; 10min, 3mA/cm2) was performed using fresh isolated porcine cornea. Intra-corneal delivery of TA was quantified “layer-by-layer” in 40Qm thick corneal lamellae to a depth of 1000Qm. TA distribution in corneal epithelium and stroma was visualized by optical coherence tomography (OCT).
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Conclusions: Iontophoresis of TA prodrugs might represent an alternative to conventional topical corticosteroid therapy for the treatment or prevention of corneal allograft rejection.

Biodegradable microparticles for the delivery of ocular therapeutics

Irene Bravo-Osuna[1,2], Cristina Garcia-Caballero[1], Esther Rodriguez-Villagra[1], Alicia Arranz-Romera[1], Irene Teresa Molina-Martinez[1,2], Rocio Herrero-Vanrell[1,2]
[1]*Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Complutense University, Madrid, Spain*
[2]*Instituto de Investigacion Sanitaria, Hospital Clinico San Carlos (IdISSC), Madrid, Spain*

Chronic and multifactorial diseases affecting the posterior segment of the eye often represent visual impairment and blindness and are becoming more prevalent in the ageing population. Currently, the treatment of retinal disorders is limited due to the difficulty in reaching effective concentrations of the active substance in the target tissues. Biodegradable microparticles (1-1000Qm size) represent an alternative to multiple administrations as they can provide long-term delivery of the active substance and eventually disappear from the site of administration. Injection of microparticulate systems is performed without the need of surgical procedures. Depending on their structure microparticles are classified in microcapsules and microspheres. Biodegradable microspheres destined for the treatment of retinal diseases can include one or more active substances. The inclusion of additives in the microspheres results especially useful if the therapeutic molecule is a protein. Depending on the disease, microspheres can be injected by different routes (intraocular and periocular).
Herrero-Vanrell R, Bravo-Osuna I, Andrés-Guerrero V, Vicario-de-la-Torre M, Molina-Martínez IT. The potential of using biodegradable microspheres in retinal diseases and other intraocular pathologies. Prog Retin Eye Res. 2014;42:27-43
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Introduction to Allergic Conjunctivitis

Essen Akpek
Johns Hopkins University, The Wilmer Eye Institute, USA

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.

Abstracts

Current and Emerging Treatments for Atopic Keratoconjunctivitis

Bennie Jeng
Ophthalmology and Visual Sciences,
University of Maryland School of Medicine, USA

Atopic keratoconjunctivitis (AKC) is one of several forms of allergic eye disease, but it is one of them that can lead to vision loss if not treated appropriately and aggressively. AKC typically begins in the late teen years, but can present as early as age 7 years. It can persist into the 4th and 5th decades of life, and it is usually perennial, but it can have seasonal exacerbations. Symptoms include itching, tearing, burning, pain, redness, and blurred vision. Signs include severe eczema of the eyelids and periorbital skin, chronic inflammation of the conjunctiva with thickening and hyperemia, inferior forniceal foreshortening, and keratopathy including neovascularization and ulcerations. Treatment consists of topical antihistamine drops, mast cell stabilizers, and topical immunosuppressives such as tacrolimus, pimicrolimus and steroid ointments. Systemic therapy with cyclosporine, azathioprine, mycophenolate mofetil and even biologics may also be necessary to control AKC.

Vernal Kertoconjunctivitis; Global Impact

Andrea Leonardi
Neuroscience, Ophthalmology Unit, University of Padua, Italy

Vernal keratoconjunctivitis (VKC) is an unusually severe sight-threatening allergic eye disease, occurring mainly in children. Conventional therapy for allergic conjunctivitis is generally not adequate, therefore persistent inflammation can lead to permanent visual loss. Children with VKC present with severe ocular signs and symptoms, associated with tissue remodelling and fibrosis. Corneal involvement may be assessed by vital staining and the use of confocal microscopy. However, both in clinical trials and in clinical practice, the Oxford and Van Bijsterveld tests do not seem to be adequate for evaluation of the surface damage in VKC because the staining patterns proposed by these tests are different from the staining patterns typical of VKC. For this reason we propose a new modified CLEK scoring system to better evaluate limbal and central corneal involvement in VKC. Multiple mediators, cytokines, chemokines, growth factors, proteases and enzymes are over-expressed in VKC and may be evaluated using different methods. Interestingly, proteomic and gycomic techniques, reveal the presence of low abundant and high abundant proteins and glycoproteins with pro- and anti-inflammatory properties. Understanding inflammation in ocular allergy may provide indication for a rational treatment of these diseases and future potential therapeutic approaches including immuno-modulators, such as cyclosporine and tacrolimus.

Iluveien

Albert Augustin
Department of Ophthalmology, Klinikum Karlsruhe, Germany

Inflammation plays a significant role in the pathogenesis of diabetic retinopathy and diabetic macular edema (DME). Iluvien (FAc implant) is a very long-acting, second-line therapy indicated for the treatment of chronic DME. The product consists of a non-bioerodable microimplant (dimensions: 3.5 mm x 0.37 mm) that contains 190 Qg of FAc and delivers 0.2 Qg FAc/day for up to 36 months. The implant is administered intravitreally using a 25-gauge injector, which creates a self-sealing wound. After a brief burst, levels of FAc in the aqueous humor have been shown to stabilize by 6 months (1.18 ng/ml) and are sustained through to 36 months (0.55 ng/ml). The FAME studies recruited patients with DMO that was unresponsive to previous macular laser treatment. Patients were also required to have a foveal thickness ≥250 Qm despite at least one prior focal/grid macular laser photocoagulation treatment and BCVA in ETDRS letter score between 19 and 68 (Snellen equivalent range, 20/50–20/400).
Treatment with 0.2 Qg/day FAc implant (n=375) led to rapid improvements in retinal thickness compared with sham (control) treatment (n=185). At 6 weeks, foveal thickness had rapidly decreased from 461.1 to 345.7 Qm (–115.4 Qm) in the 0.2 Qg/day FAc implant-treated group compared with a change from 451.3 Qm to 450.4 Qm (–0.9 Qm) in the sham control group. VA was also significantly improved by the FAc implant. The proportions of patients with a ≥15-letter improvement after 24 months was 28.7 % and 16.2 % (Δ, 12.5 %; p=0.002) and after 36 months was 28.7 % and 18.9 (Δ, 9.8 %; p=0.018) in FAc implant- and sham-treated patients, respectively.30 The FAME studies also show the efficacy of the FAc implant is greatest in patients with chronic DME. This is the population in which the FAc implant is indicated. In these patients the proportions with a ≥15-letter improvement at 36 months were 34.0 % and 13.4 %, respectively (Δ, 20.6 %; p<0.001).These results indicate that the FAc implant is an effective treatment in a group of patients who have not responded to prior treatment with first-line therapies such as laser and others. Rationale for anti-inflammatory therapy and results as well as common side effect rates (cataract, IOP-increase) will be reported in detail.

Abstracts

Sustained release dexamethasone (Ozurdex) for uveitis

Will Ayliffe, Lister Hospital Chelsea and City University London
Medical Moniter to SANTEN

Will Ayliffe
Ophthalmology, The Lister Hospital, UK

In an age of austerity, the costs of treatment are concerning health care providers regardless whether re-imbursement is via the public purse, insurance companies or the individual patients themselves.
Increasing interest in re-evaluating older drugs has been stimulated by the discovery that combinations or local routes of administration are efficacious and safe.
Ozurdex, a sustained-release biodegradable intravitreal implant containing 0.7 mg of dexamethasone was approved in 2009 for the treatment of macular edema following retinal vein occlusion. Case reports of its efficaciousness in non-infectious posterior uveitis soon followed.
The HURON study, a phase-3, sham-controlled trial, of 229 patients with intermediate (81%) or posterior (19%) uveitis. Participants were randomised to a single administration with Ozurdex® 0.7mg (n = 77), a lower dose 0.35mg implant (n = 76) or a sham procedure (n = 76), and followed for up to 26 weeks.
At 8 week a vitreous haze score of zero was significantly greater with Ozurdex® (47%) than w sham (12%) persisting to week 26.
43% gaining ≥ 15 letters compared to 7% of sham treated, but had increased cataract and raised intraocular pressure.
Summary:
Ozurdex adds another treatment modality to managing uveitis. Unlike various alternatives it is FDA approved.
However, Ozurdex® is costly (£1,044 per dose plus administration costs, estimated at £620. A typical patient may require 2-3 implants per year and the economics of dealing with raised intraocular pressure and cataract, must also be factored in.
Nevertheless, this treatment has an important role in the management of posterior uveitis.

JDE-003, A NOVEL, TOPICAL, CROSS-LINKED HYALURONIC ACID (HA) GEL, PROMOTES REGENERATION OF DAMAGED CORNEAL CELLS FOLLOWING VARIOUS TYPES OF OCULAR CORNEAL TRAUMA

MaryJane Rafii, MaryJane Rafii[1], Brenda Mann[2], David Williams[3], Glenwood Gum[4], Barbara Wirostko[1]
[1]*Executive Management, Jade Therapeutics, USA*
[2]*Executive Management, SentrX Animal Care, USA*
[3]*Veterinary Ophthalmology, St John's College, UK*
[4]*Preclinical Services, Absorption Systems Inc, USA*

Representing up to 18% of emergency room traumas, ocular injuries are highly prevalent among both civilians and military personnel. Occupational injury/trauma – as well as corneal surgery resulting in epithelial defects – can lead to secondary corneal infections, inflammation, and vision loss if not treated promptly. Jade Therapeutics Inc.'s proprietary 0.75% HA polymer, JDE-003, is a cross-linked, thiolated carboxymethylated HA currently being manufactured by SentrX Animal Care and sold into the veterinary market. This corneal repair gel has the ability to bind to CD44 receptors, thus stimulating epithelial cells to proliferate, migrate, and heal corneal defects.
Methods: Two studies were conducted. 1) 28-day GLP rabbit safety/tolerability study with JDE-003 dosed 6x/day OU vs. vehicle. 2) masked randomized study in 29 cats with real-world corneal stromal persistent ulcers treated with JDE-003 vs. control TID (iDrop Vet Plus 0.25% HA) until healing.
Results: JDE-003 exhibited excellent safety and tolerability in rabbits and demonstrated accelerated time to healing over control in cats with resident sterile stromal corneal ulcers. JDE-003 healed in 21.0 +/- 11.0 days, while iDrop healed in 31.8 +/- 10.3 days (p = 0.01).
Conclusions: A novel, bio-adherent and biodegradable HA eyedrop, JDE-003 is well tolerated and effectively promotes corneal tissue repair/healing while preventing adhesions and scar formation. This product has been used successfully in thousands of animals. Jade and SentrX are in the process of scaling to good manufacturing practice (GMP) standards to pursue a human indication for corneal healing and repair with an IND submission anticipated later this year.

NOVEL SPLEEN TYROSINE KINASE (SYK) INHIBITOR FOR THE TREATMENT OF FUNGAL KERATITIS

Michael Thormann[1], Eric Pearlman[2]
[1]*Drug Discovery, Origenis GmbH, Germany*
[2]*Institute for Immunology, University of California, USA*

Purpose: To prove that a non-steroidal antiinflammatory kinase inhibitor provides an efficient way to combat the sight-threatening inflammatory response in Fungal Keratitis.
Methods: An animal model of Fungal Keratitis has been studied. Fusarium infected eyes were treated with antifungal alone or a combination of antifungal and a novel antiinflammatory SYK inhibitor. Levels of fungal load and markers of inflammation were determined.
Results: The treatment of Fusarium infections with a suitable antifungal alone reduces fungal load but does not reduce the inflammatory response and corneal scarring. The combination treatment with an antifungal and a novel non-steroidal antiinflammatory SYK inhibitor reduces both, the fungal load and the inflammatory response and restores eyes without inflammatory infiltrate and haze.
Conclusions: SYK inhibitors reduce inflammatory response to fungal infection in vivo and can prevent corneal scar formation and loss of sight when given in combination with a suitable antifungal drug.

Abstracts

A novel therapeutic non-steroidal drug for inflammatory eye diseases

Franz Obermayr[1], Stefan Strobl[2], Gerhild Wildner[3]
[1]*Dept. of Development, Panoptes Pharma, Austria*
[2]*Dept. of Discovery, 4SC Discovery, Germany*
[3]*Dept. of Ophthalmology, Clinic of the University of Munich, Germany*

Panoptes is developing small molecule drugs for severe eye diseases with unmet medical need. PP-001, a small molecule drug, was discovered by a structure-based docking approach with several million virtual compounds. Followed by a lead optimization program, PP-001 was chosen for further development based on target efficacy and pharmacokinetic properties. PP-001 is a highly specific nano-molar inhibitor of dihydroorotate dehydrogenase, an essential enzyme of the de novo pyrimidine pathway and a well-established target in inflammatory diseases. PP-001 preferentially targets T cells and inhibits the expression of IFN-γ, IL-17 and VEGF. This mode of action makes PP-001 very suitable for the development as a novel drug for T cell mediated inflammatory eye disease such as uveitis, dry eye etc. Formulations of PP-001 for topical, intraocular and systemic applications have been developed and showed in vivo proof of concept in several models of experimental autoimmune uveitis (EAU) and other models. In a chronic rat model of experimental autoimmune with chorioretinal neovascularization (CNV) as late sequel PP-001 inhibits CNV formation. This data together with excellent tolerability warrant the use of PP-001 as a novel and highly potent therapy for chronic inflammatory diseases such as uveitis and dry eye disease.

CLT-28643 significantly improves the surgical outcome of glaucoma surgery in pre-clinical models.

MARIO FSADNI[1,2], Grit Zahn[2], Patrizia Caldirola[2], Ingeborg Stalmans[3], Martin Spitzer[4]
[1]*Managing Director, International Pharm-Med Ltd, UK*
2-, Clanotech AB, Sweden
[3]*Department of Ophthalmology, University Hospitals Leuven, Belgium*
[4]*Department of Ophthalmology, Universitaetsaugenklinik Tuebingen, Germany*

Purpose: CLT-28643, an α5β1-integrin inhibitor with potent anti-fibrotic and anti-angiogenic effects with no cytotoxicity, was investigated in 2 models of glaucoma filtering surgery. Different dose regimen and administration routes were compared to mitomycin C (MMC).

Methods: Study 1, rabbit model (n=8 eyes): 2 Qg CLT-28643 in a single subconjunctival injection (SCJ), and SCJ+ eyedrops were compared to MMC and placebo. Study 2, mouse model: filtering surgery (n=20 eyes). Group 1 received a single SCJ of 2 Qg; Groups 2 and 3 repeated SCJ on days 0, 3, 7, 14 and 21 (2 and 1 Qg, respectively). Group 4 received topical eye drops 3 times daily containing 10 Qg. Group 5 was given MMC 0.02% for 2 minutes and Group 6 repeated SCJ injections of placebo. In both studies, treatment outcome was studied by a masked observer every other day by clinical investigation of the bleb until postoperative day 28.

Results: In both experiments, surgical outcome was improved in all treatment groups compared to placebo treated eyes. In the mouse study, the dose-response curve was observed in the efficacy of the SCJ, with the repetitive administration of 1Qg being significantly inferior to, the single injection of 2 Qg or topical administration (10 Qg) comparable to, and the repetitive injection of 2 Qg significantly superior to MMC.
Conclusions: These data suggest that administration of the α5β1-integrin inhibitor CLT-28643 has therapeutic potential as an adjunct to glaucoma surgery, possibly with a superior efficacy to MMC when used at the optimal dose.

The Valuation Process: How much is my product worth?

Barry Butler
Managing Partner, Point Guard Partners, LLC, USA

Innovators should understand how potential partners and investors value their technology and how to use these techniques to determine an accurate value of their product or company. Discounted cash flow (DCF) analysis, net present value (NPV), risk adjustment, and analyisis of comparables are presented and explained.

Nitric Oxide (NO): an emerging target for intraocular pressure (IOP) lowering

Ennio Ongini
R&D, Nicox Research Institute, Italy

Intraocular pressure (IOP) is a known modifiable risk factor for glaucoma. Lowering IOP can reduce risk of progression of glaucomatous visual field loss. Current medications for lowering IOP target aqueous humor formation and/or the uveoscleral outflow pathway. To date no therapy exists that primarily targets the conventional outflow pathway by enhancing aqueous humor drainage through the trabecular meshwork and Schlemm`s canal. Nitric oxide (NO) is an endogenous cell-signaling molecule produced by NO synthases, well-known for its role in vasodilation, through its action on smooth muscle cells. Converging evidence indicates that NO is involved in multiple physiological ocular functions, including modulation of IOP. In primary open-angle glaucoma (POAG), NO activity is impaired. Nitric oxide donation has been shown to mediate IOP lowering effects in both preclinical models and clinical studies, primarily through cell volume and contractility changes in the conventional outflow tissues. Recently, the IOP lowering effect of NO deriving from the NO-donating prostaglandin (F2α) receptor agonist, Vesneo™ (latanoprostene bunod) has been validated in patients with glaucoma and ocular hypertension. In a Phase 2 study latanoprostene bunod was found to be more effective than the reference drug, latanoprost, in lowering IOP, apparently via a dual mode of action combining NO donation and FP-receptor activation. Currently, the activity of other NO-donating prostaglandins as well as of novel NO-donors are being assessed in experimental models of elevated IOP.

Abstracts

Efficient and Effective Drug Delivery Systems: The Mobius Experience

Ed Timm
Chief Executive Officer, Mobius Therapeutics, LLC, USA

Mobius Therapeutics™ believes that retasking of molecules is more efficient than drug discovery. Standard of care indications creates NDA's with less burdensome provisions. The resulting entity creates 6 products in multiple subspecialties. Revenues fund new solutions to existing problems for evolving products and procedures.
• Mitosol® (mitomycin for solution) Kit for Ophthalmic Use - the gold standard for antifibrotics in glaucoma surgery.
• Mitosol® for surface ablation is initiating a clinical trial.
• Fuzzy Fiber™ inherently inhibits production of FGF-2, mitigating encapsulation.
• Mobius ABX™ - the first antibiotics bearing an ophthalmic indication to treat endophthalmitis, resolving issues of shelf life, supply chain, etc.

Delivering Drugs and Biologics to the Retina

Paul Ashton
President & CEO, pSivida Corp, USA
Executive, pSivida Corp, USA

Purpose
Ophthalmology has undergone a revolution with the anti-VEGFs. However, the practicality of regular injections limits efficacy and will severely hinder development of similar treatments for dry-AMD and glaucoma. We are developing technologies to provide long term (6-12 months) therapy from a single injection.
Methods
We are using two technologies, Durasert which delivers drug molecules for years after a single application and underlies Alimera's ILUVIEN® (approved in the US and EU) and Tethadur, designed to deliver biologics for up to 6 months. Release rates from Durasert implants were measured in-vitro, assessing the effects of various bioerodible polymers. Implants are now being evaluated in various models of wet and dry-AMD. A clinical study of similar implants has been initiated in glaucoma.
Tethadur is a highly porous micro-particle injected as a suspension. Stability studies indicate that large molecules (including ant-bodies) are stable for over 6 months. In-vitro release data shows prolonged release. Pre-clinical testing of Tethadur based systems to deliver VEGF targeting biologics in ongoing.
Results and Discussion
Our bioerodible Durasert systems can provide constant sustained release for in excess of 12 months. Devices are designed to provide a period of long term sustained release of drug (during which time bio-erosion does not significantly affect release) and followed by a bulk-erosion process.
Tethadur loaded anti-bodies (up to 20% w/w) were stable on storage for over 6 months. Release studies showed long term release, pre-clinical studies are continuing.

Information on RVL-1201 and the pharmacologic treatment of ptosis

Barry Butler
CEO, Revitalid, Inc., USA
Managing Partner, Point Guard Partners, LLC, USA

Blepharoptosis (ptosis) is a common condition that develops in people as they age. It is estimated that 11.5% of people over 50 years of age in the United States have clinically relevant ptosis.
RVL-1201 is an investigational drug being studied for the treatment of age-related ptosis. In a small pilot study (34 subjects), two dose regimens of RVL-1201 were compared to its vehicle for two weeks. Palpebral fissure distance (PFD) and Humphrey visual field (HVF) were analyzed. RVL-1201 exhibited numerical improvements in both PFD and HVF at all time points compared to vehicle. Onset of action was quick, with improvement in both PFD and HVF at the Hour 2 time point on Day 1, and long lasting, with effects on both endpoints being evident at the Hour 12 time point on Day 14. The effect of RVL-1201 was consistent throughout the two-week period. RVL-1201 was well tolerated in this study.
A Phase 3 trial of RVL-1201 is currently underway in the USA.

Why aren't there more new pharmacotherapies for dry eye?

Gary Novack
R&D, PharmaLogic Development, Inc., USA
Pharmacology and Ophthalmology, University of California, USA

Worldwide, there are only a handful of pharmaceutical agents approved for the treatment of dry eye disease. In 2007, the Tear Film and Ocular Surface society published the Dry Eye Workshop providing a comprehensive consensus on the diagnosis, epidemiology and treatment of dry eye disease. Both TFOS and the European Medicines Agency (EMA) held events 4-5 years ago to stimulate new therapies. As of March 2015, only one additional novel treatment has been approved since those TFOS & EMA meetings. The author will discuss whether this paucity of new therapies is due to the disease, the drugs, or the way in which we conduct our clinical trials. The author will also give an update on new pharmacotherapies as of July 2015.
Novack GD. Why aren't there more pharmacotherapies for dry eye? Ocul Surf 2014;12 (3);446-447.

Abstracts

Autologous serum for OSD

Bennie Jeng
Ophthalmology and Visual Sciences, University of Maryland School of Medicine, USA

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

Intense Pulse Light Treatment for Dry Eye Disease due to Meibomian Gland Dysfunction, a 3-year retrospective study

Rolando Toyos, Rolando Toyos
Ophthalmology, Toyos Clinic, USA

MGD is the leading cause of evaporative dry eye disease. The purpose of this study was to determine the clinical benefits of Intense Pulse Light treatment for Dry Eye Disease. A retrospective noncomparative interventional case series was conducted with 91 patients presenting with severe dry eye syndrome. Treatment included IPL and gland expression at a single outpatient clinic over a 30 month study. Pre/Post tear breakup time data were available for a subset of 78 patients. Primary outcomes included change in tear breakup time, self reported patient satisfaction, and adverse events. Physician judged improvement in dry eye tear breakup time was found for 68 of 78 patients (87%). 93% of patients reported post treatment satisfaction with improvement of dry eye symptoms. IPL is a promising treatment for DED and warrants more study.

Diagnosis of Inflammatory Dry Eye using Inflammadry

Herbert Kaufman
Ophthalmology, Pharmacology and Microbiology, Herbert Kaufman, USA

Inflammadry is a rapid, inexpensive ,reliable ,office test approved both in Europe and the USA for the diagnosis of infallmatory dry eye. Utilising lateral flow detection of MMP 9 in tears, it not only diagnoses dry eye but can serve as a guide for antiinflammatory therapy such as cyclosporine of steroids.

Hybrid Formulations for the Treatment of Glaucoma and Dry Eye

Rocio Herrero-Vanrell[1,2], Marta Vicario-de-la-Torre[1,2], Vanessa Andres-Guerrero[1,2], Daniela Quinteros[3], Santiago Palma[3], Daniel Allemandi[3], Jose Manuel Benitez-del Castillo[2,4], Irene Teresa Molina-Martinez[1,2]
[1]*Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Complutense University, Spain*
[2]*Pharmaceutical Innovation in Ophthalmology, Sanitary Research Institute of the San Carlos Clinical Hospital (IdISSC) and the Ocular Pathology National Net (OFTARED) of the Institute of Health Carlos III, Spain*
[3]*Department of Pharmacy and Pharmaceutical Technology, Facultad de Ciencias Quimicas, Universidad Nacional de Cordoba, Edificio de Ciencias II, Ciudad Universitaria, Argentina*
[4]*Ocular Surface and Inflammation, Ophthalmology Department, San Carlos Clinical Hospital, Spain*

Treatment of glaucoma is usually performed with continuous instillations of hypotensive eye drops. Despite the usefulness of topical route, chronic administration of antiglaucoma medications is usually associated with adverse reactions due to the drug or excipients included in the formulation. Among the excipients employed in eye drops, preservatives are the most related to surface alterations. Elimination of antimicrobial agents from the topical formulations is not always enough to avoid non desired effects and the ocular surface might be altered. The development of hybrid formulations including components able to improve the symptoms dry eye is an important challenge in the development of chronic antihypertensive therapies.

Quinteros D, Vicario-de-la-Torre M, Andrés-Guerrero V, Palma S, Allemandi D, Herrero-Vanrell R, Molina-Martínez IT. Hybrid formulations of liposomes and bioadhesive polymers improve the hypotensive effect of the melatonin analogue 5-MCA-NAT in rabbit eyes. PLoS One. 2014, 20; 9(10):e110344. doi: 10.1371/journal.pone.0110344.

Acknowledgements- This work has been supported by FIS PI10/00645, FIS PI10/0093, MAT 2013-42127-R, RETIC (OFTARED) 12/0034; UCM Research Group 920415 (GR3/14) and CONICET (FONCyT PICT 2010-0380).

Abstracts

Inhibition of Subretinal fibrosis in Choroidal Neovascularization

David Hinton
USC Eye Institute and Pathology, Keck School of Medicine of the University of Southern California, USA

Background: Subretinal fibrosis is an end stage of neovascular age-related macular degeneration (nAMD). An initial step of the pathogenesis is an epithelial-mesenchymal transition (EMT) of retinal pigment epithelium (RPE) cells. αB-crystallin is known to play multiple roles in AMD, including cytoprotection and angiogenesis. However, the role of αB-crystallin in subretinal EMT and fibrosis is not known. Methods: αB-crystallin-/- mice (6-8 weeks old) on the 129 S6/SvEvTac background were utilized. For generation of choroidal neovascularization (CNV), laser photocoagulation was applied to each fundus using a coverslip as a contact lens on day 0 (4 lesions/eye). The volumes of the CNV and choroidal fibrous tissue were measured in choroidal flat mounts on days 7, 21 and 35. Primary cultures of human RPE cells were established from donor eyes. αB-crystallin expression levels were downregulated using siRNA and overexpressed using plasmid vectors. Results: We found attenuation of subretinal fibrosis after regression of laser-induced CNV and a decrease in mesenchymal RPE cells in αB-crystallin KO mice as compared to WT mice. In vitro, overexpression of aB-crystallin induced EMT, whereas suppression of αB-crystallin induced a mesenchymal- epithelial transition. TGF-β2-induced EMT was further enhanced by overexpression of αB-crystallin but was inhibited by suppression of αB-crystallin. Silencing of aB-crystallin inhibited multiple fibrotic processes. Inhibition of αB-crystallin enhanced mono-tetra ubiquitination of SMAD4, which can impair its nuclear localization. Conclusions: αB-crystallin is an important regulator of EMT, acting as a molecular chaperone for SMAD4, and is a potential therapeutic target for preventing subretinal fibrosis development in nAMD

“Novel HIF-regulated therapeutic targets and diagnostic markers in Diabetic Eye Diseases”

Akrit Sodhi
Ophthalmology/Retina, The Wilmer Eye Institute at Johns Hopkins, USA

The anticipated rise in the global prevalence of diabetes will undoubtedly result in a concurrent increase in the number of patients with vision impairment from diabetic eye disease, already the most common causes of severe vision loss in the working-age population in the developed world. Clinical trials assessing the efficacy of therapies targeting vascular endothelial growth factor (VEGF) have demonstrated a major improvement in vision in a minority of diabetic patients. This underscores the need for a better understanding of the pathogenesis of diabetic eye disease. In this regard, hypoxia is a driving force for diabetic macular edema (DME) and diabetic retinopathy (DR) by stabilizing the transcription factor, hypoxia-inducible factor (HIF)-1α and promoteing the transcription and secretion of angiogenic cytokines, including VEGF. Interestingly, we recently found that retinal Müller glial cells strictly require HIF – but not VEGF – to promote both vascular permeability and angiogenesis, implicating additional HIF-dependent factors in diabetic eye disease. Using gene expression analysis, we identified angiopoietin-like 4 (ANGPTL4) as a novel cytokine potently upregulated by HIF-1 in hypoxic Müller cells in vitro and in the ischemic inner retina in vivo. ANGPTL4 is critical and sufficient for the promotion of both vessel permeability and angiogenesis. Expression of ANGPTL4 is increased in the aqueous and vitreous of diabetic patients, independent of VEGF levels, correlates with the presence of diabetic eye disease, and localizes to areas of DME and retinal neovascularization. Collectively, our results suggest that targeting both ANGPTL4 and VEGF may be necessary to effectively treat diabetic eye disease.

Visual restoration by retinal progenitor sheet transplants

Magdalene Seiler[1,2], Robert E. Lin[2], Alexander de Guzman[2], Bibo Khatib[2], Bryce T. McLelland[2], Anuradha Mathur[2], Leonard Kitzes[2], Biju B. Thomas[3], Robert B. Aramant[2]
[1]*Physical Medicine & Rehabilitation, UC Irvine, USA*
[2]*Stem Cell Research Center, UC Irvine, USA*
[3]*Ophthalmology, USC, USA*

Purpose: Retinal degenerative diseases (RD), such as age-related macular degeneration and retinitis pigmentosa, lead to irreversible loss of photoreceptors and RPE. Replacing both photoreceptors and RPE with retinal sheet transplants restores visual responses in RD models and in phase 1-2 clinical trials. The present study provides electrophysiological evidence that implanted fetal retinal sheets restore light responses in a novel immunodeficient RD rat model [SD-Foxn1 Tg(S334ter)3Lav] (RD nude rats) that has been developed to test transplanted human tissue.
Methods: Rat E19 fetal retinal sheets were transplanted to the subretinal space of RD nude rats (P30-P40), using a custom-made instrument. Size and locations of transplants were imaged over time using high-resolution SD-OCT before electrophysiological testing at 2-5.5 months after transplantation. After overnight dark-adaptation, visual responses were recorded from multiple locations in the superior colliculus (SC).
Results: OCT scans showed subretinal placement and retinal layer development of transplants. In transplanted RD rats, robust responses were observed in a cluster of recording sites corresponding to the location of the transplant in the retina whereas almost no responses could be elicited by the same stimulus in the non-treated RD nude rats. In normal control rats, visual responses were robust in all areas of the SC.
Conclusions: Retinal sheet transplants were stable for several months in RD nude rats. The integration of transplants into the host retina is sufficient to restore SC light responses. We will next test visual responses from human fetal and stem cell-derived retinal progenitor sheet transplants in these animals.
Support: CIRM TR4-06648

Photoreceptor Transplantation into Pre-Clinical Models of Retinal Degeneration

Marius Ader[1], Tiago Santos-Ferreira[1], Manuela Voelkner[2], Henrike Stutzki[3], Oliver Borsch[1], Mike Karl[2], Guenther Zeck[3]
[1]CRTD, TU Dresden, Germany
[2]*German Center for Neurodegenerative Diseases, DZNE, Germany*
[3]*NMI, at the University of Tuebingen, Germany*

Visual impairment and blindness due to the loss of photoreceptors represent one of the main causes for disability in industrialized societies. Currently no established therapies are available to rescue lost visual function. Cell replacement strategies by means of transplantation represent promising treatment approaches. In recent years methods were developed to isolate, enrich and inject photoreceptors into animal models of retinal degeneration. Here, donor cells survived and differentiated into mature cells that functionally integrated into the host tissue. The majority of photoreceptor transplantation studies so far used the mouse as a model system, thereby focusing on rod photoreceptors. Rods are functional in dim light conditions and the nocturnal mouse retina is rod dominated. In contrast, human vision mainly depends on daylight vision provided by cone photoreceptors that also allow color detection. As the mouse retina is a poor source for cones, we recently took advantage of cone-only retinas of neural retina leucine zipper-deficient (Nrl-/-) mice as a comprehensive source for transplantation studies. Following injection of cone-like photoreceptors into a mouse model of cone degeneration we demonstrated by microelectrode array analysis functional integration of donor cells and recovered responses to high light stimuli, including contributions to ON, ON-OFF, and OFF signaling pathways, thus, providing the proof-of-concept for the feasibility of daylight vision restoration upon cell transplantation in the mammalian retina. Based on the work with primary cells we are currently evaluating the use of pluripotent stem cell-derived photoreceptors generated within 3D retinal organoids for transplantation into mouse models of retinal degeneration.

Pluripotent stem cell derived and cell carrier supported RPE replacement in large-eyed preclinical animal models

Fabian Thieltges[1], Tanja Ilmarinen[2], Heli Skottman[2,] Timothy Blenkinsop[3], Zengping Liu[1], Sudawadee Somboonthanakij[4], Warapat Wongsawad[4], Martina Herwig[1], Ralf Brinken[1], Norbert Braun[6], Nicole Eter[5], Frank Holz[1], Sally Temple[3], Jeffrey Stern[3], Boris V. Stanzel[1]
[1]*University Eye Hospital, University of Bonn, Germany*
[2]*University of Tampere, BioMediTech, Finland*
[3]*NSCI, Neural Stem Cell Institute, USA*
[4]*Eye Institute, Mettapracharak Eye Institute, Thailand*
[5]*University Eye Hospital, University of Muenster, Germany*
[6]*Geuder AG, Geuder AG, Germany*

Transplantation of retinal pigment epithelium (RPE) is being developed as a cell replacement therapy for age-related macular degeneration (AMD). Human embryonic and adult human RPE stem cells (hESC and hRPESC, resp.) are known potential sources that are currently being pursued towards the clinic. Polarized monolayers of SC-derived RPE were shown to grow on biostable polyester (PET) membranes. They were found to be similar to fetal hRPE monolayers and to have near-native characteristics. Stamped pieces of RPE monolayers on the carrier were loaded into a custom-designed surgical instrument and transplanted subretinally in the rabbit, a large-eyed animal model. Compared to fetal and hRPESC derived RPE, hESC-RPE xenografts showed better preservation of the neural retina overlying the implant. Histology obtained 4 weeks after implantation confirmed a continuous polarized human RPE monolayer on PET. We demonstrate that the xeno-RPE monolayer implant survived well and retained its polarization. Moreover, our initial data suggest a distinctly advantageous tolerance of hESC derived RPE xenografts in rabbit subretinal space.

Retinal oxygen extraction in humans

Leopold Schmetterer, Rene Werkmeister, Gerold Aschinger, Doreen Schmidl, Gerhard Garhoefer
Medical Physics and Clinical Pharmacology, Medical University of Vienna, Austria

Normal function of the human retina depends on proper oxygen supply. The primate inner retina is oxygenated via the retinal circulation. We developed a method to calculate total retinal oxygen extraction based on measurement of total retinal blood flow using dual-beam bidirectional Doppler optical coherence tomography and measurement of oxygen saturation by spectrophotometry. Measurements were performed in 8 healthy subjects while breathing ambient room air and 100% oxygen. Total retinal blood flow was 44.3 3 9.0 ml/min during baseline and decreased to 18.7 3 4.2 Ql/min during 100% oxygen breathing (P < 0.001) resulting in a pronounced decrease in retinal oxygen extraction from 2.33 3 0.51 Ql(O2)/min to 0.88 3 0.14 Ql(O2)/min during breathing of 100% oxygen. The method presented in this paper may have significant potential to study oxygen metabolism in hypoxic retinal diseases such as diabetic retinopathy.

VASCULAR IMAGING WITH THE RETINAL FUNCTION IMAGER (RFI)

Nicole Stubiger[1], Jianhua Wang[2], Janet Davis[2], Delia DeBuc[2]
[1]*Ophthalmology, Charite CBF, Germany*
[2]*Bascom Palmer Eye Institute, University of Miami, USA*

Purpose: Recent advances on optical imaging techniques enable imaging the retinal microvasculature at the capillary level. Herein we present the feasibility and applicability in diagnostic imaging of the retinal blood flow (BF) velocity in patients with retinal vasculitis using a commercially available Retinal Function Imager (RFI, Optical Imaging Ltd, Rehovot, Israel).
Methods: The RFI is a fundus camera-based device and was originally designed to measure the BF velocity directly and noninvasively in retinal vessels while using the hemoglobin in the red blood cells as an intrinsic motion-contrast agent. In a pilot study we measured the BF velocity with the RFI in 12 patients (m:f=2:10) with a mean age of 52312 years. Ten of these patients suffered from Birdshot Chorioretinopathy and two patients had a retinal vasculitis of unknown origin. We compared these data with an age matched healthy control group (n=11 volunteers).
Results: In the control group the blood flow velocity in the arteries was 3.730.9 mm/s and in the retinal veins 2.330.4 mm/s. Comparing these data with the retinal BF velocities of the study group, we achieved significant differences. The vasculitis patients disclosed an arterial blood flow velocity of 2.5 31.6mm/s (p0.0001) and a venous BF velocity of 1.731.0 mm/s (p0.001).
Conclusions: With the RFI we could show for the first time, that in patients with retinal vasculitis the arterial as well as the venous BF velocity are significantly reduced. Thus, imaging the retinal vasculature with the RFI could offer both - a diagnostic and quantifying tool in retinal vasculitis patients and, in addition, a facility for assessing the effectiveness of treatment.

Diabetic macular edema: Bridging the gap between imaging and therapy

Matthias Bolz
Department of Ophthalmology, General Hospital Linz, Austria

In the last years imaging of retinal changes secondary to diabetic macular edema gave new detailed insight into pathomorphologic and functional changes. At the same time several new therapeutic strategies have been provided by several companies, such as highly advanced laser techniques, intravitreal anti-VEGF of cortisole treatments or surgical means. The aim of this talk is to give an overview about characteristic findings in retinal imaging in this very specific retinal disease and to provide a system of categorization enabling the physician to make an individualized treatment decision.

Bacterial Inhibition of Corneal Wound Healing

Robert M Shanks, Kimberly Brothers, Stella Nicholas, Eric Romanowski
Ophthalmology, University of Pittsburgh, USA

The corneal epithelium provides a crucial barrier protecting the eye. Its integrity requires efficient wound healing which can be compromised during bacterial infection. We found that bacterial cells and secretomes from several species of Gram-negative and Gram-positive bacteria inhibit human and porcine corneal epithelial cell migration using in vitro and ex vivo wound healing models. Secretomes from 95% of Serratia marcescens, 71% percent of Pseudomonas aeruginosa, 29% of Staphylococcus aureus strains, and other bacterial species inhibited corneal epithelial cell migration. Migration of human foreskin fibroblasts was also inhibited by S. marcescens secretomes indicating that the effect is not cornea specific. Mutation of bacterial genes involved in lipopolysaccharide (LPS) biosynthesis prevented the bacteria inhibiting corneal epithelial cell migration. LPS depletion of S. marcescens secretomes with polymyxin B agarose rendered the secreted fractions unable to inhibit corneal epithelial cell migration. Purified S. marcescens LPS inhibited corneal epithelial cell migration in vitro and wound healing ex vivo, unlike LPS from waaG and waaC mutants, or Escherichia coli. Together these data suggest that S. marcescens LPS is sufficient for inhibition of corneal epithelial wound healing. This study presents a novel host-pathogen interaction with implications for corneal ulcers and other medical problems where bacteria impact wound healing, such as chronic wounds, and provides evidence that secreted LPS can be involved in the inhibitory mechanism.

The Resurgence of Penicillin-Susceptible Staphylococcus aureus Isolated from Infectious Keratitis

Regis P. Kowalski[1,2], Lisa Karenchak[1,2], Eric Romanowski[1,2], Robert Shanks[1,2], Deepinder Dhaliwal[1,2], Alex Mammen[1,2]
[1]*Ophthalmology UPMC Campbell Laboratory, University of Pittsburgh, USA*
[2]*Ophthalmology/UPMC/Campbell Laboratory, University of Pittsburgh, USA*

Introduction: Penicillin is not considered a first-line antibiotic for the treatment of Staphylococcus aureus (SA) keratitis. This consideration is supported by low concentrations achieved in the blood-serum after systemic administration, rather than concentrations achieved in the cornea by using topical therapy. We re-evaluated the in vitro susceptibility of pencillin for SA isolated from infectious keratitis patients to determine trends of antibiotic susceptibility, and the potential of topical penicillin to re-emerge as a treatment for SA keratitis.
Methods: MICs were determined on 333 SA isolated from keratitis patients between 1993 to 2014 to penicillin and oxacillin.The 22 years were divided into 5 time periods: 1993-1997 (N=105), 1998-2001 (N=51), 2002-2005 (N=53), 2006-2009 (N=53), and 2010-2014 (N=68). The SA were grouped as MSSA and MRSA. The MSSA MICs for penicillin were analyzed non-parametrically. Percent susceptibilities were determined based on the serum standard (MIC < 0.12 Qg/ml), and arbitrary concentrations that may be reached in topically treated corneas (4, 8,16, 32, and 64 Qg/ml).
Results: SA were comprised of 251 (75%) MSSA and 82 (25%) MRSA. The descriptive statistics of the MSSA for MIC50, MIC90, median, and range were 4, 64, 4, and 0.03 - 128 Qg/ml, respectively. The median MIC for '2010-2014' (2 Qg /ml) was statistically lower (p=0.005) than '1993-1997' (16 Qg/ml) indicating increased penicillin susceptibility. Susceptibility based on the serum standard was 10% (25/251). Corneal concentrations based on 4, 8, 16, 32, and 64 Qg/ml would increase susceptibilities to 50% (126/251), 57% (144/251), 69% (174/251), 82% (207/251), and 94% (237/251), respectively.
Conclusions:The MICs of SA isolated from cornea samples to penicillin have decreased over the last 22 years indicating that topical penicillin may have a renewed potential as an effective antibiotic for the treatment of MSSA keratitis. In vivo rabbit topical treatment studies for correlation are warranted.

Abstracts

Cross-linking in infectious keratitis

Irina S. Barequet
Goldschleger Eye Institute, Sheba medical Center, Tel Aviv University, Israel

Purpose: To review the antimicrobial effect of Corneal Cross-linking in infectious keratitis (photoactivated chromophore for keratitis).
Methods: Review of the literature and presentation of the experience in patients with progressive keratitis refractive to antibiotic therapy.
Results Following CXL most cases showed a rapid reduction in symptoms and decreased ulcer size with complete resolution and scarring
Conclusions: Positive effect of photoactivated chromophore for keratitis becomes a potentially important therapeutic tool in the era of multi-drug resistant microorganisms.

Fusarium and Non-Fusarium Fungal Corneal Infections During the Worldwide ReNu-Related Fusarium Keratitis Event of 2004-2006

John D. Bullock
Community Health, Wright State University, USA

BACKGROUND: In May 2006, Bausch and Lomb (B&L) was cited by the Food and Drug Administration for improper storage/transport temperatures of their multi-purpose contact lens solution, ReNu with MoistureLoc (RML, containing the antimicrobial agent, alexidine 0.00045%) [Arch Ophthalmol 2008;126:1493-1498]. The Centers for Disease Control and Prevention suggested disinfection failure as the cause of this event [JAMA 2007;298:2867-2868]. Our previous studies indicated: that heating RML in its bottle resulted in decreased ability of RML to inhibit Fusarium organisms [Arch Ophthalmol 2011;129:133-136] and resulted in a loss of antimicrobial capability against 12 non-Fusarium fungal organisms [Eye & Contact Lens 2012;38:222-226]; and, that alexidine absorbed into the wall of the RML bottle [N Engl J Med 2014;370: 88-89]. In 2009-10, judges, quoting B&L`s own research, ruled that there was no association between RML and non-Fusarium infections [http://law.justia.com/cases/new-york/other-courts/2009/2009-52571.html and http://www.law360.com/articles/150536/renu-lens-solution-mdl-slashed-by-100s-of-suits]. The purpose of the present study was to investigate whether there was an increased incidence of non-Fusarium fungal keratitis during the time of the Fusarium keratitis event of 2004-2006.

METHODS: Data from a multicenter study of fungal keratitis [Ophthalmology 2011;118:920-926] were analyzed using the Poisson distribution [Cornea 2008;27:1013-1017].

RESULTS: The probability that the observed number of cases of Fusarium keratitis was merely a chance variation from the expected (baseline, endemic) number was 5.2x10-38.
The probability that the number of observed cases of non-Fusarium fungal keratitis was merely a chance variation from the expected number was 1.2x10-9.

The Evaluation of Topical SPL, a Novel Dendrimer Antiviral, against Adenovirus in NZW Rabbit Ocular Models

Eric Romanowski[1], Kathleen Yates[1], Robert Shanks[1], Oliver Bernhard[2], Jeremy Paull[2], Regis Kowalski[1]
[1]*The Charles T. Campbell Ophthalmic Microbiology Lab, Department of Ophthalmology, University of Pittsburgh School of Medicine, USA*
[2]*Starpharma, Pty Ltd., Australia*

Purpose: There is no FDA or EMA approved antiviral therapy for adenovirus ocular infections. Dendrimers are novel nanoscale macromolecules that have the ability to be designed to interact polyvalently with a target and act as virucidal agents. SPL is a polyanionic dendrimer. SPL's unique size, shape, and highly charged surface allow attachment to targets on viruses which then prevent viral attachment and/or adsorption to cells. The goals of the current study were to evaluate the ocular tolerability and anti-adenoviral efficacy of topical SPL in separate NZW rabbit ocular models. Methods: Topical 5% SPL 3% SPL, Vehicle, and 0.5% Cidofovir were evaluated for ocular tolerability in uninfected rabbit eyes and for antiviral efficacy in the Ad5/NZW rabbit ocular model. Results: There were no differences in Draize scores among the groups during treatment. 5% SPL (Days 3, 5, 7, 9), 3% SPL (Days 3, 5, 7, 9) and Cidofovir (Days 7, 9) significantly reduced daily viral titers compared with Vehicle. 5% SPL (7d), 3% (4.5d) and Cidofovir (5d) significantly reduced the Duration of Viral Shedding compared to Vehicle (9d). Conclusions: 5% SPL and 3% SPL demonstrated significant antiviral efficacy compared with VEH in the Ad5/NZW rabbit ocular model. Both 5% and 3% SPL demonstrated significantly better efficacy than CDV, during the Early Phase of Infection (Days 1-5). SPL induced "Minimally Irritating" to "Practically Non-Irritating" Draize scores in the NZW rabbit ocular tolerability model. Further development of SPL as a topical antiviral for adenoviral ocular infections is indicated.

Abstracts

Different practice patterns in endophthalmitis prophylaxis in different parts of the world

Andrzej Grzybowski
Dept. of Ophthalmology, University of Warmia and Mazury, Poland

Different practice patterns in endophthalmitis prophylaxis are used in different parts of the world. The use of povidone iodine for conjunctival sac irrigation and skin disinfection is best accepted world-wide. On the other hand, the use of antibiotics raises much controversies. They are used in some countries only intracameraly, in other only topically, or both topically and intracameraly. Different antibiotics are used intracameraly, including mostly cefuroxime, moxifloxacin and vancomycin. There is even more differences in topical antibiotic use, including their sort, pre- and postoperative use, dosage and duration. There is increasing number of studies presenting the evidence that intracameral antibiotics protect against endophthalmitis, whereas the use of topical antibiotics is off label and based on very limited scientific foundations. Interestingly, however, it was shown that endophthalmitis rate in centers using only intracameral antibiotics and only topical antibiotics might be very similar.

Visual Loss Caused by Cobalt Neurotoxicity from Hip Implants

Konrad P. Weber
Departments of Neurology and Ophthalmology, University Hospital Zurich, University of Zurich, Switzerland

Cobalt neurotoxicity may lead to retinopathy and optic neuropathy causing progressive bilateral visual loss. A frequent cause for cobalt intoxication is abrasion from defective hip implants. Most often, after replacement of a fractured ceramic prosthesis, residual fine ceramic particles grind down the metal head replacement. Premature wearing of metal-on metal prostheses may also be the culprit. Helpful laboratory signs for cobalt toxicity include polycythemia and hypothyroidism. Metallosis may be apparent on conventional hip x-rays and elevated cobalt levels in whole blood confirm the diagnosis. Treatment of choice is removal of the source of cobalt intoxication by revision of the defective hip prosthesis. Based on a clinical case, the purpose of this talk is to raise awareness about cobalt neurotoxicity as an insidious cause of chronic bilateral visual loss. With aging of the population and the increasing number of hip implants, neuro-ophthalmologists may encounter this entity more frequently in the future.

New horizons in optic pathways gliomas treatment

Nitza Goldenberg-Cohen
Pediatric Ophthalmology Unit, Schneider Childrens Medical Center of Israel, Israel

The Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
Glial tumors of the brain are the leading cause of cancer-related death and morbidity in children. Their diagnosis/prognosis relies mainly on clinical and histopathological factors. Recently, exciting advances in pediatric oncology have revealed the molecular basis of pediatric glioma as well as important genetic differences between pediatric and adult brain malignancies.
There are currently no effective treatments for gliomas, other than surgery and radiation and the effective treatments only provide short-term relief from the cancer, while substantially contributing to patient morbidity.
Novel molecular markers/pathways identified provide a better understanding of the pathogenesis of gliomas and critical markers for therapy that will help refine pathological grading. Three different pathways are involved in glioma tumorigenesis. BRAF is a serine/threonine kinase in the RAS/RAF/MAPK kinase pathway, which is overactivated in the majority of the pilocytic astrocitomas. Another major signaling cascade is the PI3-kinase (PI3K)/mTOR pathway, known to be upregulated in the majority of high- and low-grade pediatric gliomas. Dual PI3K/mTOR inhibitors are undergoing clinical trials. The third mechanism involves angiogenesis and treatment might be directed to its inhibition.
The integration of molecular studies may improve therapeutic targeting to decrease recurrence, prolong survival and minimize toxicity, thus enabling personalized therapies based on the molecular fingerprint of individual tumors

The OCT as a window to the brain

Andrzej Grzybowski
Dept. of Ophthalmology, University of Warmia and Mazury, Poland

Optical coherence tomography (OCT) is a noninvasive imaging technique that allows us to monitor the retinal nerve fiber layer (RNFL). This structure contains the axons of the retinal ganglion cells, which form the optic nerves, chiasm and optic tracts. Since retinal axons are nonmyelinated until they penetrate the lamina cribrosa, the RNFL is an ideal structure to visualize any process of neurodegeneration, neuroprotection or regeneration. Therefore, OCT has been applied in several areas in neurology over the last decade, becoming a hot topic and generating great enthusiasm among neurologists and ophthalmologists. The use of OCT to quantify retinal axonal loss is a promising tool to evaluate disease progression in numerous neurodegenerative disorders, including multiple sclerosis, Parkinson disease, Alzheimer disease, intracranial hypertension, and schizophrenia and may be used as a biological marker of neuroaxonal injury. An overview of the advancements in the development of OCT as a novel technology that enables objective analysis of the processes of neurodegeneration within the retina will be given.

Abstracts

Glaucoma surgery: where are we?

Jeffery Schultz
Ophthalmology, Montefiore Medical Center/Albert Einstein College of Medicine, USA

Rational Approach to Glaucoma Surgery
The approach to glaucoma surgery has been a constant pendulum constantly phasing between efficacy and safety. New improvements in efficacy come at the cost of patient safety and new safer procedures don't seem to work that well at lowering IOP. How and when should we approach surgical intervention in our patients? A rational and individualized approach will be discussed to surgical intervention.

Why aren't there more new pharmacotherapies for glaucoma?

Gary Novack
R&D, PharmaLogic Development, Inc., USA
Ophthalmology and Pharmacology, University of California, Davis, USA

At present, all the medications that we use to treat glaucoma are approved on the surrogate endpoint of a reduction of elevated intraocular pressure (IOP). Since the late 1970's, there have been three "paradigm shifts" in the pharmacological treatment of glaucoma – from pilocarpine to timolol, from timolol to prostaglandins, and now with the expiration of some patents, the introduction of generic prostaglandins. Since the turn of the century, eight molecules have been approved in the United States to treat elevated IOP. Some of these were reformulations of the originally approved product, and three were fixed-dose combinations . Only a few were novel molecules, however, and none was a new class. Unlike other ophthalmic diseases, we understand well how to measure elevated IOP, and have a clear definition of clinically significant changes. The author will present hypotheses for this paucity of new therapies. The author will also give an update on new pharmacotherapies as of July 2015.
Novack GD. Why aren't there more pharmacotherapies for glaucoma? Glaucoma Today (in press).

ROCK inhibitors: ready for prime time

Brian Levy
Chief Medical Officer, Aerie Pharmaceuticals, USA

The most recent innovation in drug development for patients with Glaucoma is the clinical development of ROCK inhibitors for the lowering of IOP. Longitudinal studies have shown that lowering of IOP is the only modifiable risk factor for protecting the optic nerve from further damage when the IOP is relatively high. However it is also known that the site of the pathology leading to relatively high IOP appears to lie within the drainage mechanism of the eye at the trabecular meshwork. Activation of Rho in trabecular meshwork cells induces myosin light chain phosphorylation which stimulates the formation of stress fibers and focal adhesions, which leads to increased contractility. The inhibition of Rho modulates cellular contractility and stiffness of the trabecular meshwork and Schlemm's canal, potentially enhancing the outflow of aqueous through the previously impaired outflow mechanism.
The presentation at this innovation session will focus not only on the clinical IOP lowering effects of ROCK inhibition, but also the pre-clinical work which suggests that ROCK inhibition may provide benefits that go beyond simply lowering IOP, with the potential for modifying and even reversing the pathology existing at the primary outflow facility of the eye. In addition ROCK inhibition has also shown the potential for neuroprotection in various pre-clinical models of optic nerve damage. The data presented will provide compelling clinical and pre-clinical data that suggests that ROCK inhibition is indeed ready for Prime Time.

Glaucoma Drug Delivery: Concepts

Anuj Chauhan
Chemical Engineering, University of Florida, USA

Conventional ophthalmic drug by eye drops is very inefficient with a low bioavailability of 1-5%. Also, glaucoma patients frequently instill eye drops multiple times each day, which is a cause for reduced compliance. The bioavailability can be increased to about 50% by using drug eluding contact lenses but commercial contact lenses release drugs in a burst which can cause toxicity. Our lab has focused on developing contact lenses that can deliver ophthalmic drugs for significantly longer durations compared to commercial lenses, but without sacrificing any of the critical optical, mechanical or transport properties. Additionally we have designed other devices for glaucoma therapy including fornix inserts and puncta plugs. This talk will briefly discuss the limitations of eye drops and the pros and cons of other approaches with a focus on drug eluting contact lenses. The talk will also include a recent in vivo study in a Beagle dog glaucoma model. This study focused on showing that vitamin E loaded contact lenses can simultaneously release multiple ophthalmic drugs and manage glaucoma more effectively compared to eye drops. Results show that the contact lenses can achieve double the IOP reduction of eye drops with a 10-fold lower dose. Additionally, it may be feasible to achieve extended IOP reduction longer than the lens-wear duration through creation of drug depots in the eye, which may significantly improve the compliance.

Abstracts

Glaucoma Drug Delivery: Update

Carol Rasmussen
Ophthalmology & Visual Sciences, University of Wisconsin-Madison, USA

Small molecule topical eye drop therapy is the most common first treatment option for elevated intraocular pressure (IOP). While easy for a patient to use, absorption of topical drops through the conjunctival mucosa can lead to systemic effects. The short drug-eye contact time may require frequent applications, leading to patient adherence issues. New iterations of fixed dose combination drugs, with multiple mechanisms; targeting the trabecular meshwork (TM) and ciliary muscle (CM) are moving through clinical trials, showing efficacy and safety. Topical drop formulation changes using polymer-based gelling systems, liposomes and nanospheres are in development to increase bioavailability. Implantable extended-release devices using microparticles and nanoparticles would free patients from burdensome topical drop regimens, as would other sustained release strategies. Contact lenses and microneedles as delivery vehicles are additional promising strategies. Gene transfer techniques can produce robust and long-term (2 years) expression of reporter genes in the primate outflow pathway in vivo, with low immunogenicity.
Most glaucoma patients will be prescribed multiple topical drops of varying classes of compounds to control their disease. Patient adherence is an ongoing issue that impacts treatment outcomes. There continues to be a need for novel therapeutics, alternative delivery methods and long-term therapeutic strategies such as gene therapy.

Noncompliance with Glaucoma Therapy: The Magnitude of the Problem

George L. Spaeth
Glaucoma Department, Wills Eye Hospital, USA

"Noncompliance" comes in many forms, ranging from not using medications as instructed, to not keeping appointments. The issue is usually considered due to patient errors. However, those patient errors are frequentlhy the result of physician errors. The effect in on patients` health is presumably large. Not only is frequency high - some studies suggesting that only around 10% of patients are using medications properly one year after the medications were advised, - but in terms of preservation of vision. Few (or no) studies have actually measured the effect of noncompliance, or of failure to return for appointment, on the rate of progression of glaucoma. None have considered the possibly beneficial effect of noncompliance by the large number of patients in whom medications that were not needed, or were inappropriate, were advised.
By diagnosing accurately, staging the severity of disease validly (I suggest using the Disc Damage Likelihood Scale), determining the rate of change of the disease - structurally and functionally, the duration the disease will continue (usually in terms of estimated years of life remaining), and socioeconomic factors - including the specific characteristics of the patient under consideration -- problems with inappropriate use of medications should be able to be reduced.

Injectable Intraocular Drug Delivery for IOP Lowering: Opportunities and Challenges

Dale Heuer
Ophthalmology, Medical College of Wisconsin, USA

Given the high prevalence of non-adherence with topical ocular hypotensive therapy, direct administration of medications to glaucoma suspects and patients is intuitively advantageous and therefore the recent interest in developing sustained-release approaches is certainly welcome by clinicians. Some of the potential practical hurdles to implementation of sustained-release injections will be discussed, including: patient acceptance; clinician work-flow impact; and medication and professional services payment/ reimbursement issues.

Glaucoma Stents as Vehicles for Drug Delivery

Paul Harasymowycz
Ophthalmology, University of Montreal, Canada

Bellevue Ophthalmology Clinic, Montreal Glaucoma Institute, Canada
Current and future trabecular bypass stents and Schlemm`s canal scaffolds offer the potential for local drug delivery or a potential reservoir through which anti-scarring and outflow enhancing medications, as well as tissue enhancing growth factors and cultured trabecular stem cells may be delivered in order to prevent tissue scarring, decrease IOP, and improve or reverse diseased or damaged cellular function.

Punctal Plugs as Reservoirs for Glaucoma Drug Delivery

Brian Flowers
Ophthalmology Associates, Glaucoma Specialist, USA

The challenge of compliance with daily eyedrop therapy is well known. There are ongoing efforts to address this issue with novel forms of drug delivery. Punctal plugs are one such method, that has been used to deliver a variety of compounds ranging from glaucoma medications to anti-inflammatory drugs. The issues that must be overcome are efficacy, tolerability and retention of the devices. We will discuss the current state of research in this area.

Abstracts

Non Punctal Extraocular Drug Delivery in Glaucoma Patients

James Brandt, James Brandt
Department of Ophthalmology & Vision Science, University of California, Davis, USA

The reliable sustained delivery of glaucoma medications without patient involvement in daily drug dosing is a long-sought goal. Sustained delivery of glaucoma medications should ideally be effective, of long duration and reversible if a patient has an adverse reaction to the active agent being used. Furthermore, as sustained release duration increases to time ranges of months or longer, patients should be able to determine easily that the drug and/or device is still present so that they do not go untreated between office visits.
The Helios™ implant is a polymer-based device that resides in the conjunctival fornix that in pre-clinical and Phase 1 studies has demonstrated sustained delivery of clinically-relevant doses of bimatoprost. The device is well-tolerated and provides sustained release of glaucoma drugs over a clinically-relevant duration. The device has a high retention rate and patients can easily determine if the device has been lost or dislodged.
This talk will review early clinical data of the Helios™ bimatoprost implant and plans for future clinical investigations of this novel drug-delivery platform.

Glaucoma Drug Delivery: The Importance of Surveillance

Kuldev Singh
Ophthalmology, Stanford University, USA

While considerable attention is given to noncompliance with medical therapy as a risk factor for the progression of glaucomatous disease, little has been written on the importance of appropriate follow up in determining disease course. Just as the regular use of medications does not guarantee a halting of vision loss, the impact of noncompliance on visual outcomes varies substantially between individual glaucoma patients. Given that laser and surgical options are also available for glaucoma therapy, regular surveillance of those with the disease maximizes the opportunity to offer non-medical therapeutic options for those in whom medical therapy is ineffective for any of several reasons, including noncompliance.

Pediatric CXL

Omur Ucakhan-Gunduz
Department of Ophthalmology,
Ankara University School of Medicine, Turkey

Pediatric keratoconus has unique properties such as faster progression and more severe disease at the onset. We performed corneal collagen crosslinking (CXL) to 30 eyes of 30 pediatric patients with progressive keratoconus. The mean age of patients was 15.632.1 years (12-18 years). All patient eyes underwent CXL with the standard protocol The mean UDVA improved from 0.8730.40 LogMAR (~20/160) to 0.6130.34 LogMAR (~20/580) (p<0.001), and CDVA from 0.3730.26 LogMAR (~20/50) to 0.1730.16 LogMAR (~20/32) at the end of 24 months (p<0.001). The mean spherical equivalent refraction improved from -6.4734.06 D to -5.8033.90 D, and the mean Kmax significantly decreased from 57.636.7 D preoperatively to 56.032.0 D at 2 years. No sight threating complications were seen in any patient eye. Corneal collagen crosslinking seems to be safe and effective in halting the progression of keratoconus in pediatric patients at 2 year follow-up.

Evaluating Progression in Keratoconus to Assess Cross Linking Efficacy

Penny Asbell, Sarah E. Brown, Rubinee Simmasalam,
Neha Gadaria, Nataliya Antonova
Icahn School of Medicine, Mount Sinai, USA

Purpose: Ultraviolet corneal collagen cross-linking (CXL) has been shown to possibly delay, halt, or even reverse disease progression in keratoconus. Understanding of the efficacy of CXL, however, is hampered by the varying definitions and metrics used to evaluate corneal changes. To understand the issues a review of how progression is analyzed in CXL trials was undertaken
Methods: A review of the peer reviewed publications on progression in keratoconus and the results of major CXL studies to date was performed. An IRB approved retrospective analysis of changes in autokeratometry (AutoK) and simulated keratometry (SimK) over time in 186 patients with keratoconus were analyzed using linear regression.
Results: The CXL literature varies widely in terms of criteria for progression and parameters for successful outcomes. Multiple inclusion criteria for progression makes it difficult to evaluate results for long term efficacy of CXL. Linear regression analysis of changes in corneal curvature in patients with keratoconus using autokeratometry (AutoK) and simulated keratometry (SimK) failed to reveal significant slopes over up to three years (p>0.05), with only 15% of eyes exhibiting an increase of 2D or more in average AutoK or SimK.
Conclusion: Better-defined metrics for progression in keratoconus are needed. Larger, long-term randomized clinical trials with clearer inclusion criteria and outcome measures may more clearly establish the role of CXL in the management of keratoconus and help identify the best candidates for CXL.

Abstracts

Corneal collagen cross-linking: Past, present, and future

James Reidy
Ophthalmology, The State University of New York at Buffalo, USA

First introduced by the Dresden group in the late 1990`s, photochemical corneal collagen cross-linking utilizing topically applied riboflavin and ultraviolet A irradiation is the first true treatment for ectatic disorders of the cornea. There has been more than a decade of world-wide clinical experience with this technique. Numerous studies have established that cross-linking is effective in stabilizing progressive ectasia, improving visual, topographic, and abberometric parameters. The standard treatment protocol is safe and has a low rate of complications. We will review strategies that are designed to improve drug delivery, reduce treatment time, increase efficacy of cross-linking, and improve patient comfort while maintaining an excellent saftey profile.

Drops for Presbyopia

by Herbert E Kaufman, M.D. and Almamoun Abdelkader M.D.,PHd

Herbert Kaufman, Almamoun Abdelader
Ophthalmology, Pharmacology and Microbiology,
Louisiana State University, USA

A small pupil,like an Accufocus implant can give presbyopes good reading vision.The patented combination of Carbachol and Brimonidine is synergistic and one drop permits good reading vision in presbyopes 45-55 year old.Treating only one eye avoids symptoms of dimness, distance vision remains good , and the effect lasts 8-10 hours.The combination is tolerated for at lease 3 months.

Information on RVL-1201 and the pharmacologic treatment of ptosis

Barry Butler
CEO, Revitalid, Inc., USA
Managing Partner, Point Guard Partners, LLC, USA

Blepharoptosis (ptosis) is a common condition that develops in people as they age. It is estimated that 11.5% of people over 50 years of age in the United States have clinically relevant ptosis.
RVL-1201 is an investigational drug being studied for the treatment of age-related ptosis. In a small pilot study (34 subjects), two dose regimens of RVL-1201 were compared to its vehicle for two weeks. Palpebral fissure distance (PFD) and Humphrey visual field (HVF) were analyzed. RVL-1201 exhibited numerical improvements in both PFD and HVF at all time points compared to vehicle. Onset of action was quick, with improvement in both PFD and HVF at the Hour 2 time point on Day 1, and long lasting, with effects on both endpoints being evident at the Hour 12 time point on Day 14. The effect of RVL-1201 was consistent throughout the two-week period. RVL-1201 was well tolerated in this study.
A Phase 3 trial of RVL-1201 is currently underway in the USA.

Contact Lens Discomfort - Causes and Treatment

Omur Ucakhan-Gunduz
Department of Ophthalmology,
Ankara University School of Medicine, Turkey

Despite new contact lens fits, 10-50% of contact lens wearers discontinue lens wear within the first 2 to 3 years due to discomfort. This discomfort can be in the form of irritation, dryness, soreness, redness or inconvenience. This talk will focus on lens and patient-specific reasons for discomfort symptoms such as dry eye, contact lens deposits, mechanical, frictional, and allergic factors, and the clinical management of these conditions.

Neurobiology of Contact Lens Discomfort

Pedram Hamrah
Cornea Service, New England Eye Center,
Tufts Medical Center, USA
Department of Ophthalmology, Tufts University, USA

This short review characterizes the neurobiology of contact lens-related discomfort. The evidence for specific machanism involved in contact lens discomfort are limited. This review will summarize underlying neurobiological mechanisms in dry eye disease, ocular surface inflammation, the role hyperosmolarity on ocular surface nociceptors, and mechanisms of ocular pain and discomfort. These mechanism could be applied and are relevant to the understanding of contact lens discomfort. Discomfort of the ocular surface due to contact lens wear is likely to be multifactorial and highly complex, and may include components of contact lens solutions, desiccation, inflammation, friction, mechanical stimulation. Additionally, sensory input will arise from stimulation of the lid margin, palpebral and bulbar conjunctiva, and the cornea.

Myopia progression

Omur Ucakhan-Gunduz
Department of Ophthalmology,
Ankara University School of Medicine, Turkey

Myopia progression is a significant public health problem affecting up to 85% of the population in Asian countries. Furthermore, the prevalence of myopia seems to be increasing worldwide. By the year 2020, the estimated number of myopes will be around 2.5 trillion in the world. Several hypotheses have been put forward to explain myopic progression, and accordingly, several measures have been advocated to control it including, atropine 0.05% eye drops, specific muscarinic antagonists (pirenzepine 2%), bilateral distance undercorrection, bifocal/multifocal spectacle lenses, monovision and most recently orthokeratology or soft bifocal contact lenses. Recent studies report favorable outcomes particularly with the use of orthokeratology lenses. Despite all efforts, there are several confounding factors in the pathogenesis of myopia progression and for now there appears to be no one, simple, effective way of stopping the development or slowing the progression of myopia

Oral External Eye Diseases
Topical steroids protects the lacrimal functional unit of dry eye patients from desiccating stress

Jose Pinto-Fraga XE "Pinto-Fraga, Jose Abstracts:"[1,2], Alberto Lopez-Miguel XE "Lopez-Miguel, Alberto Abstracts:"[1,2,3], Maria Jesus Gonzalez-Garcia XE "Gonzalez-Garcia, Maria Jesus Abstracts:"[1,2], Itziar Fernandez XE "Fernandez, Itziar Abstracts:"[1,2], Alberto Lopez-de-la-Rosa XE "Lopez-de-la-Rosa, Alberto Abstracts:"[1], Amalia Enriquez-de-Salamanca XE "Enriquez-de-Salamanca, Amalia Abstracts:"[1,2], Michael Stern XE "Stern, Michael Abstracts:"[4], Margarita Calonge XE "Calonge, Margarita Abstracts:"[1,2]
[1]*IOBA (Institute of Applied OphthalmoBiology), University of Valladolid, Spain*
[2]*CIBER-BBN, Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine, Spain*
[3]*VISION I+D ,SL, IOBA, Spain*
[4]*Allergan Inc, Allergan, USA*

Purpose: To assess the efficacy of topical 0.1% fluorometholone for protect the lacrimal functional unit in moderate-to-severe dry eye disease (DED) patients when exposed to adverse environments.
Methods: Single-center, double-masked, parallel clinical trial (clinicaltrials.gov Identifier # NCT02051023). Participants randomly received topical 0.1% Fluorometholone or polyvinyl alcohol for 22 days. Corneal and conjunctival staining, conjunctival hyperemia, tear break-up time (TBUT), tear osmolarity and Symptom Assessment in Dry Eye questionnaire (SANDE) were assessed during baseline (V1), at day 21 before and after exposure to controlled adverse environment (V2 and V3), and at day 22 after 24 hours from the adverse exposure (V4). Main outcomes measures were the percentage of patients showing an increase ≥1 point in corneal staining and the percentage with a reduction ≥2 points in SANDE score, at V3 and V4.
Results: After 21-day treatment, improvements for corneal and conjunctival staining, conjunctival hyperemia, and TBUT were significantly higher ($p \leq 0.03$) for the FML group than for the LIQUIFILM group. No changes in osmolarity were observed. After the adverse exposure the LIQUIFILM group showed a significant ($p=0.03$) higher percentage of patients with a ≥1 grade increase in corneal staining than the FML group (63.1%, 95% confidence interval (CI): 38.6-82.7; 23.8%, 95% CI: 9.1-47.5, respectively). No significant differences between groups were found at V4. No adverse events were observed throughout the whole study.
Conclusions: Three-week topical 0.1% fluorometholone therapy is safe and effective to reduce ocular surface signs in DED patients and to prevent DED exacerbation in patients exposed to adverse conditions.

IL- 17 inhibitors

Sofia Androudi
Ophthalmology, University Hospital of Larissa, Greece

The central role of autoreactive T cells in the pathogenesis of noninfectious uveitis— described in both experimental models and affected patients— has provided a rationale for treatment of this disease with immunosuppressive medication. Interleukin (IL)-17A, secreted by T-helper (Th)17 cells, is recognized as one of the principal proinflammatory cytokines in immune-mediated inflammatory diseases. Higher levels of IL-17A have been found in the peripheral blood of patients with uveitis, in association with systemic immune-mediated conditions, such as Vogt–
Koyanagi–Harada syndrome and Behçet's disease, compared with healthy controls or affected patients with quiescent uveitis. Reported substantial elevation in IL-17A expression in the serum of patients with active uveitis and in animal models of uveitis and demonstrated that IL-17A inhibition suppresses disease activity.
Recent observations on the specific role of IL-17A in the pathogenesis of Behçet's disease also indicate that IL-17A inhibition could be beneficial in the treatment of ocular and nonocular disease manifestations.
Interleukin-17 augments TNF-responses, and IL-17 inhibition alters the severity and course of the disease. Interleukin-17B and IL-17C are associated with TNF-production and contribute to the exacerbation of inflammatory conditions. Interleukin-17A is implicated in immune regulation at mucosal sites and potentially the eye.

Abstracts

TNF inhibitors: present and future

Christoph Deuter
Centre for Ophthalmology, University of Tuebingen, Germany

Since they are available, TNF inhibitors found increasing use in the treatment of uveitis and scleritis. Although still off-label for ocular disorders, they are included in the recommendations for the treatment of severe forms of uveitis associated with Behcet´s disease and juvenile idiopathic arthritis, two entities with poor prognosis so far. However, TNF inhibitors are also used for severe cases of other forms of non-infectious ocular inflammation if conventional immunosuppressive drugs fail. Currently there are five TNF inhibitors commercially available, approval of one of them for the treatment of non-infectious uveitis affecting the posterior eye segment is expected in the near future. However, there are open questions to be answered regarding the use of TNF inhibitors in ocular inflammation, addressing e.g. long-term side effects, the necessity to prevent from autoantibody development, and whether and when treatment can be discontinued. So far TNF inhibitors are available only for intravenous and subcutaneous application. But attempts to develop a formulation for topical use have been already undertaken.

IL-1 antagonists for the treatment of uveitis

Michal Kramer
Department of Ophthalmology, Rabin Medical Center,
Uveitis Service, Israel
Sackler School of Medicine, Tel Aviv Univesity, Israel

Biologic agents, despite targeting specific molecules, are still non-specific therapies. Anti TNF-α agents are widely used off label for uveitis, while other biologic agents are still creeping into the treatment of uveitis. Wise use of these agents will be possible only if we unravel the critical pathogenic pathway of each of the uveitis diseases.
IL-1 is a pro-inflammatory cytokine and a key factor in innate immunity. IL-1β, a member of the IL-1 family, binds initially to IL-1 receptor (IL-1R) followed by accessory protein (IL-1RAcP). This complex induces biologic effects by induction of other inflammatory mediators.
IL-1 plays a role in auto-inflammatory processes, when innate immunity is activated. Cumulative experimental and clinical data point to its role in the pathogenesis of Behcet`s disease and Intermediate uveitis. Systemic juvenile idiopathic arthritis is currently viewed as an autoinflammatory disease, with IL-1 having a major role, unlike the articular form. Experimental data show that IL-1 is not essential for the development of uveitis, however IL-1 antagonist has an important natural immunosuppressive role within the eye.

Current available anti IL-1 antagonists include: anakinra (recombinant human IL-1R antagonist); canakinumab (human immunoglobulin G1 anti-IL-1β monoclonal antibody) and gevokizumab (recombinant humanized anti-IL-1β antibody).
Limited data exists regarding the effectiveness of anakirna and canakinumab in refractory cases of uveitis. Gevokizumab which was granted an orphan drug designation for the treatment of noninfectious uveitis, is currently under phase 3 trial for intermediate, posterior and panuveitis in general and specifically related to Behcet`s disease.

The horizons of biologically designed drugs for ocular inflammation

Uwe Pleyer, Uwe Pleyer
Ophthalmology, Charite, Germany

Ocular inflammation may affect different areas of the eye and remains an important cause of preventable vision loss. With the advent of biologic agents the treatment paradigm for many diseases has progressed tremendously. This includes extra- and intraocular inflammation, but also conditions like macular degeneration. This presentation aims to highlight important advances in the options available for the treatment of ocular inflammation. In this perspective, the latest advances of therapies in autoimmune inflammatory diseases, especially uveitis, disease will be covered.

Indications for ocular tapping in anterior viral uveitis

Soon-Phaik Chee
Cataract Service, Ocular Inflammation & Immunology Service,
Singapore National Eye Centre, Singapore

An infectious etiology should be suspected when a patient presents with hypertensive anterior uveitis. Other than sarcoidosis, syphilis and toxoplasmosis, herpetic infections such as caused by herpes simplex (HSV), herpes varicella zoster (VZV) and cytomegalovirus (CMV) should be considered. Serological tests even when positive do not confirm an ongoing ocular infection. Subjecting the sampled aqueous to analysis by multiplex polymerase chain reaction and/or intraocular antibody assay (Goldmann Witmer coefficient) may provide direct evidence of an infectious etiology. False negatives may occur and some eyes require an additional procedure. Real time PCR of the same aqueous sample gives an indication of the viral load and guides therapy. Repeat tap when the eye appears quiescent will allow confirmation of control of infection and therapy can then be adjusted.

Abstracts

Available PCR primers, the definition of positive and negative errors, pros and cons: PCR vs. Goldmann-Witmer technique

Jolanda de Groot-Mijnes
Ophthalmology and Medical Microbiology, University Medical Center Utrecht, Netherlands

The most common causes of viral AU in the western world are herpes simplex virus, varicella zoster virus, rubella virus and cytomegalovirus, which may present with overlapping ophthalmological characteristics. If a definitive diagnosis based on the clinical presentation and history cannot be made intraocular fluid analysis may be of value.
Several PCR assays for the detection of either virus have been developed. In addition, Goldmann-Witmer analysis to determine intraocular antibody production can be applied. For HSV, VZV and CMV AU PCR and GWC appear to contribute equally and are complimentary. However, for rubella virus-associated uveitis, including Fuchs and Fuchs-like heterochromic uveitis, the GWC seems superior over PCR. Positive test outcomes depend on several factors most notably the infectious agent, reflected in the nature of the infection, and time of sampling. Sensitivity, specificity, advantages and disadvantages of these two types of diagnostic assays will be discussed.

Defining the Patient Population For Implantable MIGS Devices

Kuldev Singh
Ophthalmology, Stanford University, USA

The appropriate population of patients in whom to test novel minimally invasive glaucoma surgical procedures or devices must reflect a balance to develop a robust estimate of the procedure's efficacy while being careful to not significantly compromise safety. The stage of disease is generally classified as mild, moderate or severe based on the degree of glaucomatous optic nerve damage measured by the severity of visual field loss. Patients without definitive glaucoma should not be recruited into MIGS studies as they do not require glaucoma surgery. On other end of the spectrum, those with severe disease should be excluded to prevent them from potentially receiving insufficiently effective novel therapies as well as to avoid putting them at high risk of vision loss if washout of medications is required in the protocol.

Cataract Surgery as IOP Lowering Procedure

James Brandt
Department of Ophthalmology & Vision Science, University of California, Davis, USA

Data from the Ocular Hypertension Treatment Study (OHTS) and the control arms of several registration studies for MIGS devices (e.g., the iStent™) have demonstrated that cataract extraction by phacoemulsification can often lower intraocular pressure by several mmHg. In this talk I will review the quality of the evidence that cataract extraction alone can reliably and predictably lower IOP among patients with glaucoma; I will also provide guidelines for determining when clear cornea cataract surgery alone, cataract surgery plus a MIGS procedure, or more aggressive incisional surgery are indicated. The effect of cataract surgery on IOP control in previously-filtered eyes will also be reviewed.

Implantable MIGS Devices: Canal Based

Paul Harasymowycz
Ophthalmology, University of Montreal, Canada

Bellevue Ophthalmology Clinic, Montreal Glaucoma Institute, Canada
Trabecular bypass stents and Schlemm`s canal scaffolds offer patients and their physicians a safer surgical alternative in the management of glaucoma, and have resulted in a large paradigm shift in the glaucoma treatment algorithm. These devices are currently most often implanted when combined with cataract surgery or in pseudophakic patients, and result in IOP lowering by permitting aqueous humour to egress through the eye`s natural outflow pathways. Patient selection, surgical techniques and efficacy, as well as complications will be discussed.

Implantable MIGS Devices: Suprachoroidal Space

Brian Flowers
Ophthalmology Associates, Glaucoma Specialist, USA

A therapeutic gap exists between extremely safe medical and laser treatment and traditional glaucoma surgery. Minimally invasive glaucoma surgeries (MIGS) are meant to fill that gap. Currently available trabecular meshwork based MIGS procedures perform very well with respect to safety, but are less than ideal with regard to efficacy. The suprachoroidal space has a greater potential for IOP lowering, as long as safety concerns can be addressed. The Transcend Cypass suprachoroidal stent has just completed its US phase 3 trial, and the Glaukos iStent Supra is midway through its US Phase 3 trial. Available data suggests both may represent an improvement with respect to our ability to treat glaucoma surgically in a safe but effective manner.

Abstracts

Safety Endpoints and Patient Related Outcomes for MIGS Devices

George L. Spaeth
Glaucoma Department, Wills Eye Hospital, USA

At present it is impossible to compare the safety and the value of surgical procedures used to treat glaucoma because there is no standard system of considering either issue. Clearly,not all complications are equally important to patients, and the value of the surgery to patients depends on the specific needs and wants of patients, which varies.
This presentation will suggest a standardized method of considering both these issues, and suggests that the profession needs to convene a meeting specifically to develop an internationally acceptable method.

Effectiveness Endpoints for MIGS Devices

Dale Heuer
Ophthalmology, Medical College of Wisconsin, USA

Most commercially-available or currently-investigational minimally-invasive glaucoma surgery (MIGS) devices are targeted at the treatment of patients with mild to moderate glaucoma in whom profound intraocular pressure (IOP) reduction may not always be clinically necessary and for whom reduction of ocular-hypotensive-medication burden may also be an important consideration. Complicating IOP, visual acuity (VA), and visual field (VF) outcome measures for MIGS interventions is the frequent combination of MIGS device implantation with cataract surgery, which itself frequently reduces IOP and typically improves VA and VF. With those caveats as background (and drawing on the American Academy of Ophthalmology's Preferred Practice Pattern Guildeline. Primary Open-Angle Glaucoma, the European Glaucoma Society's Terminology and Guidelines for Glaucoma, and the World Glaucoma Association's Guidelines on Design and Reporting of Glaucoma Surgical Trials), potential effectiveness endpoints for MIGS Devices will be presented.

Neuroprotection – are we making any progress?

Leonard Levin
,, University of Wisconsin, USA
,, McGill University, Canada

Most optic neuropathies either have no proven treatment (e.g. ischemic optic neuropathy, Leber hereditary optic neuropathy, or traumatic optic neuropathy) or are treated with therapies that slow down but do not completely halt visual loss (e.g. compressive optic neuropathy, inflammatory optic neuropathy, or glaucoma). These unmet needs have led to the development of neuroprotective therapies for optic nerve disease, none of which have yet led to approved therapies.

This lecture will address three recent advances in development of therapeutics for neuroprotection in optic neuropathy: (1) Expansion of biological strategies to include novel pathways and new delivery methods; (2) Improvement in clinical trial designs for neuroprotection, particularly better methods for assessing visual field and structural measures over time; (3) Development of in vivo imaging techniques that can serve as biomarkers for proof of concept studies and for addressing the "Princess and the Pea" problem in translational research.

Neuroregeneration in non-glaucomatous optic neuropathies

Jeffrey Goldberg
Ophthalmology, UCSD, USA

Retinal ganglion cells degenerate in glaucoma and other optic neuropathies, and regenerative failure leads to permanent loss of vision in these diseases. RGC axons injured in the optic nerve fail to regrow back to their targets in the brain, and the cell bodies die a short time afterwards. Here we will discuss recent data revealing new signalling pathways regulating RGC survival and regeneration, and approaches to reversing regenerative failure in the visual pathway.

Abstracts

A Recombinant AAV2/2 Carrying the Wild-Type ND4 Gene for the Treatment of LHON: Preliminary Results of a First-In-Man Study and Upcoming Pivotal Efficacy Trials

Scott Uretsky[2], **Jose Alain Sahel**[1], Anne Galy[2], Nitza Thomasson[2], Geraldine Honnet[3], Marisol Corral Debrinsky[4], Jean-Philippe Combal[2], Serge Fitoussi[2], Catherine Vignal[5]

[1]*Ophthalmology, CHNO Institut de la Vision, France*
[2]*GenSight Biologics, GenSight Biologics, France*
[3]*Genethon, Genethon, France*
[4]*Institut de la Vision, Institut de la Vision, France*
[5]*Neuro-Ophthalmology, CHNO and Fondation Rothschild, France*

Purpose:
We report preliminary results of an ongoing, first-in-man, open-label, dose-escalation, safety trial of gene therapy (rAAV2/2-ND4) in patients with ND4 LHON. Allotopic expression allows ND4 expression with the nuclear machinery.
Methods:
Four cohorts each comprised of 3 patients with the G11778A ND4 mutation and severe vision loss (≤20/200) received ascending doses (9E+09-3E+10-9E+10-1.8E+11vg/eye) of intravitreal (IVT) rAAV2/2 containing the wild-type ND4 gene. Paracentesis and intra-ocular pressure (IOP) lowering treatment preceded IVT. Treatment was followed by 24-hour in-patient observation. Follow-up visits including general and ophthalmic examinations, immune-monitoring and assessment of adverse events (AE, SAE) occurred up to 48-weeks. Bio-dissemination (blood/urine/tears) was evaluated for two weeks post-IVT. A data safety monitoring board (DSMB) evaluated the safety of each cohort prior to dose escalation.
Results:
15 patients were screened, 12 included (mean disease duration 7.2 years). 52 AEs occurred. Thirty-two were post-treatment ocular AEs, the most common being IOP elevation (n=7), anterior chamber (n=7) or vitreous (n=6) inflammation. All were mild except one. One SAE unrelated to the study drug occurred. No treatment-related systemic AE occurred and no AE lead to study discontinuation. The DSMB approved dose escalation subsequent to each cohort.
Conclusion:
Overall safety and tolerability of a single IVT injection of rAAV2/2-ND4 was good. Post-IVT IOP elevation (mechanistic) and mild ocular inflammation (pre-clinical studies) occurred as expected; both were mild and reversible with local treatment. No dose-related toxicity has been noted. The highest tolerated dose of rAAV2/2-ND4 will be used to study clinical efficacy in more recently affected LHON ND4 patients.

Neuroprotection in optic neuritis

Kenneth Shindler
Ophthalmology and Neurology, University of Pennsylvania, USA

Optic neuritis is an inflammatory demyelinating disease of the optic nerve that occurs idiopathically or in association with the central nervous system (CNS) demyelinating disease multiple sclerosis (MS). Up to 60% of patients with optic neuritis develop some permanent visual loss including decreased acuity, color vision, contrast sensitivity and/or visual field loss. Axonal damage and loss of neurons occurs in optic neuritis and MS, including loss of retinal ganglion cells (RGCs), and this neuronal loss leads to permanent neurological dysfunction. While corticosteroids reduce inflammation and hasten recovery, no significant improvement in final visual outcome is achieved with steroid treatment, suggesting that additional interventions are needed to preserve visual function for optic neuritis patients. Identifying novel therapies that prevent neuronal loss following optic neuritis therefore has tremendous potential for preventing permanent visual loss. Neuroprotective therapies that work in optic neuritis also have potential to prevent loss of retinal neurons in other eye diseases, and loss of other CNS neurons in MS as well, if the therapy targets a common mechanism of neuronal cell damage. Experimental optic neuritis induced in animal models of MS exhibits many features of the human disease, including optic nerve inflammation, demyelination, axonal truncation, and loss of RGCs with associated decrease in visual function. Novel therapies sharing an ability to reduce oxidative stress attenuate RGC loss and preserve RGC function, and represent potential new treatments for optic neuritis. The potential role of SIRT1 activating compounds and other new therapies, and their pathway to clinical use, will be discussed.

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Index

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Index

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Windman Productions Ltd,
Tel: +49 8914367059
Borsigstr. 9, 10115 Berlin, Germany
Email: info@windman.co.il
www.windman.co.il