

AOPT | Association for Ocular
Pharmacology and Therapeutics

13th Scientific Meeting

February 16th-19th, 2017

Florence (Italy)

OCULAR THERAPEUTICS: VISION OF HOPE IN A CHANGING WORLD



Association for Ocular
Pharmacology and Therapeutics

www.aopt.org

INDEX

THANKS TO OUR SPONSOR.....	pag. 4
WELCOME MESSAGE.....	pag. 7
AOPT MEMBERSHIP INFORMATION.....	pag. 8
AOPT PAST MEETINGS.....	pag. 9
YOUR AOPT BOARD.....	pag. 10
YOUR LOCAL ORGANIZING COMMITTEE.....	pag. 12
TRAVEL AWARD WINNERS.....	pag. 13
GENERAL INFORMATION.....	pag. 14
INFORMATION FOR PRESENTERS.....	pag. 15
PALAZZO DEGLI AFFARI PLAN.....	pag. 16
PROGRAM AT-A-GLANCE.....	pag. 17
KEYNOTE SPEAKER.....	pag. 18
SCIENTIFIC PROGRAM.....	pag. 19
IT-ARVO PROGRAM.....	pag. 27
PLATFORM ABSTRACT.....	pag. 29
POSTER SESSION.....	pag. 89

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YOUNG INVESTIGATOR TRAVEL AWARDS



Association for Ocular
Pharmacology and Therapeutics



UNTHSC/Elena and Tom Yorio

WELCOME MESSAGE



Welcome to the 13th Scientific Meeting of the Association for Ocular Pharmacology and Therapeutics (AOPT). The topic of this year's conference is Ocular Therapeutics: Vision of hope in a changing world.

We are thankful for our Italian hosts who have put together an exciting meeting at a great venue at the Firenze Fiera Congress Center here in Florence Italy. The meeting agenda is packed with exciting new information set in thirteen sessions as well as a special treat with a visit to the Uffizi Museum.

The Association for Ocular Pharmacology and Therapeutics is a global not-for-profit organization for scientists and individuals from all disciplines related to ocular pharmacology and its therapeutic applications. AOPT- has a diverse, multi-national membership composed of preclinical and clinical scientists, students, and healthcare professionals. Members are from academic institutions, pharma and biotech industries, device companies, clinics and private practice.

AOPT's mission is to serve as a global forum and network for the publication, dissemination and exchange of information and knowledge on treatments of eye diseases, from basic and clinical ocular pharmacology and therapeutics to related disciplines such as pharmacokinetics and dynamics, metabolism, translational research, safety, drug delivery, and pharmaceuticals.

This conference brings together those individuals at the forefront of scientific advancement related to ocular pharmacology and therapeutics. The agenda is rich in provocative presentations that we hope stimulate productive discussions.

What better place to set a new vision for ocular therapeutics than in Florence the "Cradle of the Renaissance".

Tom Yorio, PhD, FARVO

President, AOPT

AOPT MEMBERSHIP INFORMATION

There are four classes of membership in AOPT: Regular Members, Associate Members, Contributing Members, and Emeritus Members.

REGULAR MEMBERS

The Regular Membership represent individuals demonstrating a genuine interest in or making significant contribution to ocular pharmacology and therapeutics. This may be evidenced by a) scientific publications; b) attendance at pharmacological, ophthalmological, optometric, or visual science meetings; c) direct involvement in research. A candidate for membership completes the online membership form and pays the appropriate membership dues. Membership is for two years. A subscription to the Journal of Ocular Pharmacology and Therapeutics is optional.

ASSOCIATE MEMBERS

Associate Membership is for predoctoral and postdoctoral students. A candidate for this membership must have a pre-doctoral, or post-doctoral student status, and must complete the online membership form and pay the appropriate membership dues.

CONTRIBUTING MEMBERS

Contributing Membership is restricted to corporations, associations, and individuals who support the objectives of AOPT but do not satisfy the requirements of Regular Membership or individuals elected to membership in any class who voluntarily choose to become Contributing Members. A candidate for contributing membership completes the online membership form and pays the appropriate membership dues.

EMERITUS MEMBERS

Any Regular Member may make a written request to the Treasurer that his/her membership be transferred to that of an Emeritus Member. The request is subject to approval of the membership committee. Emeritus Members have all the rights and privileges of Regular Members, except those of voting and holding elective office.

AOPT PAST MEETINGS

MEETING	DATE	LOCATION	ORGANIZER
TWELFTH MEETING	FEB 26 - MAR 1, 2015	CHARLESTON, SC	DAN STAMER
ELEVENTH MEETING	FEBRUARY 7-10, 2013	ALICANTE, SPAIN	JUANA GALLAR MARTINEZ
TENTH MEETING	FEBRUARY 17-20, 2011	FT. WORTH, TX	TOM YORIO / ABBOT CLARK
NINTH MEETING	FEBRUARY 18-21, 2009	SALZBURG, AUSTRIA	HERBERT REITSAMER
EIGHTH MEETING	FEBRUARY 9-11, 2007	SAN DIEGO, CA	JOHN LIU / ACHIM KRAUSS
SEVENTH MEETING	FEBRUARY 3-5, 2005	CATANIA, SICILY, ITALY	FILIPPO DRAGO
SIXTH MEETING	FEBRUARY 1-4, 2003	KONA, HI	PETER KADOR
FIFTH MEETING	NOVEMBER 2-5, 2000	BIRMINGHAM, AL	JIMMY BARTLETT
FOURTH MEETING	JANUARY 28-31, 1999	IRVINE, CA	ACHIM KRAUSS
THIRD MEETING	OCTOBER 22-24, 1997	BETHESDA, MD	PETER KADOR
SECOND MEETING	AUGUST 15-17, 1996	LOS ANGELES, CA	DAVID LEE
FIRST MEETING	JANUARY 26-29, 1995	NEW ORLEANS, LA	HERB KAUFMAN
OCULAR PHARMACOLOGY SYMPOSIUM	AUGUST 8-10, 1993	NOVI, MI	HITOSHI SHICHI

YOUR AOPT BOARD



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MARINA ZICHE

TRAVEL AWARD WINNERS

Biagioni Martina Tuscan Doctorate School in Neuroscience,
CNR Neuroscience Institute, Pisa, University of Florence, Italy

Cupri Sarha Department of Drug Sciences, University of Catania, Italy

Daszynski Damian Department of Pharmaceutical Sciences,
University of Nebraska, Omaha, Nebraska, USA

Fidilio Annamaria Department of Biomedical and Biothecnological Sciences,
University of Catania, Italy

Harper Angelica Department of Cell Biology,
University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

Johnson William Department of Ophthalmology, Duke University, Durham,
North Carolina, USA

Joubert Fanny Institut de la Vision, Equipe S12,
UMR_S968 INSERM, UMR_7210 CNRS, UPMC, Paris

Kelley Ryan Skaggs School of Pharmacy and Pharmaceutical Sciences,
University of Colorado Anschutz Medical Center, Aurora, Colorado, USA

Landowski Michael Department of Ophthalmology, Duke University, Durham,
North Carolina, USA

Lazzara Francesca Department of Biomedical and Biotechnological Sciences,
University of Catania, Catania Italy

Liu Yang North Texas Eye Research Institute,
University of North Texas Health Science Center, Fort Worth Texas, USA

Mishra Manish Kresge Eye Institute, Wayne State
University School of Medicine, Detroit, Michigan, USA

Mody Avani North Texas Eye Research Institute,
University of North Texas Health Science Center, Fort Worth Texas, USA

Patel Gaurang North Texas Eye Research Institute,
University of North Texas Health Science Center, Fort Worth Texas, USA

Pattabiraman Padmanabhan Department of Ophthalmology, Case Western Reserve
University, Cleveland, Ohio, USA

Perdices Lorena Institute for Health Research of Aragón (IIS Aragón), Zaragoza, Spain

Platania Chiara B. M. BIOMETEC University of Catania, Italy

Roubeix Christophe Department of Ophthalmology,
Charite University Medicine Berlin, Germany

Schmitt Heather Department of Ophthalmology,
University of Wisconsin-Madison, Charter St. Madison, USA

Smedowski Adrian Department of Physiology,
Medical University of Silesia, Katowice, Poland

Stefanov Antonia Institute of Neuroscience, National Research Council, Pisa, Italy

Toro Mario Department of Ophthalmology, University of Catania, Italy

Webber Hannah North Texas Eye Research Institute,
University of North Texas Health Science Center, Fort Worth Texas, USA

Yu Bo Tulane University, New Orleans, Louisiana LA, USA

GENERAL INFORMATION

On-site Registration Desk

Thursday February 16th, 15.00-17:15

Friday February 17th, 08.30-10:30

Fees:

Regular Members: € 425,00

Non-Members: € 525,00

Students, Post Doc: € 250,00

Name Badges

All participants must wear their name badges during the meeting.

Badges allow admission to all sessions, breaks, lunches, receptions and the banquet.

Accompanying Persons

You can register as many accompanying persons as you want.

Fees:

Welcome reception and banquet: € 120,00

Banquet only: € 80,00

Accompanying persons are not allowed to attend scientific sessions and exhibition area.

Welcome Reception

The welcome reception will be held on thursday february 16th from 18.40 to 20.00 in the exhibit area, first floor.

AOPT business meeting

The AOPT business meeting will be held on friday february 17th from 16.40 to 17.40

All AOPT members are encouraged to attend.

AOPT Banquet

The AOPT banquet open to all regitered participants will be held on saturday 18th from 19.00 in the Basilica da Basso.

Clothing

Clothing in business casual for all occasion.

Liability and Personal Insurance

The AOPT 2017 Organizers can not accept liability for personal accidents or loss of or damage to private property of participants and accompanying persons.

Safety and Security

We kindly request you not to leave bags, suitcases or backpacks unattended at any time during the meeting.

INFORMATION FOR PRESENTERS

Language

The official language of the AOPT 2017 Meeting is english.

Oral presentation

Presenters using a powerpoint presentation should bring it on memory stick (usb) and load in the preview room near the conference hall, between 08,15-08,30 for morning sessions during the lunch for afternoon sessions. Presenters with powerpoint and video are requested to check their presentation to be sure they work properly. Macintosh users must convert their files to powerpoint in order to be used on the pc, otherwise must bring their own computer and VGA adaptor.

Poster presentation

Posters (70 base x 100 height) need to be assembled by 08,00 on friday 17th and remain on display until sunday afternoon. During the posters session, presenters must stand at their posters to present and discuss about their work. Posters left up on sunday evening will be removed and discarded.

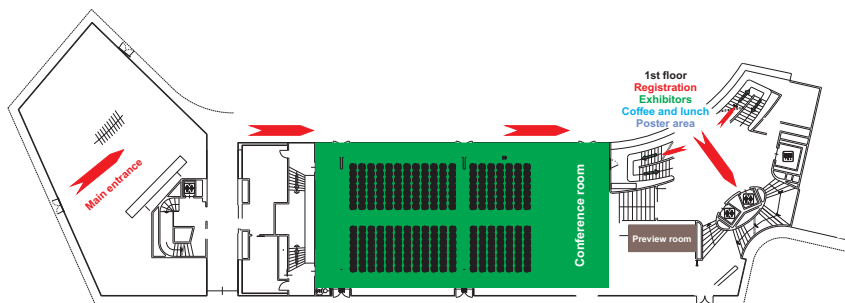
Recording policy

Recording any presentation or poster is prohibited, except by AOPT agent, or by authors.

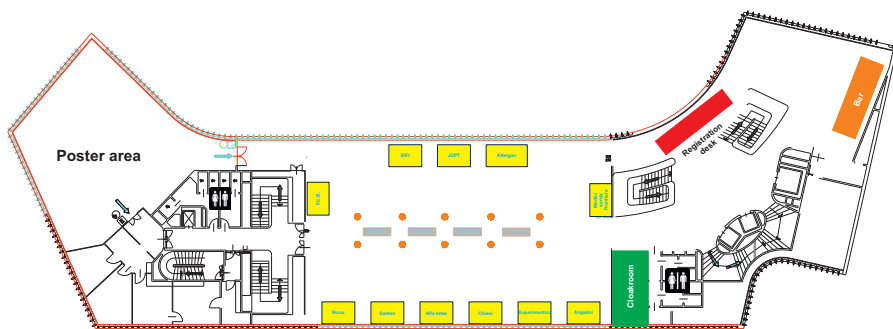


PALAZZO DEGLI AFFARI PLAN

GROUND FLOOR



FIRST FLOOR



PROGRAM AT-A-GLANCE

Thursday, February 16		Friday, February 17		Saturday, February 18		Sunday, February 19	
13:30 - 15:00	JOFF Board Meeting		SESSION 2 NEW INSIGHTS IN THE THERAPEUTIC APPROACHES TO AMD: IS THERE A HOPE FOR AN AFFORDABLE TREATMENT?	09:20 - 10:40	SESSION 6 ADVANCES IN OCULAR DRUG DELIVERY AND ITS ROLE IN PATIENTS COMPLIANCE	08:40-10:20	SESSION 10 GENETIC AND OPHTHALMIC DISEASES
			Break & Exhibits	10:20-10:40	Break & Exhibits	10:20-10:40	Break & Exhibits
			DIABETIC RETINOPATHY: A DEBATE OF INCREASING CONCERN	10:40-12:00	SESSION 7 GLAUCOMA: RESEARCH AND DRUG DISCOVERY IN THE 21 ST CENTURY	10:40-12:00	SESSION 11 OCULAR BLOOD FLOW: AN ISSUE FOR DIAGNOSIS AND THERAPY
		12:10-13:30	IT-ARVO sponsored symposium	12:00-13:30	Lunch-in-Learn	12:00-13:00	Lunch-Panel
15:00 - 16:30	AOFF Board Meeting		SESSION 4 REGULATORY ISSUES GOVERNING OPHTHALMIC DRUGS: PHARMACEUTICALS AND DRUG DEVELOPMENT IN A CHANGING WORLD	13:20 - 14:40	SESSION 8 NEUROPROTECTION IN OPHTHALMOLOGY: DO WE STILL NEED IT?	13:00-14:40	SESSION 12 TREATMENT OF REFRACTIVE ERRORS: EFFECTS, WHAT IS THE ROLE OF OCULAR PHARMACOLOGY?
			Break & Exhibits	14:40-15:00	Break & Exhibits	14:40-15:00	Break & Exhibits
		15:10 - 16:40	SESSION 5 YOUNG INVESTIGATOR	15:00-16:20	SESSION 9 OCULAR IMAGING: THE STATE OF THE ART AND THE FUTURE OF GLOBALIZED MEDICINE	15:00-16:40	SESSION 13 OCULAR SURFACE DISEASES: AN EMERGING CONCERN IN OPHTHALMOLOGY
		16:40 - 17:40	AOFF general business meeting	16:20-17:30	PANEL DISCUSSION THE ENDOCRINEAL INSERTS TO REDUCE THE BURDEN OF ENDOCRINEAL INFECTIONS IN AMD AND DME	16:40-17:00	Closing remarks
		17:15 - 17:20	Opening remarks				
		SESSION 1 BIOMARKERS AND TECHNOLOGY FOR SURVIVING THE DISEASE: EARLY DETECTION OF DISEASE AND TARGETED THERAPIES		17:20 - 18:40	POSTER SESSION BRUSH AND DUBINS	17:40 - 19:00	
				SESSION 3 FUNGAL KERATITIS: A MAJOR CAUSE OF BLINDNESS AND VISUAL IMPAIRMENT WORLDWIDE, ESPECIALLY IN DEVELOPING COUNTRIES		17:30-18:40	
				NETWORK ADDRESS			
				BANQUET DINNER BASTIEN DA MASO		19:00-21:30	

KEYNOTE SPEAKER

ERIC PEARLMAN PhD.

Director of Institute for Immunology
University of California, Irvine

Prof. Pearlman started his studies at University of Glasgow, he earned his PhD in Microbiology at University of Texas (Health Sciences Center – San Antonio). He started his academic research studying “river blindness” – onchocerciasis. Eric Pearlman was part of the research group that found out that a bacterium, living inside the worm *Onchocerca volvulus*, was the real cause of inflammation and blindness, rather than the worm itself.

These results have been published on Science in 2002.

In 2005-2006, there was an outbreak of fungal keratitis in USA, northern Europe and UK; those corneal infections were difficult to treat and were related to contamination by *Fusarium solani* of a lens care product. Furthermore, this fungal keratitis is a major cause of blindness in developing world, because spores (*conidia*) are common in the soil and in the air of rural areas.

Currently, Pearlman’s research is focused on *Fusarium* keratitis and his research group developed an animal model of this disease, in order to identify the biochemical mechanism of this infection and best pharmacological targets, to further develop new therapies.



SCIENTIFIC PROGRAM

THURSDAY, FEBRUARY 16

15:00-17:15	Registration
17:15-17:20	Opening remarks

SESSION 1

BIOMARKERS AND TECHNOLOGY FOR SUBTYPING EYE DISEASE: ENABLERS OF TRANSLATIONAL MEDICINE AND TARGETED THERAPIES

Moderators: Oliver Zeitz, Dan Stamer

17:20-17:40	Outside-ophthalmology perspective: State-of-the-art for biomarkers in oncology Friedhelm Bladt
17:40-18:00	Mining retinal imaging data for biomarkers of disease and therapy Sebastian Waldstein
18:00-18:20	The potential of ocular exosomal biomarkers as therapeutic targets, and diagnostic and prognostic indicators Mikael Klingeborn
18:20-18:40	Tearfilm biomarkers Leopold Schmetterer
18:40-20:00	WELCOME RECEPTION

FRIDAY, FEBRUARY 17

SESSION 2

NEW INSIGHTS IN THE THERAPEUTIC APPROACHES TO AMD: IS THERE A HOPE FOR AN AFFORDABLE TREATMENT?

Moderators: Cathy Bowes Rickman, Chiara Eandi

09:20-09:40	From AMD-associated polymorphisms to drug target identification Florian Sennlaub
09:40-10:00	Complement signaling at the RPE: Implications for AMD Olaf Strauss
10:00-10:20	Placental growth factor: An additional therapeutic target for AMD Sandro De Falco
10:20-10:40	Effects of Anti-C5a therapy on early and wet models of AMD Cathy Bowes Rickman
10:40-10:50	BREAK AND EXHIBITS

SESSION 3

DIABETIC RETINOPATHY, A DISEASE OF INCREASING CONCERN

Moderators: Marina Ziche, Ash Jayagopal

- 10:50-11:10 iPSCs as a novel strategy for vascular repair in the retina
Maria Grant
- 11:10-11:30 Angiogenic/inflammatory activity of humor vitreous in proliferative diabetic retinopathy
Marco Presta
- 11:30-11:50 B2R signaling in neo-angiogenesis
Sandra Donnini
- 11:50-12:10 Imaging vascular dysfunction in diabetic retinopathy
Ash Jayagopal
- 12:10-13:30 LUNCH PANEL
IT-ARVO sponsored symposium

SESSION 4

REGULATORY ISSUES GOVERNING OPHTHALMIC DRUGS: PHARMACOECONOMICS AND DRUG DEVELOPMENT IN A CHANGING WORLD

Moderators: Filippo Drago, Peter Kador

- 13:30-13:50 Challenges to the economic evaluation of interventions for retinal conditions: A review of NICE technology appraisals in retinal vein occlusion and diabetic macular edema
Chrissy Almond
- 13:50-14:10 Combination therapies in retinal diseases: Anticipated hurdles for regulatory approval and health technology assessment. Is there a risk for patient access to new innovative medicine in ophthalmology?
Jean Claude Castanier
- 14:10-14:30 Off-label drug use in ocular pharmacology
Lucia Gozzo
- 14:30-14:50 Clinical prevention of cataracts in diabetic dogs by kinostat
Peter Kador
- 14:50-15:10 BREAK AND EXHIBITS

SESSION 5

YOUNG INVESTIGATOR SESSION

Moderators: Malinda Fitzgerald, Alessia Pascale

- 15:10-15:25 Treatment of HDAC3 selective inhibitor prevents retinal ganglion cell nuclear atrophy and apoptosis after acute and chronic optic nerve injury
Heather Schmitt

15:25-15:40	Neuroprotection and neuroregeneration of Retinal Ganglion Cells using products of peripheral nerves predegeneration Adrian Smedowski
15:40-15:55	Epigenetics as a code for mitochondrial DNA mismatch and its dysfunction in diabetic retinopathy Manish Mishra
15:55-16:10	P2X7 receptor as a pharmacological target in diabetic retinopathy Chiara Platania
16:10-16:25	Spleen derived monocytes in subretinal inflammation Christophe Roubexis
16:25-16:40	The role of canonical Wnt signaling and K-cadherin in the maintenance of intraocular pressure Hannah Webber

AOPT GENERAL BUSINESS MEETING

16:40-17:40

POSTER SESSION

Moderators: Shusheng Wang, Julie Crider

17:40-19:00

SATURDAY, FEBRUARY 18

SESSION 6

ADVANCES IN OCULAR DRUG DELIVERY AND ITS ROLE IN PATIENT'S COMPLIANCE

Moderators: Uday B. Kompella, Claudio Bucolo

08:40-09:00	Biodegradable implants for sustained drug release: Manufacturing considerations, drug stability, and drug release Uday B. Kompella
09:00-09:20	What delivery strategy for poorly soluble drugs? Robert Gurny
09:20-09:40	Sustained release microtechnologies for the treatment of neurodegenerative diseases of the posterior segment Maria Del Rocio Herrero Vanrell
09:40-10:00	Melanin binding and active transport in the RPE: Impact on ocular drug delivery and pharmacokinetics Arto Urtti

10:00-10:20 Recent advances in the application of lipid-based nanocarriers to ocular drug delivery
Rosario Pignatello

10:20-10:40 **BREAK AND EXHIBITS**

SESSION 7

GLAUCOMA: RESEARCH AND DRUG DISCOVERY IN THE XXI CENTURY

Moderators: Carol Toris, Padmanabhan Pattabiraman

10:40-11:00 NCX 667, a lead nitric oxide (NO)-donating compound for a new class of ocular hypotensive agents
Francesco Impagnatiello

11:00-11:20 New glaucoma drainage device designs for lowering of IOP
Carol Toris

11:20-11:40 New highly effective and long-acting anti-glaucoma drug, new periorbital delivery method
David Woodward

11:40-12:00 Glycosylation status of clusterin, a secretory chaperone protein, regulates phagocytic activity and apoptosis in trabecular meshwork cells
Padmanabhan Pattabiraman

12:00-13:20 **LUNCH-N-LEARN**

Keynote speaker **Eric Pearlman**

Lab managing&career negotiation **Carol Toris & Thomas Yorio**

Working in Industry**Achim Krauss**

Starting a company/entrepreneurship **Peter Kador & Robert Gurny**

The balancing act-Research, teaching...life in general **Malinda Fitzgerald**

Peer Review **Dan Stamer**

SESSION 8

NEUROPROTECTION IN OPHTHALMOLOGY: DO WE STILL NEED IT?

Moderators: Neville Osborne, Iok-HouPang

13:20-13:40 Enhancement of mitochondrial function non-invasively as a means to provide neuroprotectionin ophthalmology?
Neville Osborne

13:40-14:00 The challenges in conducting neuroprotection studies
Iok-Hou Pang

14:00-14:20 Modulating autophagy to achieve retinal neuroprotection
Rossella Russo

14:20-14:40 Melatonin prevents photoreceptors death during aging
Gianluca Tosini

14:40-15:00 **BREAK AND EXHIBITS**

SESSION 9

OCULAR IMMUNE DISORDERS IN THE TIME OF GLOBALIZED MEDICINE

Moderators: Pedram Hamrah, Juana Gallar

- 15:00-15:20 Immunological basis for ocular graft versus host disease and novel therapeutic targets
Sabrina N. Copsel
- 15:20-15:40 Targeting inflammation: Pathogenesis and novel treatments for dry eye
Chiara Bonzano
- 15:40- 16:00 Rationale and mechanisms of neuro-regenerative therapy in patients with ocular surface disease
Pedram Hamrah
- 16:00- 16:20 Neuroanatomical, behavioral and electrophysiological data in a mouse model of dry eye
Fanny Joubert

PANEL DISCUSSION

Moderators: Achim Krauss, Teresio Avitabile

- 16:20-17:30 The endovitrear inserts to reduce the burden of endovitrear injections in AMD and DME

KEYNOTE ADDRESS

Moderator: Thomas Yorio

- 17:30-18:40 Fungal keratitis, a major cause of blindness and visual impairment worldwide, especially in developing countries
Eric Pearlman
- 19:00-21:30 **BANQUET DINNER**

SUNDAY, FEBRUARY 19

SESSION 10

GENETIC AND ORPHAN EYE DISEASES

Moderators: Cheryl Rowe-Rendleman, Santi Spampinato

- 08:40-09:00 Focus on retinitis pigmentosa (RP): translatability of success in animal models of orphan and genetic diseases of the eye
Claire Gelfman

- 09:00-09:20 Progesterone analogs as neuroprotectants in animal models of retinitis pigmentosa
Tom Cotter
- 09:20-09:40 Neuroprotection in inherited retinal degenerations: Role of antioxidants and neurotrophins to preserve or rescue cone function
Benedetto Falsini
- 09:40-10:00 The metabolic and redox signaling controlled by the rod-derived cone viability gene NXNLI
Thierry Léveillard
- 10:00-10:20 Development of investigational gene therapy for RPE65-mediated inherited retinal disease
Daniel Chung
- 10:20-10:40 **BREAK AND EXHIBITS**

SESSION 11

OCULAR BLOOD FLOW: AN ISSUE FOR DIAGNOSIS AND THERAPY

Moderators: Jeffrey Kiel, Leopold Schmetterer

- 10:40-11:00 Regional differences in blood flow as the basis for understanding retinal vascular disease
Toke Bek
- 11:00-11:20 Novel treatment for diabetic retinopathy by drug repositioning
Taiji Nagaoka
- 11:20-11:40 Retinal and choroidal vascular responses to electrical brain stem stimulation in rats
Clemens Strohmaier
- 11:40-12:00 Retinal oxygen extraction in diabetes and glaucoma
Doreen Schmidl
- 12:00-13:00 **LUNCH PANEL**

SESSION 12

TREATMENT OF REFRACTIVE ERROR DEFECTS: WHAT IS THE ROLE OF OCULAR PHARMACOLOGY?

Moderators: Christine F. Wildsoet, Caterina Gagliano

- 13:00-13:20 Can drug delivery help solve the problem of myopia?
Heather Sheardown
- 13:20-13:40 Efficacy of atropine for progressive myopia in Europeans: two year results and comparison with results from East Asia
Jan-Roelof Polling

- 13:40-14:00 Orthokeratology combined with long-term instillations of very small atropine concentrations: A pre-evaluation of the myopia stabilizing effect
Elena Tarutta
- 14:00-14:20 Design, synthesis, and characterization of a selective inhibitor for retinaldehyde dehydrogenase (ALDH1A) enzymes
Angelica Harper
- 14:20-14:40 Medication crosslinking of the sclera: An experimental implementation of a technology of sclera strengthening treatment of myopia
Elena Iomdina
- 14:40-15:00 **BREAK AND EXHIBITS**

SESSION 13

OCULAR SURFACE DISEASES: AN EMERGING CONCERN IN OPHTHALMOLOGY

Moderators: **David Goldblum, Christophe Baudouin**

- 15:00-15:20 Corneal gene therapy: Beyond viral vectors
Alexander V. Ljubimov
- 15:20-15:40 Severe ocular allergies: From pathophysiology to future therapies
Andrea Leonardi
- 15:40-16:00 Gabapentin eye drops for the treatment of ophthalmic pain and ocular surface inflammation
Dario Rusciano
- 16:00-16:20 Altered electrical activity of corneal sensory receptor fibers during regeneration after corneal microkeratome lesion in the guinea-pig
Juana Gallar
- 16:20-16:40 Unique hydrogel technology in vitro model representing corneal layers
Agne Žiniauskaitė
- 16:40-17:00 Closing remarks



IT-ARVO

Italy Association for Research
in Vision and Ophthalmology

IT-ARVO CHAPTER MEETING

Florence (Italy) Palazzo degli Affari

Friday 17 February - 12:10/13:30

Horizon AMD: the drugs

Moderators: Claudio Bucolo, Chiara Eandi

12:10-12:30 Wet AMD: update on pharmacological therapy

Chiara Eandi

University of Torino, Eye Clinic, Torino, Italy

12:30-12:50 Atrophic AMD: a panorama of new molecules with realistic future

Monica Jablonski

University of Tennessee Health Science Center, Hamilton Eye Institute, Memphis, TN, USA

12:50-13:10 Pharmacological strategy for atrophic AMD

Konstantin Petrukhin

Columbia University, Eye Institute Research Annex, New York, NY, USA

13:10-13:30 Liver X receptor ligands: new candidates to treat dry AMD?

Goldis Malek

Duke University, Albert Eye Research Institute, Durham, NC, USA



PLATFORM ABSTRACT

OUTSIDE-OPHTHALMOLOGY PERSPECTIVE: STATE-OF-THE-ART FOR BIOMARKERS IN ONCOLOGY

FRIEDHELM BLADT

Director, Oncology Biomarker Strategists, Berlin, Germany

Cancer treatment has made big advances in the past decade with the introduction of so-called targeted therapies. These small molecule inhibitors or antibodies against distinct molecular features of cancer cells should specifically increase antitumor efficacy and reduce unwanted adverse drug reactions, thus increasing the benefit for patients. Successful examples are e.g. imatinib for the treatment of chronic myeloid leukemia or crizotinib for the treatment of ALK-mutated lung cancer. These drugs were usually accompanied by programs to identify patients harboring these alterations, usually so far on the genetic or genomic level. The success of such biomarker enriched drug development programs has changed the perception and understanding of how precision medicine programs should be developed in oncology. To optimize success of new drugs, key factors include the rational selection of preclinical model systems, selection of (clinically suitable) biomarkers for patient selection and also the careful development of pharmacodynamic and safety biomarkers. Emerging technologies like RNA based selection, next generation sequencing and the use of liquid biopsies and more sensitive methods allowing to analyze circulating tumor (stem) cells or free DNA/RNA/miRNA might further change the diagnostic landscape in the coming years. The current approaches and limitations of biomarker programs in oncology will be highlighted here.

MINING RETINAL IMAGING DATA FOR BIOMARKERS OF DISEASE AND THERAPY

SEBASTIAN WALDSTEIN

Department of Ophthalmology
Medical University of Vienna, Austria

The introduction of high-resolution in-vivo imaging has revolutionized diagnosis and management of retinal diseases. However, modern imaging generates a prohibitively large amount of data that remains untapped by human observers. At the same time, research in computational image analysis is advancing rapidly. Machine learning and artificial intelligence methods are starting to open a window of opportunity to capture the wealth of biomarkers provided by modern imaging: Sophisticated segmentation algorithms are capable of detecting several known retinal and choroidal layers as well as pathognomonic lesions. Moreover, discovery of hitherto unknown biomarkers with massive image datasets (“Big Data”) by unsupervised machine learning are beginning to be realized. This contribution will provide an overview of current developments in the area of computational analysis of retinal imaging biomarkers, as well as a perspective of future applications in clinical practice and research. It will include a brief overview of relevant known imaging biomarkers, summarize developments in biomarker discovery and discuss the role of machine learning in the establishment of future clinical trial endpoints.

THE POTENTIAL OF OCULAR EXOSOMAL BIOMARKERS AS THERAPEUTIC TARGETS, AND DIAGNOSTIC AND PROGNOSTIC INDICATORS

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Interest in utilizing 30 -150 nanometer sized exosomes and other extracellular vesicles (EVs) as biomarkers of disease has increased exponentially in recent years. EVs (including exosomes) have several unique features that define ideal biomarkers: (i) a lipid bilayer provides protection for their RNA, DNA, and proteins cargo; (ii) they contain tissue-, cell-, or disease-specific proteins and nucleic acids; and (iii) their hardness enables a wide range of methods for isolation and enrichment from a range of body fluids (e.g. plasma, serum, urine, aqueous humor, tears and vitreous).

To identify biomarkers for retinal disease, we defined the proteome of exosomes from the retinal pigmented epithelium (RPE), which forms the outer blood-retinal barrier in the eye. The RPE is a highly polarized barrier, leading to the directional secretion of proteins, lipoprotein particles and EVs. Such a division dictates directed interactions between RPE and the systemic circulation (basolateral side) and the retina (apical side). As a model, we used primary cultures of differentiated porcine RPE monolayers on permeable supports.

EVs were isolated from conditioned medium bathing either apical or basolateral RPE surfaces, from which exosomes were purified and processed for proteomic profiling. In parallel, EV size distribution and concentration were determined. Using protein correlation profiling mass spectrometry, a total of 556 proteins were identified in exosome preparations, 465 of which were uniquely released apically, and 16 uniquely released from the basolateral side. Basolaterally released exosomes and EVs from RPE cells theoretically enter the systemic circulation and thus basolateral-RPE specific exosomal proteins that we identified, such as Bestrophin-1, represent targets for immunoisolation of RPE-derived exosomes from blood.

These data serve as a foundation for comparative studies aimed at elucidating the molecular pathophysiology of retinal diseases and to help identify potential therapeutic targets and systemic biomarkers for such diseases.

TEARFILM BIOMARKERS

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Dry eye disease (DED) is a multifactorial disease affecting the ocular surface. The prevalence of the disease is high and multiple risk factors including age, female-gender and environmental factors have been described. A problem in patients with DED is that signs and symptoms correlate poorly.

This is a problem for clinical care and treatment monitoring as well as for approval of novel treatments, because regulatory authorities request superiority versus vehicle in both symptoms and one sign. Classical signs include tear film break up time and Schirmer test. Both techniques share problems in terms of reproducibility and subjectiveness. In the present talk novel biomarkers for DED will be discussed. An overview of pros and cons of imaging parameters, molecular parameters and tear osmolarity parameters will be provided.

FROM AMD-ASSOCIATED POLYMORPHISMS TO DRUG TARGET IDENTIFICATION

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Age-related macular degeneration (AMD) is a highly heritable major cause of blindness characterized by subretinal inflammation. Of all genetic factors, variants of Complement factor H (CFH) are associated with greatest linkage to AMD. Using loss of function genetics and orthologous models of AMD, we provide mechanistic evidence that deficiency in CFH completely prevents pathogenic subretinal accumulation of mononuclear phagocytes (MP) and accelerates resolution of inflammation. We show that MP-persistence arises secondary to binding of CFH to CD11b/CD18, which obstructs physiologically-occurring thrombospondin-1 (TSP-1)-CD47-mediated elimination of MPs from the subretinal space. The AMD-associated CFH402H isoform markedly increased this inhibitory effect on microglial cells, indicating a causal link to disease etiology. Pharmacological activation of CD47 accelerated resolution of both subretinal and peritoneal inflammation, which may be exploited in the therapy for chronic inflammatory diseases, including AMD.

COMPLEMENT SIGNALING AT THE RPE: IMPLICATIONS FOR AMD

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Purpose: Age-related macular degeneration involves functional changes or degeneration (AMD) of the retinal pigment epithelium (RPE). Polymorphisms in complement genes are associated with the AMD-risk. These polymorphisms lead to a less efficiently controlled alternative pathway of the complement cascade and to accumulation of active complement compounds in the outer retina. This has led so far to research about the effects of the terminal complement complex on the RPE. Thus the purpose of the study is to investigate the effects of the anaphylatoxins C3a and C5a on RPE cells.

Methods: Increases in intracellular free Ca²⁺ in response to anaphylatoxins were investigated by Ca²⁺-imaging in ARPE-19 cells using fura-2 as Ca²⁺-sensitive fluorescence probe. Down-stream signaling was investigated by western-blot analysis of phosphorylated proteins, qPCR and multiplex analysis of secreted proteins.

Results: ARPE-19 cells but also native human RPE cells express the anaphylatoxin receptors C3aR, C5aR as well as the C3 and C5. C3a and C5a led to increases of intracellular free Ca²⁺. Using double stimulation we detected interactive signaling between C3aR and C5aR where C5a appeared as a dominating factor. The downstream Akt-kinase, PI3-kinase are activated and the transcription factors FOXO1 and FoxP3 are phosphorylated. The stimulation by C3a or C5a or the combination of both changed the secretion of chemokines/cytokines.

Discussion: It appears that the RPE is an active player in the local regulation of complement activity. The RPE reacts to TCC but also to the anaphylatoxins and can thus react with secretion of immune modulatory factors upon complement activity.

PLACENTAL GROWTH FACTOR: AN ADDITIONAL THERAPEUTIC TARGET FOR AMD

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Placental Growth Factor (PlGF), the second member of Vascular Endothelial Growth Factor (VEGF) family discovered, is redundant in physiological process but undoubtedly involved in pathological angiogenesis. It specifically binds VEGF receptor 1 that is expressed in endothelial cells but also in many other cellular types, among which pericytes and the inflammatory cells.

Indeed, PlGF/VEGFR1 axis mediates both neovessels formation and stabilization as well as the inflammation associated to pathological angiogenesis. In preclinical models of pathological angiogenesis, the genetic ablation or the biochemical inhibition of PlGF strongly impair neovessels formation. Recent evidences corroborating the view that the inhibition of PlGF function may be considered for therapeutic treatments in AMD and other ocular neovascular diseases will be presented.

EFFECTS OF ANTI-C5A THERAPY ON EARLY AND WET MODELS OF AMD

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Purpose: Patients with age-related macular degeneration (AMD) are grouped into three major categories: early, late “dry” and “wet” AMD. Complement activation has been strongly implicated in the AMD disease process. However, the mechanism by which chronic complement activation leads to the chorioretinal pathology seen in AMD and how to best target complement dysregulation pharmacologically remains unclear. We tested the impact of pharmacologically targeting C5a, a product of complement activation that is an immune cell chemoattractant and pro-inflammatory mediator in two mouse models of AMD.

Methods: Early “dry” AMD-like pathology (sub-RPE deposit formation, RPE damage and vision loss) was quantified in aged (90 weeks) complement factor H heterozygous (Cfh+/-) mice fed a high fat, cholesterol-enriched (HFC) diet for 8 weeks (Cfh+/-~HFC) ± 30 mg/kg anti-C5a therapy administered 1x/week by intraperitoneal injection over 8 weeks. Choroidal mononuclear phagocyte (MNP) populations were quantitatively assessed by intra- and extravascular flow cytometry. “Wet” AMD-like pathology was quantified using the laser choroidal neovascularization (CNV) model in C57BL/6J mice ± anti-C5a therapy administered one day prior to CNV induction and at day 5 and 11 post laser treatment.

Results: Systemic anti-C5a therapy blocks MNP recruitment into the RPE/choroid, but does not appear to protect Cfh+/-~HFC mice from the early AMD-like pathology (RPE damage and visual function loss), which develops over the 8 weeks of HFC diet. In contrast, anti-C5a treatment reduces CNV lesion size in the “wet” AMD-like pathology seen in the laser CNV model.

Conclusions: These findings establish a role of C5a in choroidal monocyte recruitment and suggests that blockade of C5a may be a viable monotherapy for CNV in AMD.

IPSCS AS A NOVEL STRATEGY FOR VASCULAR REPAIR IN THE RETINA

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Vascular complications due to diabetes mellitus (DM) are the result of sustained vascular injury with insufficient vascular repair. In chronic diabetes, vascular reparative mechanism can be lost resulting in development of microvascular complications (MVC), such as diabetic retinopathy (DR). We assessed the reparative function of progenitor cells that circulate in the peripheral blood of diabetic individuals and found that the vascular wall-derived progenitor cells, endothelial colony forming cells (ECFCs), were depleted in diabetics with MVC. Bone marrow-derived progenitor cells, CD45+CD34+ were dysfunctional in diabetics with MVC. We found that human inducible pluripotent stem cells (hiPSCs)-derived ECFCs displayed the ability to form functional and durable blood vessels in vivo and conferred therapeutic revascularization by connecting with and remaining integrated with host rodent vessels long term. We characterized a mesoderm subset (SSEA5-KNA+ cells) generated from hiPSCs that gives rise to ECFCs. Finally, we used hiPSCs to generate CD34+CD45+ cells and tested the impact of co-administration of these cells with ECFCs within the vitreous. The addition of CD34+CD45+ cells with ECFCs resulted in the enhanced survival, function and reparative ability of the ECFCs. This beneficial effect was mediated by reducing retinal oxidative stress and inflammation. In summary, current interventions to foster normal vascular remodeling and restoration of blood flow to the ischemic and injured retina are limited. Our findings would support that hiPSC represent a novel tool to facilitate retinal vascular restoration and that combinations of vascular progenitors work synergistically to optimize repair.

ANGIOGENIC/INFLAMMATORY ACTIVITY OF HUMOR VITREOUS IN PROLIFERATIVE DIABETIC RETINOPATHY

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Diabetic retinopathy (DR), a major complication of diabetes mellitus, is the leading cause of visual impairment in the working-age population. It begins as non-proliferative retinal abnormalities and progresses to moderate and severe proliferative diabetic retinopathy (PDR) characterized by neovascularization and a persistent grade of inflammation. Even though laser photocoagulation represents the gold standard therapy for PDR, anti-angiogenic vascular endothelial growth factor (VEGF) inhibitors are widely used. However, several limitations to anti-VEGF interventions exist, including local and systemic adverse effects and poor response in a significant percentage of patients. Furthermore, production of other angiogenic factors and pro-inflammatory mediators may nullify and/or cause resistance to anti-VEGF therapies. Indeed, angiogenesis and inflammation are closely related processes that play a pivotal role in ocular diseases associated with retinal neovascularization. Thus, a tight cross talk may exist between angiogenesis and inflammation in PDR, inflammatory responses contributing to neovessel formation and vice versa.

Starting from the observation that diabetic patients treated with salicylates for rheumatoid arthritis showed a lower incidence of DR, the effect of intravitreal administration of anti-inflammatory corticosteroids (e.g. triamcinolone acetonide) has been investigated. However, beneficial effects can be transient and associated with steroid-related adverse events.

This calls for a better understanding of the cross talk between angiogenesis and inflammation in PDR in order to identify novel anti-inflammatory approaches able to suppress retinal neovascularization.

To this aim, the study of the biological effects exerted by PDR vitreous on endothelial cells may represent a useful tool to investigate the relationship between neovascular and inflammatory responses in preclinical *in vitro* and *in vivo* experimental models.

B2R SIGNALING IN NEO-ANGIOGENESIS

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Purpose: Abnormal retinal vascular permeability is the leading cause of vision loss in diseases such as diabetic retinopathy, exudative macular degeneration, retinal vascular occlusions, and others. The main cytokine involved in ocular vascular permeability is vascular endothelial growth factor (VEGF). VEGF antagonists have been successfully used as new treatment for diabetic retinopathy, however, local side effects and systemic complications have been reported.

New therapeutic approaches to selectively block VEGF angiogenic and permeabilizing actions, while sparing VEGF protective and trophic actions are needed. Kinins, such as bradykinin (BK) and kallidin, play a primary role in the development of diabetic retinopathy by enhancing vascular permeability, leukocytes infiltration, and other inflammatory mechanisms. These deleterious effects are mediated by kinin B1 and B2 receptors (B1R and B2R), which are expressed in diabetic human and rodent retina. In this study we assessed the contribution of B2R signaling in angiogenesis.

Methods and Results: We demonstrated that BK, through the activation of its B2R, enhances vascular permeability and promotes angiogenesis in in vitro and in vivo models, which are significantly inhibited by the B2R antagonist, Fasitibant. In endothelial and circulating pro-angiogenic cells, B2R stimulation elicited NF- κ B activation, leading to COX-2 overexpression, PGE-2 production and VEGF output. B2R antagonist prevented the BK/NF- κ B axis and the ensuing amplification of inflammatory/angiogenic responses.

Conclusion: Based on our findings, BK/B2R system appears to be involved in the control of angiogenesis, and Fasitibant has the properties to be further studied as an alternative drug in treatment of diabetic retinopathy and macular degeneration.

IMAGING VASCULAR DYSFUNCTION IN DIABETIC RETINOPATHY

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Vascular inflammation and barrier integrity damage are associated with initiation and progression of diabetic retinopathy. Imaging strategies are continuously being developed to improve clinical management of this disease, by enabling early detection, staging of disease, and assessment of therapeutic response in patients. In this presentation, emerging strategies for imaging diabetic retinal vasculature in the clinic will be presented, including instrumentation, contrast agents, and image processing technologies. Applications of these approaches in imaging hypoxia, blood-retinal barrier dysfunction, and vascular inflammation will be discussed as important examples.

CHALLENGES TO THE ECONOMIC EVALUATION OF INTERVENTIONS FOR RETINAL CONDITIONS: A REVIEW OF NICE TECHNOLOGY APPRAISALS IN RETINAL VEIN OCCLUSION AND DIABETIC MACULAR EDEMA

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Purpose: To identify the main challenges to the economic evaluation of interventions for retinal conditions as part of health technology assessment.

Methods: Review of UK National Institute for Health and Care Excellence technology appraisals for the treatment of macular oedema due to retinal vein occlusion (3) and diabetic macular oedema (4).

Results: The main challenge identified was adequately to capture the quality of life (QoL) improvement provided by treatment. Patients can be treated in their best-seeing eye, worse-seeing eye or both with implications for visual acuity, and hence quality-of-life benefit. Clinical trial data are often collected for the treated eye only, or separately to the non-treated eye, whereas in practice it is the impact on the whole person that is important. Other issues included appropriateness of valuation of QoL and the extrapolation of data beyond clinical trials.

Conclusions: Over time, advances have been made in the economic evaluation of these treatments in response to feedback from previous technology appraisals. However, further advances could be made as long-term efficacy data become available and with changes to the way data are collected in clinical trials.

COMBINATION THERAPIES IN RETINAL DISEASES: ANTICIPATED HURDLES FOR REGULATORY APPROVAL AND HEALTH TECHNOLOGY ASSESSMENT IN FRANCE

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The French HTA process assess the value of all products irrespective of their indication or mode of action. A committee of 21 members decides for 66 million of French inhabitants and focus mainly on clinical effectiveness. There is no regional regulation or funding. The country is highly centralized.

The HTA body (HAS) uses several tools to advise the payer organization and the Ministry of Health on value.

These tools are:

- The global medical value (SMR) which drives the reimbursement rate from 0%, 15%, 30%, 65% to 100%. This decision is mainly driven by the ratio safety/efficacy and the willingness to fund from a solidarity and ethical point of view.
- The additional medical benefit (ASMR) from 1 to 5 impacts heavily the price negotiation.
- The target of the eligible population for setting a price volume agreement, if applicable
- The conditions for prescriptions such as restrictions to specialists or hospital or prior request of multi-team assessment or prior authorization from the sick fund or a special formulary called “médicament d’exception”.

The economic value is assessed by HAS only for very innovative drugs through the QALY/ICER system however the genuine French payers are more interested on the budget impact modelling.

The economic committee (CEPS) negotiates the price, the volume and the funding on top of the DRG (if applicable), depending on the value assessment delivered by the French HTA body, namely HAS.

In ophthalmology care, for future innovative compounds access are likely to be heavily challenged. The reason is that the HTA body focus mainly on the primary end-point. This HTA has set the bar for a substantial improvement at 10 letters (2 lines) improvement, on top of the best optimized SOC. Thus it will be important to be successful in France to focus rather on refractory patients, fast progressors or increase the length the trial, to capture the relevant benefit.

For dry MD and geographic atrophy an important proportion of avoidance of fovea involvement will be a must have. Non inferiority is always challenged by HAS (French HTA body) and this has been translated in no launch in France of several products in Keratitis or chronic glaucoma.

Ultimately to successfully launch a product or a technology in France, there is more need for early pipeline review and more interaction between “trialists” and researchers on the one hand, and HTA and payer experts, on the other.

OFF-LABEL DRUG USE IN OCULAR PHARMACOLOGY

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According to the EMA, off-label use “relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.” Off-label prescribing is not currently regulated at European level but some Countries adopted specific rules. From 2014, Italy permits off-label use of less costly safe and effective drugs even in presence of authorized alternatives with higher cost. Then, bevacizumab was re-listed as therapeutic option for AMD.

We analyzed data from the Registries and the Pharmacovigilance Network between 2014 and 2016, in order to evaluate the use of bevacizumab, ranibizumab and aflibercept and ADRs reports.

We found in Sicilian Registries 122 treatments with bevacizumab for AMD, 5,542 with ranibizumab (2,498 for AMD), 2,365 with aflibercept (1,839 for AMD). In Sicily, 63 ADRs were reported with ranibizumab (43 non-serious, 7 serious with 1 death, 13 undefined), 5 ADRs were reported with aflibercept (3 non-serious regarding treatment failure, 2 serious with 1 death) and no ADRs were reported for bevacizumab. At national level, 153 ADRs were reported with ranibizumab (69 non-serious, 65 serious with 3 deaths, 19 undefined), 26 ADRs were reported with aflibercept (9 non-serious, 17 serious with 2 deaths) and 25 ADRs were reported for bevacizumab (4 non-serious, 19 serious with 1 death, 2 undefined).

A discussion regarding off-label use of intravitreal bevacizumab is still in place for the putative increased risk for patient safety and for economic consideration. An European harmonized approach would be of great value to improve off-label drug use.

CLINICAL PREVENTION OF CATARACTS IN DIABETIC DOGS BY KINOSTAT

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Purpose: Bilateral cataracts develop in a majority of diabetic dogs within the first year of diabetes. A 9-month randomized, masked, multicenter, placebo controlled Proof of Efficacy Clinical Trial was conducted to determine whether the topical aldose reductase inhibitor Kinostat® can significantly reduce the clinical development of blinding cataracts.

Methods: Newly diabetic dogs of all sizes, breeds, and sex with only equatorial vacuoles of less than 3600 present and no other ocular disease were recruited at 11 centers in the United States and 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 administered the topical formulations TID. Dogs not developing cortical cataracts during the 9-month period are then given Kinostat® with ophthalmic evaluations required at 6-month intervals.

Results: Of the 179 dogs recruited, 127 successfully completed the 9 month study and were analyzed for efficacy. The results confirm that the daily administration of Kinostat® to diabetic dogs significantly ($p=0.0169$) prevents cataract formation with the placebo group being 2.18 times more likely to develop cataracts. Long-term administration showed prevention up to 6 years. A required toxicology study found that daily application of Kinostat® 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: Kinostat® is the first drug to significantly reduce the clinical development of diabetic cataracts and represents an alternate treatment paradigm that reduces the need for cataract surgery.

TREATMENT OF HDAC3 SELECTIVE INHIBITOR PREVENTS RETINAL GANGLION CELL NUCLEAR ATROPHY AND APOPTOSIS AFTER ACUTE AND CHRONIC OPTIC NERVE INJURY

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Purpose: In retinal ganglion cells (RGCs) affected by optic nerve crush (ONC), HDAC3 regulates nuclear atrophy as an early response to axonal injury. Conditional knockout of Hdac3 and HDAC3 selective inhibition with RGFP966 prevent nuclear atrophy post ONC. Systemic dosing of RGFP966, which crosses the blood brain barrier, is necessary however for application to chronic models of optic nerve injury.

Methods: Investigation of an intravitreal injection of RGFP966 was done to assess optimal dosing for prevention of nuclear atrophy and apoptosis up to 14 days after ONC. Intraperitoneal (IP) doses (range of 0-10mg/kg) were given and assessed by mass spectrometry and immunofluorescence for histone deacetylation and RGC survival after ONC. DBA/2J mice, which develop glaucoma, were treated IP between 6-10 months with the most effective dose; 2mg/kg every 3 days. Sustained release of RGFP966 was investigated using intravitreal injection of drug mixed with microparticles and subcutaneous injection of drug mixed with hydrogel.

Results: A 2μM intravitreal injection of RGFP966 provided transient protection after ONC, and a 2mg/kg intraperitoneal injection of RGFP966 every 3 days was optimal for protection against cell loss up to 4 weeks after ONC. Importantly, inhibition of HDAC3 activity with repeated systemic dosing of RGFP966 protected against RGC loss in aged DBA/2J mice. Preliminary results indicate that sustained release of RGFP966 from intravitreally injected microparticles or subcutaneously injected hydrogel protected against histone deacetylation induced 4 weeks later.

Conclusion: Extended release of HDAC3 inhibitor RGFP966 may serve as a therapeutic for chronic neurodegenerative diseases such as glaucoma.

NEUROPROTECTION AND NEUROREGENERATION OF RETINAL GANGLION CELLS USING PRODUCTS OF PERIPHERAL NERVES PREDEGENERATION

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Purpose: To investigate neuroprotective effects of intravitreal therapy using peripheral nerve predegeneration products-sciatic nerve homogenate and activated Schwann cells-towards Retinal Ganglion Cells (RGC) in rat glaucoma model.

Methods: Experimental glaucoma was induced in Wistar rats unilaterally using "the Bead Model". The right eye served as a healthy control. Animals received either intravitreal injection of Schwann cells-isolated from injured sciatic nerve-on 2nd day after glaucoma induction, either sciatic nerve homogenate-on day 2nd, 7th or 14th after glaucoma induction. PBS injection was used as a negative control. Animals were bred up to 6 weeks and intraocular pressure was monitored using laboratory tonometer. After 6 weeks, animals were sacrificed, eyes with optic nerves were enucleated and processed for histology and immunohistochemistry. RGC survival was compared by counting RGC bodies and optic nerve axons from control and treated eyes.

Results: In group treated with sciatic nerve homogenate, injection performed on 14th day following glaucoma induction was correlated with the highest RGC survival (28% RGC loss in treated group vs 40% RGC loss in control group; $p < 0.05$). In group that received Schwann cells transplantation, there were significant differences between RGC bodies and optic nerve axons counts when compared with PBS treated eyes (22% RGC loss in treated group vs 45% loss in control group; $p < 0.05$). Immunofluorescent staining for GAP-43 showed neurites outgrowth within optic nerves in eyes treated with Schwann cells.

Conclusions: Products of peripheral nerve predegeneration-sciatic nerve homogenate and Schwann cells, revealed to have potent neuroprotective and pro-regenerative activity towards RGC in glaucoma model.

EPIGENETICS AS A CODE FOR MITOCHONDRIAL DNA MISMATCH AND ITS DYSFUNCTION IN DIABETIC RETINOPATHY

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Purpose: Mitochondrial dysfunction plays a significant role in the development of diabetic retinopathy, and its DNA (mtDNA) is damaged with increased mtDNA-mismatch, fueling into a futile cycle of free radicals. Compared to the other regions, the damage is more at the displacement loop (D-loop) of the mtDNA, a non-coding region important for mtDNA transcription and replication. DNA methyltransferases (Dnmts), enzymes that methylate cytosine-base forming 5-methylcytosine (5mC), are activated and 5mC can be spontaneously deaminated to thymine, causing DNA-mismatch. Our aim is to understand the role of mtDNA methylation in mitochondrial DNA-mismatch and dysfunction in the development of diabetic retinopathy.

Methods: Human retinal endothelial cells incubated in high glucose, with or without Dnmt inhibitor (5-Aza-2'-deoxycytidine, 5-Aza; 1μM) were analyzed for mtDNA methylation and mismatch using methylated-DNA immunoprecipitation and surveyor-nuclease digestion kits respectively. In same cell preparations, mitochondrial function was evaluated by measuring mtDNA encoded Cytochrome b (Cytb) gene transcription and electron transport chain complex-III activity.

Results: High glucose increased mtDNA-mismatch at the D-loop compared to the other mtDNA regions. At the D-loop region, DNA methylation was also increased by ~2.5-fold. Regulation of Dnmt activity by 5-Aza ameliorated glucose-induced increase in mtDNA methylation and prevented mtDNA-mismatch. In same cell preparations, 5-Aza prevented glucose-induced decrease in Cytb expression, and the activity of complex-III.

Conclusions: Dnmt inhibitors, via regulating the levels of mtDNA methylation, ameliorate mtDNA-mismatch, and prevent mitochondrial dysfunction. Thus, identification of pathways leading to aberrations of mtDNA sequence could help identify novel therapeutic targets to inhibit the development of diabetic retinopathy.

P2X7 RECEPTOR AS PHARMACOLOGICAL TARGET IN DIABETIC RETINOPATHY

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Purpose: To build and validate an in-silico/in-vitro approach for discovery of new anti-inflammatory ligands (P2X7 inhibitors) to be used for treatment of diabetic retinopathy.

Methods: Homology modeling, protein contact network analysis, molecular docking, MM-GBSA calculations were carried out in order to built and validate an in-silico approach aimed in finding new ligands, selective toward the P2X7 receptor. Several P2X7 ligands have been studied by the in-silico approach described, the most promising P2X7 inhibitor has been tested on human retinal pericytes, cultured with high glucose levels (25 mM). The effects of the P2X7 inhibitor have been assessed by cell viability, LDH and IL-1 β levels.

Results: We have generated and validated an in-silico/in-vitro platform to discover novel P2X7 receptor inhibitors. The in-silico platform is able to identify selective P2X7 inhibitors, with high true positive rate. The P2X7 inhibitor with best predicted ADME properties has shown anti-inflammatory and protective activity in the described in-vitro model.

Conclusions: Our data suggested that P2X7 receptor can be an interesting pharmacological target for diabetic retinopathy. Furthermore, our in-silico/in-vitro screening platform is suitable for discovery of new and effective P2X7 inhibitors to be used for treatment of diabetic retinopathy.

SPLEEN DERIVED MONOCYTES IN SUBRETINAL INFLAMMATION

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Purpose: Angiotensin II type 1 receptor expressing mononuclear phagocytes (AT1+MPs) originating from the spleen have been shown to play an important role in the recruitment of circulating inflammatory CCR2+Mo in ischemic myocardial inflammation. The involvement of CCR2+Mo in Age Related Macular Degeneration (AMD) progression is well established.

We examined here the role of splenic AT1+MPs in subretinal inflammation and choroidal neovascularization (CNV).

Methods: Subretinal inflammation and choroidal neovascularisation (CNV) was induced by laser-injury (450mW; 250um; 50ms) in eyes of C57Bl6 or CCR2 KO mice daily treated or not by intraperitoneal AT1 antagonist Losartan (125mg/kg/day), and carrying or not subcutaneous osmotic pumps releasing systemic Angiotensin II (rug/kg/min) with or without splenectomy. 7 days after the laser impacts IBA1+ and AT1+ subretinal MPs and CD102+CNV were quantified on immune-stained retinal and RPE/choroidal flatmounts.

Results: Our immunostaining revealed 2 distinct sub-populations of subretinal MPs, IBA1+AT1--and IBA1+AT1+-MPs. Pharmacological antagonism of AT1 by losartan significantly decreased whereas AngII osmotic pumps exacerbated the number of both subretinal MP types and CNV. Interestingly, splenectomies significantly decreased subretinal MP accumulation and CNV and prevented the proinflammatory effect of systemic AngII. The deletion of CCR2 did not affect the recruitment of the AT1+MPs.

Conclusion: Our study shows that IBA1+AT1+-MPs participate in subretinal inflammation, their infiltration of the subretinal space is independent to CCR2/CCL2 pathway, but strongly favored by systemic AngII.

The observation that splenectomy prevented this effect suggests that splenic AT1+MPs participate importantly in the process. Our study might help explain why hypertension confers a risk to develop AMD.

THE ROLE OF CANONICAL WNT SIGNALING AND K-CADHERIN IN THE MAINTENANCE OF INTRAOCULAR PRESSURE

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Purpose: Primary open angle glaucoma is associated with increased intraocular pressure (IOP) and pathological changes in the trabecular meshwork (TM). Inhibition of canonical Wnt signaling in the TM raises IOP, though underlying mechanisms behind this remain unknown. We hypothesize that canonical Wnt signaling in the TM regulates IOP via cadherins junctions.

Methods: NTM cells (gift from Novartis) were treated with or without 100ng/ml recombinant Wnt3a or 1ug/ml sFRP-1 for 4-48 hours. Membrane fractions or whole cell lysates were isolated for western immunoblotting (WB) and probed for cadherins and β -catenin. NTM cells were also immunostained for cadherins or β -catenin. RNA was extracted from NTM cells for cDNA synthesis and qPCR analysis of cadherins. Ad5.CMV recombinant adenoviruses encoding K-cadherin and/or sFRP-1 were injected into eyes of 4-6 month old female BALB/c mice (n=6/group).

Conscious IOP was measured for 35 days. NTM cells were plated for cellular impedance assays using the Acea iCelligence system and transfected with 0.5nM non-targeting or K-cadherin siRNA.

Results: WB showed that Wnt3a increased β -catenin and K-cadherin expression, which was inhibited with addition of sFRP-1.

Immunostaining showed Wnt3a induced β -catenin accumulation on the cell membrane. qPCR showed Wnt3a significantly increased K-cadherin expression (n=3, p<0.01) in the TM. Our mouse study showed Ad5.CMV co-expression of sFRP-1 and K-cadherin significantly decreased sFRP-1 induced ocular hypertension (n=12, p<0.05). Cell impedance assays showed that K-cadherin knockdown reduced NTM cell growth and cellular impedance.

Conclusions: Our results suggested that K-cadherin plays a role in the regulation of TM homeostasis and IOP via the canonical Wnt signaling pathway.

BIODEGRADABLE IMPLANTS FOR SUSTAINED DRUG RELEASE: MANUFACTURING CONSIDERATIONS, DRUG STABILITY AND DRUG RELEASE

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A biodegradable implant based on poly(lactic-co-glycolic) acid (PLGA) is approved by the US FDA for sustained delivery of a corticosteroid in treating back of the eye diseases. Any competing generic product for such an implant typically requires a human clinical study comparing the generic product with the reference, brand product. Such a study, while critical, is expected to be expensive and cumbersome. The long term goal of this study is to understand differences in implant physicochemical and drug release properties based on manufacturing methods. Further, it is our goal to assess batch to batch and within batch variations in the manufactured implants. This presentation will summarize our experience to date with dexamethasone-PLGA implants manufactured using melt-compression and hot-melt extrusion methods. We discovered that dexamethasone cumulative release when monitored over several weeks exhibits a rise and a fall behavior, indicative of drug degradation in the release medium.

Using an LC-MS method, we identified over 10 major degradation products of dexamethasone during in vitro release studies. The extent of degradation was incorporated into the release profiles in order to estimate to actual drug release patterns. The observed degradation in vitro may not be relevant to in vivo release in the vitreous humor, where prolonged retention of either drug or degradation product in the vitreous humor is unlikely.

WHAT DELIVERY STRATEGY FOR POORLY SOLUBLE DRUGS?

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The development of aqueous eye drop formulations is challenging, because of poor water solubility and low corneal bioavailability of numerous drugs (APIs). For example natamycin (Natacyn®, Alcon) is on the market since many years as a suspension-based formulation, which contains 50 mg/mL of the drug in form of micrometer-sized particles. Cyclosporine (Ikervis®, Santen) is commercialized as an emulsion and fusidic acid (Fusithalmic®, Leo) and prednisolone acetate (Pred Mild®, Allergan) are also presented as suspensions.

We will present a novel innovative formulation approach for several poorly soluble APIs in form of a nanocarrier based system (PEGylated fruit acids, methoxy poly(ethylene) hexyl-substituted poly (lactic acid) (mPEGhexPLA)). Using this strategy, we successfully reduced the particle size of the existing product by a factor of up to 500 times with a particle size in the lower nano-range (approx. 10-20nm). The formulations developed are perfectly clear solutions allowing smooth transport of the drug into corneal structures without transient blurring and/or local irritation often reported after application of suspension-based preparations. In vitro activity of mPEGhexPLA nanocarriers was found comparable or superior to free, suspended particulate formulations. Corneal penetration of the novel nanocarrier based formulations was significantly increased compared to suspension-based formulations and allowed to obtain comparable tissue levels. For example, a 100x lower formulation strength of natamycin (0.05%w/w nanocarrier based formulation) showed after 6 hrs in the pig cornea comparable tissue levels as Natacyn® (5% w/w) suspension.

Given the localized nature of the infection a topical treatment is particularly attractive with lower doses. Formulation optimization of numerous suspended eye products should be envisioned in many cases in order to increase the comfort of the patient and decrease the amount of active in the formulation and therefore avoiding side effects from systemic absorption through the nasal mucosa.

SUSTAINED RELEASE MICROTECHNOLOGIES FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES OF THE POSTERIOR SEGMENT

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Purpose: Pathologies affecting the optic nerve and the retina are the major causes of irreversible blindness in elderly population. Most of them are chronic and multifactorial and require maintained concentrations of the active substance in the site of action during long periods of time. In some cases, frequent injections are needed to control the disease. Administration of neuroprotective, antiapoptotic and antioxidant substances, has demonstrated to delay the degeneration. Drug Delivery Systems emerge as therapeutic tools to avoid successive administration. Among them, microparticulate systems has gained a lot of interest as they are employed for long term delivery and multiloading purposes. The main advantage of these formulations is that they do not need surgery procedures for their administration and can be injected as a conventional injection. Furthermore, they disappear from the site of administration once the drug has been released.

Methods: Application of different microtechnologies to load particles with several active substances. Characterization of the microparticles and evaluation of the efficacy in animal models of neurodegenerative diseases of the posterior segment.

Results: Microparticles are effectively able to co-encapsulate biotechnological products and low molecular weight molecules. The particles release the therapeutic agents during long term. Therapeutic efficacy was demonstrated after MPs administration (intravitreal and periocular routes).

Conclusions: Microparticles effectively co-encapsulate biotechnological products and low molecular weight molecules. Particles release the therapeutic agents for several months. The efficacy of the formulations have been demonstrated in animals models of optic nerve and retinal degeneration.

MELANIN BINDING AND ACTIVE TRANSPORT IN THE RPE: IMPACT ON OCULAR DRUG DELIVERY AND PHARMACOKINETICS

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Retinal pigment epithelium (RPE) is a key tissue in blood retina barrier. The RPE cells are highly pigmented and, therefore, capable of binding many drugs that bind to melanin. Drug transport in the RPE might be affected by the transporter protein, but the expression of these proteins has not been quantitated in the RPE cells. We investigated melanin binding and transporter expression in the RPE, and simulated potential interplay of these factors.

Melanin was isolated from the porcine RPE and binding of more than 20 compounds to melanin was investigated.

The results indicate very broad range in melanin binding. We investigated expression of drug transporters in the RPE cells, and quantitated expression of 16 transporters, while 25 transporters were below the quantitation limit.

We carried out also cell binding studies to the isolated RPE cells and modelled the cellular kinetics. The simulations suggest that there is a significant interplay between the melanin binding and permeability of drug in the plasma membranes. This indicates that melanin binding and active drug transport together are affecting drug distribution and accumulation to the RPE cells.

RECENT ADVANCES IN THE APPLICATION OF LIPID-BASED NANOCARRIERS TO OCULAR DRUG DELIVERY

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Controlled release of drugs to the eye tissues is still an important, though challenging topic of research. The eye is an organ highly protected from extraneous compounds by anatomical, functional and biochemical mechanisms. Such defense tools often limit the time of contact of the therapeutic formulation with the eye surface and lead to an insufficient bioavailability of the applied drugs, especially at the level of the posterior segment.

Many nanotechnology strategies have been exploited for the diagnosis and cure of ocular diseases. Nanosized ocular drug delivery systems have given important results in the last years, both as topical applications on the eye surface or after intraocular administration. These colloidal carriers can be suitably engineered to overcome corneal and retinal barriers to drug penetration, protect the encapsulated drug, enhance compliance and safety of ophthalmic drugs, and prolong their activity by a controlled and/or prolonged site-specific release profile.

Although the basic research on ophthalmic delivery systems supplies many technological approaches, very few of them have been able to reach a clinical relevance or to be translated into pre-industrial or industrial applications.

The main reason lies in the complexity and specificity of the formulation parameters that ophthalmic products always require to tackle the high sensitivity of ocular tissues.

The lecture will survey some of the more recent papers and patents regarding nanotechnology applications to ophthalmic controlled and targeted drug and gene delivery, with a specific attention to lipid-based nanocarriers, such as solid lipid nanoparticles (NLC), nanostructured lipid vectors (NLC), liposomal systems, micelles, etc.

NCX 667, A LEAD NITRIC OXIDE (NO)-DONATING COMPOUND FOR A NEW CLASS OF OCULAR HYPOTENSIVE AGENTS

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Primary open-angle glaucoma (POAG) is a common ocular disorder affecting ~2% of the adult population and is the second-leading cause of blindness worldwide. The predominant risk factor for glaucoma progression is an increase in intraocular pressure (IOP), mediated via a reduction in aqueous humor outflow facility through the conventional (trabecular meshwork and Schlemm's canal) outflow pathway.

Current IOP lowering pharmacological strategies target aqueous humor production (i.e. β -blockers, carbonic anhydrase inhibitors) or drainage via the uveoscleral, nonconventional, outflow pathway (i.e. PGF $_{2\alpha}$ agonists). Therapies targeting primarily the conventional pathway consist of older cholinomimetics and a rho kinase inhibitor recently approved in Japan.

Data from a variety of experimental animal models coupled with recent clinical studies strongly support an important role of nitric oxide (NO) in lowering IOP by enhancing the facility of aqueous humor drainage via the conventional outflow route.

NCX 667, a novel NO donor synthesized by Nicox, lowers IOP in rabbit and non-human primate models of ocular hypertension following single and repeated treatment schedules.

As a consequence of NO donation, NCX 667 lowers IOP by 20% or more regardless of the specific model and animal species used. Furthermore, repeated acute dosing with NCX 667 elicits sustained IOP-lowering activity over time with no signs of tachyphylaxis or ocular discomfort.

NCX 667 is a lead compound for further development to lower IOP in POAG patients.

NEW GLAUCOMA DRAINAGE DEVICE DESIGNS FOR LOWERING OF IOP

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Over the past 10 years many drugs have come on the market that lower intra-ocular pressure (IOP) to treat glaucoma. These drugs need to be given topically one to 4 times daily. For an elderly presbyopic, arthritic patient, this can pose a challenge. Interest has turned to glaucoma drainage devices that are designed to improve aqueous humor drainage via numerous pathways. It is hoped that these devices would eliminate or reduce the need for topical drops and the compliance issues associated with their application.

This presentation will describe numerous devices that are approved for human use and some designs that are in development. Devices can be categorized into snorkles that traverse the trabecular meshwork to provide direct communication between the anterior chamber and Schlemm's canal, scaffolds and tubes that dilate Schlemm's canal, tubes inserted into the suprachoroidal space to improve uveoscleral drainage and tubes that provide communication from the anterior chamber directly to the ocular surface or subconjunctival space.

These devices reduce IOP by improving outflow facility or possibly uveoscleral outflow, or creating alternative routes that bypass the areas of greatest resistance to then allow drainage to the ocular surface. The cause of failures of these devices is predominantly clogging, erosion, or dislodging.

In summary, glaucoma drainage devices (MIGS) may be the treatment of the future for glaucoma provided side effects can be avoided. These devices would not only benefit elderly patients but patients with little to no access to a pharmacy or routine doctor visits. While research continues on understanding signaling molecules and drainage pathways and developing treatments that may eventually cure glaucoma, the MIGS are proving to be important options for IOP lowering.

NEW HIGHLY EFFECTIVE AND LONG-ACTING ANTI-GLAUCOMA DRUG, NEW PERIORBITAL DELIVERY METHOD

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Purpose: Two features define the future of glaucoma therapeutics: (1) greatly improved ocular hypotensive efficacy (2) a delivery method that improves patient convenience and compliance. These studies were intended determine whether dermal periorbital delivery of an exceptionally efficacious and potent ocular hypotensive agent 3-[(3'-fluoro-4-fluorobiphenyl-3-carbonyl) amino] phenoxyacetic acid isopropyl ester would fulfil the required criteria for a next generation anti-glaucoma drug.

Methods: Intraocular pressure was measured in ocular hypertensive and normotensive eyes of conscious monkeys, trained to accept pneumatonometry when under gentle restraint. For periorbital application the compound was formulated in polyethylene glycol and applied radially by using a roller ball device connected to a cylindrical reservoir.

Results: A single 0.006% dose of 3-[(3'-fluoro-4-fluorobiphenyl-3-carbonyl) amino] phenoxyacetic acid isopropyl ester, given as an eye drop, produced a profound decrease in intraocular pressure in "glaucomatous" monkeys that persisted for one-two weeks. It was not uncommon for a single 0.006% or 0.01% eyedrop to reduce intraocular pressure to 6-7 mmHg. Application to the periorbital dermis of a 0.1% dose to ocular normotensive monkeys produced a similarly profound reduction in intraocular pressure, which was well maintained.

Conclusions: The compound 3-[(3'-fluoro-4-fluorobiphenyl-3-carbonyl) amino] phenoxyacetic acid isopropyl ester possesses the efficacy and duration of action properties to be considered as representative of the next generation of anti-glaucoma agents. Moreover, application to the periorbital skin using a roller ball device would be a more convenient method of ophthalmic drug delivery than eye drops and is non-invasive in contrast to other "dropless" technologies.

GLYCOSYLATION STATUS OF CLUSTERIN, A SECRETORY CHAPERONE PROTEIN, REGULATES PHAGOCYTIC ACTIVITY AND APOPTOSIS IN TRABECULAR MESHWORK CELLS

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Purpose: Clusterin, an N-glycosylated secretory molecular chaperone, requires glycosylation for its secretion, chaperone activity and its role in autophagy. Clusterin is expressed in trabecular meshwork(TM), found in aqueous humor, and its mRNA levels are decreased in TM of primary open angle glaucoma (POAG). Because very little is known about its functions in TM, we investigated the regulation of clusterin expression, glycosylation, secretion, and its functional role in TM.

Method: Using immunoblotting and immunofluorescence analyses, we assessed-a) expression and secretion of clusterin in-primary human TM (HTM) cells, glaucomatous (GTM) and normal (NTM) TM lines, b) effects of stressors including TGF β 2 and elevated pressure (2X) on clusterin expression, c) role of clusterin glycosylation in HTM by expressing wild type secretory clusterin or mutant clusterin lacking glycosylation on-i) phagocytic activity by challenging HTM cells with pHRedo-labeled E.coli, ii) apoptosis using annexin-V-FITC and Akt signaling. All experiments had N>6.

Results: Immunoblotting revealed the presence of fully glycosylated and nascent unglycosylated clusterin in HTM cells. Immunofluorescence for clusterin showed punctate staining in cytoplasm. Significant ($p<0.05$) findings follow: GTM compared to NTM had higher levels (~2.3 fold) of unglycosylated and decreased glycosylated intracellular and secreted clusterin (~1.6 fold). Stressors decreased clusterin expression and glycosylation. HTM cells transfected with mutant clusterin plasmids compared to controls showed-decreased phagocytic activity (~38% lower), increased annexin-V staining and decreased phosphorylated Akt (~1.8 fold) indicating apoptosis.

Conclusion: Loss of clusterin glycosylation reduces TM phagocytic function and cellularity, demonstrating involvement of clusterin in POAG pathogenesis. Modes to enhance clusterin glycosylation may provide novel treatments for POAG. We acknowledge the support from EverSight and CTSC Core Utilization Pilot Grant Award to PPP.

ENHANCEMENT OF MITOCHONDRIAL FUNCTION NON-INVASIVELY AS A MEANS TO PROVIDE NEUROPROTECTION IN OPHTHALMOLOGY?

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The term neuroprotection in ophthalmology implies the use of pharmacological agents to slow-down insults to tissues like the retina and as a consequence preserve vision. A successful example of neuroprotection in ophthalmology is the use of VEGF antagonists in the treatment of age-related macular degeneration (AMD). However, challenges remain in providing credibility for the view that neuroprotection is a possibility for the successful treatment of diseases like diabetic retinopathy or glaucoma. For such diseases, laboratory studies suggest that if retinal mitochondrial functions can be preserved this is likely to result in neuroprotection.

However, for this idea to be tested agents will have to be delivered to the retina regularly with a prerequisite of having minimum side effects. Significantly, red light at wavelengths between 600 to 1000 nm is absorbed by the mitochondrial photoacceptor molecule cytochrome c oxidase and in the process improves mitochondrial energy metabolism thereby decreasing inflammation and enhancing cell survival. Studies on animal models with defined retinal injury, as well as retinal and optic nerve disease that mimic AMD, retinitis pigmentosa and glaucoma have now demonstrated that red light therapy attenuates cell death, protects retinal function and exerts anti-inflammatory actions.

Such studies strongly suggest that neuroprotection for various retinal diseases are achievable by use of red light as a non-invasive methodology.

Clinical trials are now being undertaken to determine ways of delivery of an appropriate amount of red light to the human retina for the treatment of both chronic and acute retinal diseases. One exciting possibility is to devise spectacles that increase the intensity of red light (in the range of 800-1000 nm) specifically but nevertheless have no effect on the normal wavelengths of the visual spectrum reaching the retina.

THE CHALLENGES IN CONDUCTING NEUROPROTECTION STUDIES

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A critical unmet medical need in many retinal diseases, such as glaucoma, is the development of neuroprotective treatment. Unfortunately, many obstacles and challenges make this effort very difficult and currently unsuccessful. This presentation will discuss some of these challenges and propose potential solutions to reduce risk and lower budgetary hurdle for development of new therapies.

MODULATING AUTOPHAGY TO ACHIEVE RETINAL NEUROPROTECTION

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Purpose: Autophagy, the cellular process responsible for degradation and recycling of cytoplasmic components through the autophagosomal-lysosomal compartment, has been implicated in acute and chronic diseases. At variance with the latter, the role of autophagic modulation in the neurodegenerative process occurring in retinal ganglion cells (RGCs) exposed to glaucoma-related stressor stimuli is still debated.

In an attempt to define autophagy efficiency as a determinant for RGC survival here we analyzed the autophagic response and the upstream regulatory mechanisms in retinas exposed to an ischemic insult.

Methods: Retinal ischemia was induced in adult wild type C57BL/6J or GFP-LC3 transgenic mice by transient elevation of intraocular pressure. Expression of autophagy related proteins (Atg) and upstream regulators (mTOR, AMPK) was studied by western blotting and immunofluorescence. RGCs were labeled by fluorogold and survival was assessed in AMBRA1+/- mice and upon rapamycin treatment or caloric restriction.

Results: The expression of the autophagosomal-associated form of Atg8 (LC3II), was significantly reduced by ischemia, while the protein accumulated in the ganglion cell layer after 6 hours of reperfusion. A biphasic modulation of the autophagic substrate p62, characterized by a significant build up during the late phase of reperfusion that followed an earlier reduction, was also reported.

Increased RGC death was observed in autophagy-deficient Ambra+/- mice subjected to retinal ischemia, while autophagy induction by rapamycin or caloric restriction improved RGC survival.

Conclusion: Our results suggest that ischemic insult induces a dynamic modulation of autophagy in the retina and identify in the catabolic pathway an important endogenous neuroprotective mechanism that can be targeted to achieve neuroprotection.

MELATONIN PREVENTS PHOTORECEPTORS DEATH DURING AGING

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Purpose: Several studies have shown that melatonin synthesis in the retina primarily occurs during the night and its levels are low during the day. Melatonin exerts its influence by binding to G protein-coupled receptors named melatonin receptor type 1 (MT₁) and type 2 (MT₂). MT₁ and MT₂ receptors activate a wide variety of signaling pathways and both receptors are present in the vertebrate photoreceptors where they form MT₁/MT₂ heteromers. Previous studies have shown that melatonin signaling is involved in the modulation of photoreceptor viability during aging and other studies have implicated melatonin in the pathogenesis of age-related macular degeneration.

Methods: Melatonin-proficient mice (C3H-f+/+) and melatonin-proficient mice lacking melatonin receptors (MT₁ or MT₂) were used for the *in vivo* studies. Photoreceptor-like cells (661 W) were used for the *in vitro*. Melatonin signaling was investigated with western blotting, immunocytochemistry and Q-PCR.

Results: Melatonin receptors knock-out mice showed a decrease in the number of cone photoreceptors during aging. Mice lacking melatonin receptors also showed an alteration in the daily activation of the AKT-FOXO₁ cell survival pathway.

In 661W melatonin activated pathways similar to what observed in rods and cones. In addition, melatonin prevented 661W cells death induced by 2 hours of exposure to H₂O₂ by preventing the activation of the Fas pathway.

Conclusions: We believe that melatonin signaling via MT₁/MT₂ heteromers protects photoreceptors during aging. The neuroprotective effects of melatonin on photoreceptors cells (and possibly other retinal cells) are exerted by suppressing the activation of Fas pathway during night-time.

IMMUNOLOGICAL BASIS FOR OCULAR GRAFT VERSUS HOST DISEASE AND NOVEL THERAPEUTIC TARGETS

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Graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (aHSCT) is a multiorgan disorder resulting from inflammatory cytokines and donor T cells which damage skin, liver, gastrointestinal tract, and the eye surface. Ocular GVHD (oGVHD) occurs in 60-90% of chronic GVHD patients and is characterized by inflammation, dry eye, Meibomian gland dysfunction, conjunctiva damage, punctate keratopathy, corneal ulceration and perforation. Our group has developed a novel pre-clinical matched unrelated donor HSCT model that results in systemic and ocular GVHD with onset kinetics similar to what is clinically observed, enabling dissection of oGVHD immune mechanisms. We demonstrated that the presence of donor T cells in ocular tissue orchestrate the recruitment of inflammatory macrophages in this compartment that contribute to the ocular damage and recently, developed a scoring index for the ocular surface and adnexa. Therefore, regulating inflammatory cells recruited to ocular tissue is proposed as a strategy to ameliorate oGVHD. A recent approach to diminish inflammatory cytokines is targeting bromodomain and extra-terminal proteins (BET). We examined the ability of a new BET inhibitor (BETi) EP313 in comparison with other BETi (JQ1 or IBET-151) to regulate inflammatory cytokines using the macrophage RAW-264 cell line after LPS stimulation. EP313 significantly decreased TNF α and IL-6 levels. To study the capacity of BETi to inhibit ocular inflammation, we utilized an in vivo model of corneal inflammation induced by topical LPS. Our data shows that BETi administered first systemically and then locally reduced corneal opacification and decreased inflammatory cytokine expression. Because ocular GVHD is promoted by inflammation and donor T cells, we reason regulating both may effectively ameliorate this disorder. Transfer of expanded regulatory T cell (Tregs) is a promising therapy to suppress donor T cells and subsequently regulate GVHD. We therefore asked if BET inhibitors (BETi) could be combined with Tregs in vivo without interfering with their phenotype/function/expansion. Strikingly, Tregs undergoing marked proliferation with a novel protocol (TNFRSF25 /CD25 stimulation) were not impaired in their expansion in the presence of EP313 and, in fact, exhibited stronger suppressive function vs Tregs expanded without EP313. Finally, we performed an aHSCT to examine the combined effect of in vivo expanded Tregs and EP313. Importantly, the clinical GVHD score of mice receiving the combination strategy of Treg expansion+EP313 was superior to all other groups and recipients of this regimen did not show ocular complications. In total, BETi treatment provides important advantages in regulating inflammation in the ocular compartment due to direct regulation of inflammatory cell function and promotion of Treg cell function. Therefore, we anticipate its combination with Treg cellular therapy will result in blocking alloreactive cells and subsequent recruitment - and function of - infiltrating cells in ocular tissue thereby ameliorating oGVHD.

TARGETING INFLAMMATION: PATHOGENESIS AND NOVEL TREATMENTS FOR DRY EYE

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The tear film, lacrimal gland, corneal and conjunctival epithelia and Meibomian glands work together as a functional unit to provide an efficient system recognized as the ocular surface. The integrity of this unit is necessary for the health and normal function of the eye and visual system.

Recent studies show that immunological mechanisms also play a pivotal role in regulating the ocular surface environment. Our studies demonstrate how anti-inflammatory factors such as the expression of vascular endothelial growth factor receptor-3 (VEGFR-3) in corneal cells, immature corneal resident antigen-presenting cells, and regulatory T cells play an active role in protecting the ocular surface.

Dry eye disease (DED) affects millions of people worldwide and negatively influences the quality of life for patients. In its most severe forms, DED may lead to blindness. The etiology and pathogenesis of DED remains largely unclear.

The aim of this presentation is to summarize the role of the disruption of afferent and efferent immunoregulatory mechanisms that are responsible for the chronicity of the disease, its symptoms, and its clinical signs and to illustrate current anti-inflammatory treatments for DED.

RATIONALE AND MECHANISMS OF NEURO-REGENERATIVE THERAPY IN PATIENTS WITH OCULAR SURFACE DISEASE

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Corneal nerves, which may be involved in the pathogenesis of dry eye disease (DED), play a significant role in ocular surface health and function and are involved in corneal epithelial maintenance, tear secretion, and blinking. In vivo confocal microscopy (IVCM) studies have observed a significantly reduced sub-basal nerve density in patients with DED, correlating to clinical severity and corneal sensation in these patients. Further, significant improvements in dry eye signs and symptoms after DED treatment were evident only in a subgroup with near-normal corneal SNFL, potentially explaining the variability of patients' response to DED therapy. In addition, abnormal morphological changes of corneal nerves by IVCM have been observed in subsets of patients with DED with more severe symptoms, suggesting an underlying attempt of corneal nerves to regenerate, presumably subsequent to the nerve degeneration. Injured nerves are known to develop hypersensitivity (hyperalgesia), or become the source of spontaneous discharge (allodynia), explaining the hyperalgesia of some patients with DED. Regenerative activity is manifested by sprouting from endbulbs and the formation of microneuromas, seen as abrupt swelling of injured nerve endings and neurite sprouting. Recent evidence has demonstrated that the treatment of patients with DED and corneal neuropathic symptoms with autologous serum tears, showed restoration of nerve topography through nerve regeneration, correlating with improvement in symptoms. This supports the notion that corneal nerve damage results in alterations in afferent trigeminal pathways to, at least in part, result in patient symptoms. Thus, given the significant overlap of DED with corneal neuropathic disease, therapeutic strategies resulting in regeneration of damaged nerves may help alleviate patient signs and symptoms.

NEUROANATOMICAL, BEHAVIORAL AND ELECTROPHYSIOLOGICAL DATA IN A MOUSE MODEL OF DRY EYE

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Purpose: Ocular surface diseases (OSDs) are among the most frequent ocular pathologies, with prevalence ranging 20% of the general population. The most frequent OSDs are dry eye disease associated with chronic ocular pain. Here we investigated the peripheral and central neuroinflammation and the ciliary nerve activity in response to dry eye induced ocular pain.

Methods: RTqPCR and immunohistochemistry were used to measure the peripheral and central neuroinflammation and wiping test was used for measuring ocular sensitivity in adult male mice topically treated for 7 days with 0.2% benzalkonium chloride (BAK). For electrophysiological experiments, the mouse corneal epithelium was injured using a trephine (1.5 mm). After 24, 48 and 72 hours, eye was placed in the two-compartment chamber and extracellular spontaneous impulse activity of the ciliary nerve was recorded.

Results: BAK-treated animals developed severe dry eye, characterized by corneal inflammation and higher corneal sensitivity. We showed increased ATF3, FOS and Iba1 immunoreactivity and higher IL-6 and TNF- α mRNA levels in the trigeminal ganglion. Interestingly ocular inflammation induced higher FOS and Iba1 positive-cells in the sensory trigeminal complex in BAK animals. Furthermore, preliminary data showed altered basal activity of the ciliary nerve and modified response after mechanical stimulation in injured cornea.

Conclusions: These works demonstrate that corneal inflammation/injury increases the corneal nociceptors activity and induced central neuroinflammatory process. Thus, altered activity in intracellular signaling might play a priming role in the central sensitization of ocular related brainstem circuits, which represents a significant factor in dry eye pain development.

FUNGAL KERATITIS, A MAJOR CAUSE OF BLINDNESS AND VISUAL IMPAIRMENT WORLDWIDE, ESPECIALLY IN DEVELOPING COUNTRIES

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The World Health Organization estimates that 1.8 million people in developing nations are blinded annually from corneal ulcers; furthermore, in developing nations in Asia and Africa, up to 65% of total corneal ulcers are caused by fungal infection. In the USA and in industrialized nations, contact lenses are the major risk factor, and an ineffective contact lens care solution was the cause of an outbreak of *Fusarium* keratitis in 2005/2006.

The vast majority of corneal infections are caused by filamentous molds of the *Fusarium* and *Aspergillus* species, which can also penetrate the vitreous and cause endophthalmitis.

Current regimens for fungal keratitis are often ineffective, with up to 60% of fungal keratitis cases requiring corneal transplantation.

Given that much of the disease manifestations leading to vision loss occur as a result of the host inflammatory response to fungal hyphae in the corneal stroma, therapies are directed not only at killing the pathogens, but also in curtailing the host immune response. Current and novel approaches to anti-fungal and anti-inflammatory therapy will be discussed.

FOCUS ON RETINITIS PIGMENTOSA (RP): TRANSLATABILITY OF SUCCESS IN ANIMAL MODELS OF ORPHAN AND GENETIC DISEASES OF THE EYE

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A well-defined preclinical path forward into the clinic is every drug developer's dream. The reality though is that even when a path has been carved, preclinical success does not always translate into success in the clinic.

The issue is even more complex when the indication under consideration is a rare disease, when the disease pathology is less well-understood, the number of patients world-wide is not so prevalent, and funding is not as accessible for pre-clinical and clinical POC studies. Retinitis pigmentosa (RP) represents a rare ocular disorder with genetic origins. It is a heterogeneous group of diseases with a variety of mutations affecting photoreceptor function and can result in blindness. Common symptoms include difficulty with night vision as well as a loss of peripheral vision. While many animal models of RP are available resulting in a better understanding of the disease pathology, there is still no cure.

This presentation will focus on animal models of RP and the types of therapeutic strategies that have been evaluated in terms of both safety and early efficacy.

The information gleaned from such studies can be used to guide clinical decisions around dosing and patient population recruitment.

A case study will be presented outlining recent data obtained using human retinal progenitor cells (hRPC) in rodent models of RP, and how that information was used to support a clinical study currently in progress.

PROGESTERONE ANALOGS AS NEUROPROTECTANTS IN ANIMAL MODELS OF RETINITIS PIGMENTOSA

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Purpose: Retinitis Pigmentosa (RP) is a condition where loss of both rod and subsequently cone photoreceptor cells leads to blindness. This research looks at the therapeutic potential of a progesterone analog (Norgestrel) as a very promising neuroprotectant molecule. Norgestrel is found in some forms of the contraceptive pill.

Methods: The rd10 and light induced mouse models of RP were both used in this study with similar results. Methods used include, ERGs, optomotor tests, immunohistochemistry and several other standard laboratory methods.

Results: The progesterone analog Norgestrel preserves retinal morphology out to day 40 well beyond the peak of cell death at day 15 in the untreated rd10 animals. Visual acuity at day 40, in the treated animals, was remarkably the same as control C57 animals, ERGs were also markedly improved.

The neuroprotective properties of Norgestrel appear to operate through its effects on both photoreceptor and microglia cells. In the former it up-regulates key cell survival pathways and also induces the production of bFGF which acts as an autocrine survival factor for photoreceptors. In addition it also stimulates photoreceptors to produce and release fractalkine which prevents microglial cells from entering the photoreceptor layer. In untreated animals microglia are responsible for the destruction of photoreceptors and Norgestrel prevents this.

Lastly, Norgestrel also acts directly on microglia to dampen the inflammatory phenotype of these cells.

Conclusions: The progesterone analog Norgestrel is a strong neuroprotectant of photoreceptors in the rd10 and other animal models of RP.

NEUROPROTECTION IN INHERITED RETINAL DEGENERATIONS: ROLE OF ANTIOXIDANTS AND NEUROTROPHINS TO PRESERVE OR RESCUE CONE FUNCTION

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Purpose: An important goal of neuroprotection in inherited retinal degenerations (IRD) is to preserve or rescue cone-mediated function, responsible of common daylight visual functions. Oxidative damage and loss of neurotrophic factors are major mechanisms that have been implicated in IRD-associated cone system dysfunction/degeneration. We report the results of pilot clinical trials on antioxidants and neurotrophic factors (performed at Fondazione Policlinico Gemelli, Università Cattolica, Rome) aimed at preserving or rescuing cone function in IRDs.

Methods: Single-center, IRB approved, Phase IIa clinical trials were performed to evaluate potential efficacy of 1. oral saffron antioxidant (20 mg/day, double-blind, placebo-controlled) on central cone function (acuity, focal macular electroretinogram, fERG) in ABCA4-related Stargardt's macular dystrophy (STARSAFo2, [clinicaltrials.gov NCT01278277](https://clinicaltrials.gov/ct2/show/study?term=NCT01278277)) 2. nerve growth factor (NGF) topical eye-drops (total dose of 1 mg in 5 ml of saline solution, open label, single-arm study) on central and peripheral cone function (acuity, fERG, Goldman visual field) in advanced RP patients (RPo1, EudraCT n. 2008-004561-26).

Results: 1. STARSAFo2: fERG stabilization was found after 6 months of saffron but not placebo administration; no change in visual acuity was observed, 2. RPo1: fERG amplitude improvements (above the 95% limits of test-retest variability) were found 30 days after NGF treatment in 3/9 patients. These changes were associated with Goldman isopter V/4e size improvements (10-40 degrees on the major axis), no change in acuity but improved subjective vision.

Conclusions: Antioxidants and NGF show promise in the clinic as potential therapeutic strategies to preserve or rescue cone-mediated function in selected subtypes or stages of IRDs.

THE METABOLIC AND REDOX SIGNALING CONTROLLED BY THE ROD - DERIVED CONE VIABILITY GENE NXNL1

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Retinitis pigmentosa is an inherited retinal degeneration that processes from the death of rods followed by dysfunction and degeneration of cones. The nucleoredoxin-like 1 gene (NXNL1) encodes by alternative splicing for the trophic factor RdCVF that stimulates aerobic glycolysis in cones by interaction with its cell surface receptor basigin-1 that is linked to the glucose transporter GLUT1. RdCVF accelerates glucose uptake by cones to sustain cone outer segment renewal. RdCVF prevents secondary cone degeneration in recessive and dominant animal models of retinitis pigmentosa. The second product of the NXNL1 gene, the thioredoxin RdCVFL protects the cones against hyperoxia. The administration of RdCVF or RdCVFL prevents visual loss in the rd10 mouse, a mouse model of recessive retinitis pigmentosa, using a non cell- and a cell-autonomous mechanism respectively. In order to translate this promising therapy towards the clinic, we have evaluated the therapeutic benefit of delivering both products of the NXNL1 gene by subretinal injection with an AAV vector targeting retinal pigmented epithelial cells and cones.

We measured the visual acuity of the rd10 mice, using optometry after subretinal injection of an AAV serotype 2 encoding for RdCVF and RdCVFL as compared to AAV2-RdCVF, AAV2-GFP and sham controls. The kinetics of the loss of visual acuity was statistically significantly retarded after injection of AAV-RdCVF-RdCVFL and very significantly considering the medical objective.

Our results demonstrate that this metabolic and redox treatment will likely be successful in preserving central vision in patients suffering of retinitis pigmentosa independently of causative mutations.

DEVELOPMENT OF INVESTIGATIONAL GENE THERAPY FOR RPE65-MEDIATED INHERITED RETINAL DISEASE

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Purpose: Several early-phase human trials provided preliminary evidence of the potential safety and efficacy of adeno-associated virus-mediated human RPE65 augmentation for RPE65-mutation-associated inherited retinal dystrophies. We report the latest results from a Phase 3, open-label, randomized, controlled trial that concluded in 2015 at Children's Hospital of Philadelphia and the University of Iowa evaluating the safety and efficacy of AAV2-hRPE65v2 (SPK-RPE65) to treat RPE65-mediated inherited retinal dystrophies (NCT00999609).

Methods: Thirty-one subjects with disease-causing biallelic RPE65 mutations were randomized 2:1 to intervention or control. Eligibility criteria included age ≥ 3 years-old; bilateral visual acuity worse than 20/60 and/or visual field less than 20 degrees in any meridian; evidence of sufficient viable retinal cells by fundus photography and optical coherence tomography; ability to be evaluated on mobility testing; and willingness to provide consent or parental permission and assent, where appropriate. Subjects in the intervention group received subretinal injections of AAV2-hRPE65v2 sequentially to each eye within an 18-day window. Control subjects did not receive AAV2-hRPE65v2 for at least 1 year from baseline, but completed the same testing regimen as those in the intervention arm. Using a standardized subretinal delivery procedure and under general anesthesia, 1.5E11 vector genomes/eye were delivered in a total volume of 300 μ l. Standardized mobility testing under different luminance conditions was the primary efficacy endpoint, with secondary endpoints including full field light sensitivity testing, assigned first eye mobility change score and visual acuity.

Results: All subjects completed Year 1 follow-up testing. Phase 3 study results include demographics, safety information, and mobility testing change score (performance at 1 year compared with baseline), and secondary endpoints of full field light sensitivity testing, assigned first eye mobility change score and visual acuity. A separate study analyzing mobility test data in untreated normal and retinal dystrophy cohorts was used to validate the mobility test's ability to distinguish low vision from normal-sighted populations, differentiate a range of performance in low vision subjects, and confirm changes in functional vision over time. The trial of 31 subjects met with statistical significance its primary endpoint, the bilateral mobility test change score ($p = 0.001$), as well as the first two of three secondary endpoints, specifically full-field light sensitivity threshold testing, or FST ($p < 0.001$), and the assigned first eye mobility test change score ($p = 0.001$). Statistical significance was not achieved for the third secondary endpoint, visual acuity ($p = 0.17$). No serious adverse events (SAEs) and no deleterious immune responses related to SPK-RPE65 were reported.

Conclusions: Results of this study, the first Phase 3 gene therapy study completed for a retinal dystrophy, provides additional evidence regarding the potential efficacy and safety of gene therapy intervention by surgical subretinal administration of AAV2-hRPE65v2 (SPK-RPE65) as measured by the primary endpoint of mobility testing, and 2 of the 3 secondary endpoints.

REGIONAL DIFFERENCES IN BLOOD FLOW AS THE BASIS FOR UNDERSTANDING RETINAL VASCULAR DISEASE

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The neurosensory structure of the retina shows distinct regional variations with derived effects on vascular structure. The foveal area which consists of the photoreceptor layer only, is nourished entirely from the choriocapillaris. The extrafoveal retina extending to the vascular arcades and thereby delimiting the macular area has a rich content of metabolically active cells and therefore needs three capillary layers. These layers are supplemented with a fourth capillary layer supplying the retinal nerve fiber layer in the arcuate areas where this layer is thick, peripheral from which the vascular density decreases towards the retinal periphery.

The branching pattern of retinal vessels is also regionally varying with a dichotomous branching pattern in the macular area and small vessels leaving at right angle to larger irradiating vessels in the retinal midperiphery.

It is likely that the regional distribution of retinal vascular lesions reflects regional variations in vascular structure. Therefore, the distribution of retinal vascular lesions is a gate for understanding the pathophysiology of retinal vascular disease. Examples of the information value in regional variations in vascular lesions will be presented and suggestions for future studies of vascular function aimed at elucidating the pathophysiology of retinal vascular disease will be proposed.

NOVEL TREATMENT FOR DIABETIC RETINOPATHY BY DRUG REPOSITIONING

TAIJI NAGAOKA

Novel Treatment for Diabetic Retinopathy by Drug Repositioning

Although diabetic retinopathy is a leading cause of blindness in Western countries, the causes of its vascular and visual pathologies are not fully understood. We have reported that the RBF may decrease in type 2 diabetics before development of retinopathy or mild retinopathy (IOVS, 2010), suggesting that the improvement of the impaired retinal blood flow may be a target for a novel treatment of diabetic retinopathy. We have examined whether any drugs that have been generally used for systemic disorders (i.e., diabetes, hyperlipidemia, hypertension) may be repositioned to treat diabetic retinopathy.

For this purpose, porcine retinal arterioles (50 μm to 100 μm in diameter) were isolated and pressurized without flow for in vitro study.

We found that some of these drugs can dilate retinal arterioles, which may contribute to improve retinal blood flow in patients with diabetes. My talk will focus on the possibility that “drug repositioning” may be a novel strategy for the treatment of diabetic retinopathy.

RETINAL AND CHOROIDAL VASCULAR RESPONSES TO ELECTRICAL BRAIN STEM STIMULATION IN RATS

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Purpose: Electrical brain stem stimulation at the coordinates of the nucleus salivatorius superior (SSN) is known to increase choroidal blood flow, but not retinal blood flow. The present study investigates the retinal and choroidal vascular responses to SSN stimulation. Furthermore, data on possible neurotransmitters is presented.

Methods: Sprague Dawley rats (n= 17) were anesthetized using pentobarbital sodium and paralyzed with gallamine triethiodide. Choroidal blood flow was measured using Laser Doppler flowmetry. Retinal vessel diameters were measured with a fundus camera customized for rats. Stimulations at the SSN coordinates were performed at 20Hz, 9 μ A, 1 ms pulse duration and 200 pulses. After baseline measurements with subsequent SSN stimulations, L-NAME (10 mg/kg) was applied intravenously and the stimulation protocol was repeated.

Results: Stimulation at the SSN coordinates increased choroidal blood flow from 248.17 ± 46.92 arbitrary units (a.u.) to 347.30 ± 60.44 a.u. ($p \leq 0.05$). Stimulation at the SSN coordinates increased the retinal arterial diameter by 6.41 ± 1.65 % and the venous diameter by 3.48 ± 1.93 % (both $p < 0.05$). L-NAME application reduced the arterial response significantly to 2.93 ± 0.91 %.

Conclusion: Electrical stimulation at the SSN coordinates yielded a significant increase in choroidal blood flow and induced retinal vasodilation, the application of L-NAME did not block the stimulation effect and thus indicates that NO is not the sole neurotransmitter.

RETINAL OXYGEN EXTRACTION IN DIABETES AND GLAUCOMA

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Purpose: We have recently presented a method to measure oxygen extraction of the human retina. This technique combines measurement of total retinal blood flow using Doppler Optical Coherence Tomography (OCT) with measurement of oxygen saturation using spectroscopic reflectometry. In the present studies we investigated whether retinal oxygen extraction is altered in early diabetes and glaucoma.

Methods: A total of 24 subjects with type 1 diabetes without diabetic retinopathy and 40 patients with primary open angle glaucoma (POAG) were included in these studies. In addition, we included a total of 64 healthy subjects who were age- and sex-matched to the patient groups. Retinal blood flow was measured by bi-directional Doppler OCT. Oxygen saturation was measured using reflectometry and oxygen extraction was calculated.

Results: In patients with diabetes we observed increased retinal blood flow and decreased retinal oxygen extraction as compared to healthy subjects ($p < 0.05$ each). Retinal nerve fiber layer thickness and multifocal electroretinography parameters were not different between the two groups. In patients with POAG we observed decreased retinal blood flow and decreased oxygen extraction ($p < 0.05$ each). The decrease in oxygen extraction was correlated with visual field defect ($p < 0.01$).

Conclusions: In type 1 diabetes we observed increased retinal blood flow and decreased retinal oxygen extraction at an early stage of the disease at which no changes in retinal function or retinal nerve fiber layer thickness could be detected. In POAG a reduction in retinal blood flow and retinal oxygen extraction was observed that correlated with the amount of visual field defect. Whether this is a cause or a consequence of the disease is unknown.

CAN DRUG DELIVERY HELP SOLVE THE PROBLEM OF MYOPIA?

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Natural barriers, including rapid tear turnover, a highly impermeable epithelial layer and isolation of delicate tissues, significantly limit the amount of drug that can be delivered to the eye.

There is a need for alternative delivery methods to enhance therapies which have the potential to treat a host of ocular conditions including myopia. An understanding of the mechanisms used to control the release of the pharmacological active as well as the novel methods to enhance residence time will be discussed with a focus on the novel delivery systems developed for anterior segment drug delivery and degradable systems which have the potential to be used in the posterior eye.

EFFICACY OF ATROPINE FOR PROGRESSIVE MYOPIA IN EUROPEANS: TWO YEAR RESULTS AND COMPARISON WITH RESULTS FROM EAST ASIA

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Purpose: Randomized controlled trials have shown the efficacy of atropine for progressive myopia, and this treatment has become the preferred practice pattern for this condition in many Asian countries. This study explores the two year effectiveness of atropine 0.5% treatment for progressive high myopia and adherence to therapy in a non-Asian country compared with studies from Asian countries.

Methods: We performed an effectiveness study of atropine eye drops for progressive myopia in Rotterdam, the Netherlands. We included 205 children (mean age 9.8 yrs. $\pm$ 3.3) of European (n=138; 67.3%), Asian (n=51; 24.9%) and African (n=16; 7.8%) descent, performed a standardized eye examination including cycloplegic refraction and axial length at baseline, prescribed atropine eye drops 0.5% daily, and examined the children every 6 months at follow up. For the comparison with our data randomized controlled trials in Asian cohorts comparing atropine high dose (0.5-1.0%) with placebo were searched in PubMed. Primary outcome was progression of myopia in a 1 and 2 year period under atropine high dose regime.

Results: Mean spherical equivalent (SE) at baseline was -6.15D ($\pm$ 3.59); mean annual progression before treatment -1.0D/yr; and the proportion of high myopes ($\leq$ -6.0D) was 40.5%. Median follow up was 23.6 months. The mean progression of SE diminished substantially during the first year -0.24D $\pm$ 1.1 and the second year -0.51D $\pm$ 0.64. We included 4 Asian studies in our analysis who had a mean difference of -0.55D (CI 0.46-0.64) in the 2 year treatment period.

Conclusion: Our study confirms that in every day patients in the western world myopia progression can be halted by atropine 0.5%. Racial differences in response to treatment could not be detected in our study neither by literature comparison.

ORTHOKERATOLOGY COMBINED WITH LONG-TERM INSTILLATIONS OF VERY SMALL ATROPINE CONCENTRATIONS: A PRE-EVALUATION OF THE STABILIZING EFFECT

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Orthokeratology lenses (OKL) and long-term atropine instillations are currently considered the most effective methods of inhibiting progressive myopia.

Purpose: First evaluation of effectiveness and safety of myopia inhibition by combining OKL with instillations of atropine microdoses.

Material and methods: 13 children aged 7 to 11.5 with acquired low (8 eyes), moderate (8) and high myopia (10), found to have progressive myopia after a 1-2-year OKL usage (6-zone DL-ESA), daily received two drops of 0.01% atropine 3 hours before wearing OKL. Beside standard examinations, we measured axial length (AL, IOL-Master, Zeiss) relative accommodation reserves (RAR), objective accommodative response (OAR, Grand Seiko WR5100K) before adding atropine and 6 months after it. Progression rate was assessed by AL increase (mm/year), also recalculated in diopters/year.

Results: Before atropine instillations, average progression rate was 0.68 D/year (0.22 mm/year); respectively, 0.74, 0.8 and 0.49 D/year (0.24, 0.26 and 0.16 mm/year) for low, moderate and high myopia. 6 months after, the figures were respectively 0.54, 0.69, 0.33 and 0.63 D/year (0.18, 0.23, 0.11, 0.21 mm/year). As observations were few, all differences are statistically insignificant. Moderate myopia showed the best inhibiting trend. Contrariwise, high myopia tended to progress faster with atropine. RAR were high: 4.0 D before atropine and -4.0 D 6 months later, which is related to pseudoaccommodation due to aberration increase in OKL users. OAR decreased slightly (from -2.7 to -2.5 D).

Conclusion: Although pre-evaluation cannot absolutely confirm the effectiveness of long-term atropine support of OKL, the observed results are positive and validate further research.

DESIGN, SYNTHESIS, AND CHARACTERIZATION OF A SELECTIVE INHIBITOR FOR RETINALDEHYDE DEHYDROGENASE (ALDH1A) ENZYMES

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Purpose: Retinaldehyde dehydrogenase 2 (RALDH2) has been identified as a potential therapeutic target for the control of postnatal ocular growth. The objective in this study was to use an intelligent-drug design approach to develop a RALDH2-selective inhibitor to further examine the role of RALDH2 in myopia.

Methods: MoleGro software was used to dock the structure of dichloro-all-trans-retinone (DAR) into models of chick RALDH2 and human ALDH2. DAR was synthesized by a modified dihalomethylithium approach. Selectivity and mechanism of inhibition was determined in vitro using NADH assays with recombinant RALDH2. The effect of DAR on retinoic acid (RA) synthesis was determined in 1) cells overexpressing RALDH2, 2) choroidal cell lysates, and 3) choroid tissue by an in vitro RA synthesis assay. Toxicity on scleral tissue was measured with a proteoglycan synthesis assay.

Results: Docking suggested selectivity of DAR to RALDH2 compared to hu-ALDH2 (MolDock score: -71.92 ± 6.83 vs. 14.41 ± 17.98). In vitro assays indicated that DAR inhibits RALDH2 in an irreversible and dose dependent manner ($IC_{50}=52.2$ nM, 20 min pre-incubation), with no significant inhibitory effect on hu-ALDH2. DAR successfully inhibited RA synthesis in 1) cells overexpressing RALDH2 ($p<0.001$), 2) choroidal cell lysates ($p<0.001$), and 3) choroid tissue ($p<0.05$). Further, DAR inhibited RA synthesis in choroidal cell lysates in a dose dependent manner with an $IC_{50}=53.6$ nM. On scleral tissue, DAR was less inhibitory on proteoglycan synthesis as compared with a non-specific inhibitor (WIN18446) ($p<0.05$).

Conclusion: The development of dichloro-all-trans-retinone will allow us to further investigate the role of RALDH2 in postnatal eye growth.

MEDICATION CROSSLINKING OF THE SCLERA: AN EXPERIMENTAL IMPLEMENTATION OF A TECHNOLOGY OF SCLERA STRENGTHENING TREATMENT OF MYOPIA

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Purpose: Experimental implementation of scleral collagen crosslinking by sub-Tenon's capsule injections of a biologically active composition, Scleratex, in the equatorial and posterior pole areas of the eye.

Material and Methods: A placebo-controlled study into the safety and effectiveness of sub-Tenon's capsule injections of Scleratex (a solution of the basic amino acid salts in the form of succinates) was performed on 47 Chinchilla rabbits (94 eyes). 0.1 ml of Scleratex or placebo solution was injected once a week under the Tenon's capsule of the experimental and the fellow eyes, respectively. The first series (4 injections) lasted 1 month, and the second series (12 injections) took 3 months. After the course of injections, all structures of 22 enucleated eyes, including retina, were studied morphologically using light microscopy, while scleral samples from the remaining 72 eyes were used to determine the elasticity modulus (on the testing machine Autograph AGS-H, SHIMADZU, Japan) and the level of collagen crosslinking (by denaturation temperature Td using differential scanning calorimetry on the calorimeter, Phoenix DSC 204, Netzsch, Germany).

Results: The weekly injections of Scleratex performed for 1 month or 3 months showed no clinical or morphological signs of local irritation, damage, or toxicity. A 15 to 20% increase in collagen crosslinking and a 1.8-fold increase in the elasticity modulus of the sclera with respect to the fellow eye were detected. This increase was accompanied by an increase in the number of cells, formation of new connective tissue on the scleral surface, and appearance of additional vessels. In total, this is an evidence of an effective trophic and sclera strengthening influence of Scleratex.

Conclusion: The outcome of experimental implementation of a minimally invasive technology for scleral collagen crosslinking shows it to be a plausible method of scleral strengthening and antidystrophic treatment of progressive myopia.

CORNEAL GENE THERAPY: BEYOND VIRAL VECTORS

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Purpose: Cornea is ideal for gene therapy with easy accessibility, immune privilege, easy transgene expression monitoring, and topical drug application. Viral vehicles (adeno-associated virus, adenovirus, herpes simplex virus type 1, and lentivirus) allowing for lasting effects, high efficiency and time-controlled action have been used to successfully transfect corneal cells.

However, as viruses may induce immune reactions, uncontrolled integration into the host genome, and are toxic for stem cells, new and safer non-viral vectors are being developed, with more focus on nanoparticles (NP).

They are fairly easy to synthesize with low costs, can accommodate large vectors, are mostly non-inflammatory, do not cause genomic modifications, and are amenable to cell targeting. NP including poly (lactide-co-glycolide) NP loaded with antifibrotic pirfenidone, inorganically-coated all-trans retinoic acid NP, elastin-like polypeptide-based NP bearing a mitogenic protein lacritin, gold NP with BMP7 gene, cationic NP with TGF- β and CTGF siRNAs, polymeric micelles with bcl-xL gene were used to promote corneal wound healing, reduce stromal haze after photorefractive keratectomy, and cell apoptosis. NP with shRNA to VEGF-A inhibited corneal neovascularization upon alkaline burns.

Methods: For corneal gene therapy we have used new nanobioconjugates (NBC) based on polymalic acid that do not have NP drawbacks: passive cellular uptake and cargo leakage leading to side effects. Diabetic corneas have wound healing alterations and impaired corneal epithelial stem cell (CESC) functions. AV gene therapy proved to be rather toxic for cultured CESC, prompting the use of nano vehicles.

Results: Non-toxic NBC were engineered to increase the expression of diabetes-downregulated c-met gene and decrease diabetes-upregulated MMP-10 and cathepsin F genes. Cell-targeted NBC increased diabetes-impaired CESC wound healing and the expression of diabetes-suppressed stem cell markers.

Conclusions: NBC and NP allowing customizable use of various drugs provide promising versatile nano vehicles for next-generation preclinical and clinical applications of corneal gene therapy.

SEVERE OCULAR ALLERGIES: FROM PATHOPHYSIOLOGY TO FUTURE THERAPIES

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Allergic conjunctivitis is often considered an easy-to treat and self limiting allergic inflammation of the conjunctiva without long term complications and potential damage for the visual function. However, ocular allergic (OA) includes a variety of inflammatory diseases of the ocular surface affecting lids, cornea, lachrymal gland and tear film, at different levels of severity. The inflammatory mechanism of seasonal (SAC) or occasional allergic conjunctivitis is typically type I hypersensitivity IgE-mediated, whereas in chronic allergic disorders, such as vernal keratoconjunctivitis (VKC) or atopic keratoconjunctivitis (AKC), the mechanisms are more complex and probably involve both IgE and T cell-mediated responses. Nevertheless, acute and chronic diseases have in common: 1) the possible sensitization to environmental allergens; 2) the IgE-mast cell activation with subsequent mediator cascade; 3) the conjunctival inflammation with a prevalence of eosinophils; 4) the presence of lymphocytes with a Th2, Th9 and Th17 profiles of cytokine production; 5) a mucosal hyper-reactivity. Corneal involvement is common in VKC and AKC associated with neuro-inflammation, tissue remodelling and fibrosis, resulting in potential corneal damage and scarring. Therefore, multiple mediators, cytokines, chemokines, growth factors, proteases and enzymes are over-expressed in severe OA.

Interestingly, transcriptomic, proteomic and glycomic techniques, reveal the presence of low abundant and high abundant proteins and glycoproteins with pro- and anti-inflammatory properties, which may represent either disease biomarker or target for new treatments. Understanding inflammation in ocular allergy may provide indication for a rational treatment of these diseases and future potential therapeutic approaches including immune-modulators, such as cyclosporine (CsA) and tacrolimus.

In particular, CsA can be considered for treatment of moderate to severe VKC and AKC. It decreases signs and symptoms, and the need for steroids. Corneal complications should be carefully monitored and anti-inflammatory therapy adjusted; in these cases, steroids must be used since the pathogenesis of the ulcer is strictly immune-mediate. Corticosteroids are preferred over CsA, since they are more effective in inhibiting the inflammatory component of corneal damage (i.e., eosinophil- and neutrophil-liberated epithelial toxic mediators). If a systemic hypersensitivity to identified allergens exists, specific immunotherapy may be considered. The indications for of anti-IgE therapies are still unclear.

GABAPENTIN EYE DROPS FOR THE TREATMENT OF OPHTHALMIC PAIN AND OCULAR SURFACE INFLAMMATION

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Purpose: Gabapentin is a synthetic molecule that targets voltage-dependent calcium channels and purinergic adenosine A1 receptors, thus eliciting analgesic, anti-convulsive and antiinflammatory responses. To date, gabapentin has been successfully used for the treatment of neuropathic pain and epileptic convulsions. However, in most of the published studies systemic gabapentin was not adequate to control corneal neuropathic pain. Therefore, aim of this study has been to study the efficacy of gabapentin eye drops to control corneal pain and ocular surface inflammation after topical instillation.

Methods: The effect of gabapentin eye drops was investigated on the inflammatory response of lipopolysaccharide (LPS)-stimulated rabbit corneal cells (SIRC) and on endotoxin-induced uveitis (EIU) in rats. Further, a rat model of corneal pain was carried out using formaldehyde as insult.

Results: A topical formulation of gabapentin was capable of reducing corneal pain and attenuate the ocular inflammatory reaction both in vitro and in vivo. Topical treatment with gabapentin significantly ($p < 0.01$) reduced clinical signs and biomarkers of inflammation such as TNF- α and IL-1 β .

Conclusions: The results generated in the present study suggest that ophthalmic formulation based on gabapentin may be useful in the treatment of inflammatory conditions associated to ocular pain. Clinical studies to evaluate this possibility may be warranted.

ALTERED ELECTRICAL ACTIVITY OF CORNEAL SENSORY RECEPTOR FIBERS DURING REGENERATION AFTER CORNEAL MICROKERATOME LESION IN THE GUINEA-PIG

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Purpose: To characterize neural activity of corneal sensory receptors in the guinea-pig cornea at different times after corneal surgical lesion.

Methods: Electrical activity of corneal sensory receptor fibers was recorded 1-60 days after performing a mid-stromal surgical lesion (4mm-diameter incomplete circular flap) with a custom-made microkeratome in anesthetized guinea-pigs of both sexes. Nerve terminal impulse activity was recorded in vitro from the excised cornea and from single ciliary nerve fibers. Responses to thermal stimulation (changing bath temperature from 34°C -basal temperature- to 20°C -cooling ramp- or 50°C -heating ramp-), mechanical (von Frey hairs) and chemical stimulation (30s-duration gas jets of 98% CO₂ in air) were analyzed in intact and lesioned eyes.

Results: Except peripheral to the lesion or at the flap hinge, no activity was recorded within the lesion area, suggesting postsurgical functional denervation. 1-3 days after microkeratome-lesion, responses of polymodal nociceptors to chemical and heat stimulation were transiently increased and mechanical threshold decreased. Spontaneous activity and mechanical threshold of mechanonociceptors were not significantly modified after surgery. Ongoing activity at basal temperature and response to cooling ramps of cold thermoreceptors were transiently increased 7-14 days after lesion and tend control values afterwards.

Conclusions: Corneal nerve fibers regenerating in lesioned corneas maintain their electrophysiological characteristics and responses to natural stimuli, albeit firing at higher frequencies the first days after injury. This may be due to sensitization induced by inflammatory mediators and/or to the well documented altered expression of sodium and potassium channels produced after nerve lesion.

UNIQUE HYDROGEL TECHNOLOGY - IN VITRO MODEL REPRESENTING CORNEAL LAYERS

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Purpose: The cornea is an effective penetration barrier to drugs applied topically onto the eye. In early drug development, it is important to evaluate the potency of a drug candidate for its ability to permeate through the cornea. The purpose of this study was to develop an in vitro model representing the corneal component layers (epithelium and stroma) using a unique hydrogel technology and human corneal epithelial cells (HCE-T).

Methods: Different hydrogel components and cross-linking techniques were used. The apparent permeability coefficient (Papp) values of low and high permeability marker molecules across the blank hydrogels and hydrogels with HCE-T cells on top of hydrogels were measured. Expression and localization of tight junction proteins, ZO-1 and occludin, were assessed using immunocytochemistry.

Results: Papp values were significantly lower for hydrogels with HCE-T cells cultured on top of the hydrogel than the Papp values for blank hydrogels. However, there were differences in the expression and localization of tight junction proteins depending on the hydrogel type where the cells were grown.

Conclusions: The use of hydrogel technology is a promising model for the corneal stroma. However, additional development is needed to obtain an in vitro model comprising all functional corneal layers and possessing adequate epithelial barrier function.



POSTER SESSION

- 1 **IN VIVO COMPARISON OF THE RESIDENCE TIME OF CROSS-LINKED COMPARED TO LINEAR HYALURONIC ACID IN RABBIT EYE**
MIRKO MUZZI¹; RITA MENCUCCI²
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- 2 **PLACENTA GROWTH FACTOR PLAYS A ROLE IN IMMUNE RESPONSE ASSOCIATED WITH CHOROIDAL NEOVASCULARIZATION**
SERGIO CRESPO-GARCIA¹, CAITLIN CORKHILL¹, CHRISTOPHE ROUBEIX^{1,2}, NORBERT KOCIOK¹, OLAF STRAUSS¹, ANTONIA M. JOUSSEN¹, NADINE REICHHART¹
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- 3 **AUTOREGULATION OF RETINAL GANGLION CELL FUNCTION TO METABOLIC CHALLENGE IN GLAUCOMA**
GIOVANNI LUCA ROMANO¹, CHOU TSUNG HANG², CLAUDIO BUCOLO¹, FILIPPO DRAGO¹, VITTORIO PORCIATTI²
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- 4 **CANNABINOIDS IN OCULAR PATHOPHYSIOLOGY**
ANNA-MARIA SZCZESNIAK, ALEX STRAIKER
 Department of Pharmacology, Dalhousie University Halifax, NS., Canada
- 5 **IN SILICO PREDICTION OF CONJUNCTIVAL DRUG PERMEABILITY**
EVA M. DEL AMO¹, EVA RAMSAY^{1,2}, THEO PICARDET¹, SEPPO AURIOLA¹, ELISA TOROPAINEN¹, MARIKA RUPONEN¹, ARTTO URTTI^{1,2}
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- 6 **INTRAVITREAL NA3 IS SUPPORTS RETINAL STRUCTURE AND FUNCTION IN THE RCS RAT**
MONICA M. JABLONSKI, XIANGDI WANG, YUNFENG SHI, AND SUMANA CHINTALAPUDI
 University of Tennessee Health Science Center, Memphis, TN 38163
- 7 **INTERACTION OF REACTIVATED ASTROCYTES AND RETINAL GANGLION CELLS FOLLOWING ENDOTHELIN ADMINISTRATION**
SHAOQING HE, HAI-YING MA, AND THOMAS YORIO
 North Texas Eye Research Institute, University of North Texas Health Science Center at Fort Worth, USA
- 8 **CHARACTERIZATION OF CALCIUM CHANNEL EXPRESSION IN PRIMARY OPTIC NERVE HEAD ASTROCYTES**
YULIYA NAUMCHUK¹, VIDHYA R. RAO^{1,2,3}, ALEXANDRA D. HEGEL^{1,3}, ALEXANDER ROCKWELL¹, VICKI HUSAK³, SIMON KAJA^{1,2,3}
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- 9 TARGETING OPTIC NERVE HEAD ASTROCYTES IN DRUG DISCOVERY FOR PRIMARY OPEN ANGLE GLAUCOMA**
SIMON KAJA^{1,2,3} VIDHYA R. RAO^{1,2,3} ALEXANDRA D. HEGEL^{1,2,3} ALEXANDER JAMIE C. FLOSS² VICKI HUSAK³ EVAN B. STUBBS JR.^{1,3}
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- 10 ALDH2 REGULATES ANGIOGENESIS**
GINEVRA NANNELLI¹ ERIKA TERZUOLI¹ MARINA ZICHE¹ AND SANDRA DONNINI¹
¹Department of Life Sciences, University of Siena, Via Aldo Moro 2, 53100, Siena, Italy
- 11 PURINERGIC RECEPTOR MEDIATED INDUCTION OF INTERLEUKIN-1 β IN MÜLLER AND MICROGLIAL CELLS IN RELATION TO GLAUCOMA**
JULIE SANDERSON¹ MATTHEW FELGATE¹ SOFIA HABIB^{1,2} PHILLIP WRIGHT¹ LEANNE STOKES¹ NUWAN NIYADURUPOLA² AND DAVID C BROADWAY^{1,2}
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- 12 AGE-RELATED DIFFERENCES AFTER BRIGHT LIGHT EXPOSURE IN BALB/C MICE**
SYMANTAS RAGAUSKAS^{1,3} TAMUNA BOLKVADZE¹ AGNE ZINIAUSKAITE¹ HENRI O. LEINONEN^{2,4} HEIKKI TANILA² GIEDRIUS KALESNYKAS¹
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³State Research Institute for Innovative Medicine, Vilnius, Lithuania
⁴Department of Pharmacology, Case Western Reserve University, Cleveland, Ohio, USA
- 13 CORNEAL SURFACE TEMPERATURE UNDER PERFLUOROHEXYLOCTANE EYE DROPS**
M. CARMEN ACOSTA, CAROLINA LUNA, SUSANA QUIRCE, ENRIQUE VELASCO, ADOLFO ARACIL, JUANA GALLAR
 Universidad Miguel Hernandez, Valencia, Spain
- 14 INNER RETINAL CHANGE IN NORMAL-TENSION GLAUCOMA**
JIE HYUN KIM, HAE-YOUNG LOPILLY PARK, CHAN KEE PARK
 Department of Ophthalmology and Visual Science,
 College of Medicine, The Catholic University of Korea, Seoul, Korea
- 15 ANTERIOR CHAMBER VERSUS POSTERIOR CHAMBER PERFUSION IN LIVING MICE DOES NOT INFLUENCE MEASUREMENT OF AQUEOUS OUTFLOW FACILITY BY CONSTANT FLOW INFUSION**
J. CAMERON MILLAR, NAVITA N. LOPEZ, GAURANG C. PATEL, TIEN N. PHAN AND ABBOT F. CLARK
 North Texas Eye Research Institute, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX USA
- 16 NOVEL TARGETS OF Δ -OPIOID RECEPTOR AGONIST FOR RGC NEUROPROTECTION**
SHAHID HUSAIN
 Medical University of South Carolina, USA

- 17 MAPRACORAT, A NOVEL SELECTIVE GLUCOCORTICOID RECEPTOR AGONIST, INHIBITS CYTOKINE SECRETION IN HUMAN MAST CELLS**
MONICA BAIULA¹, SANTI M. SPAMPINATO¹
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- 18 CIPROXIFAN, AN H3 RECEPTOR INVERSE AGONIST, LOWERS IOP AND AMELIORATES OCULAR VASCULAR REACTIVITY IN NEW ZEALAND WHITE RABBIT MODELS OF GLAUCOMA**
CECILIA LANZI¹, LAURA LUCARINI¹, MARIA CONCETTA DURANTE¹, ALESSANDRO PINI², FRANCESCO IMPAGNATIELLO³, ELENA BASTIA³, HOLGER STARK⁴ AND EMANUELA MASINI¹
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 (Neuroscience, Psychology, Drug Research and Child Health) Univesrity of Florence
- 19 EFFICACY OF A NEW FOOD SUPPLEMENT IN A MURINE MODEL OF OPTICNEURITIS**
DARIO RUSCIANO¹, MAURIZIO CAMMALLERI², FILIPPO LOCRI², MASSIMO DAL MONTE² AND PAOLA BAGNOLI²
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- 20 THE WNT SIGNALING PATHWAY IN TRABECULAR MESHWORK CELLSCAN BE MODULATED BY EXOSOMES DERIVED FROM NON-PIGMENTED CILIARY EPITHELIAL CELLS**
ELIE BEIT-YANNAI¹, SOFIA AVISSAR¹, NATALIE LERNER¹
¹Clinical Biochemistry and Pharmacology, Ben-Gurion University, Beer-Sheva, Israel
- 21 EXPRESSION OF OCULAR SURFACE MUCIN IN DRY EYE INDUCED MOUSE MODEL BY CURRENT DRY EYE TOPICAL MEDICATIONS**
INHEE MOON
 Department of ophthalmology, Severance hospital, College of medicine, Yonsei University, Seodaemun-gu, Seoul, Korea
- 22 PKC β INHIBITION IMPAIRS VEGF INDUCED OCULAR ANGIOGENESIS**
LUCIA MORBIDELLI, MARTINA MONTI, DARIA MOCHLY-ROSEN¹, MARINA ZICHE
 Department of Life Sciences, University of Siena, Via A. Moro 2, 53100 Siena, Italy and
¹Department of Chemical and Systems Biology, Stanford University School of Medicine, Stanford, CA 94305, USA
- 23 ANTIANGIOGENIC AND ANTI-INFLAMMATORY ACTIVITY OF UPARANT IN THE RABBIT CORNEA**
VALERIO CICCONE, LORENZO BAZZANI, DARIO RUSCIANO¹, VINCENZO PAVONE², MARIO DE ROSA³, MARINA ZICHE AND LUCIA MORBIDELLI
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²Department of Chemical Science, University of Naples "Federico II" via Cintia, 80126 Napoli, Italy; ³Department of Experimental Medicine, Second University of Naples, Napoli, Italy
- 24 LIGHT-INDUCIBLE RHODOPSIN MUTANTS (TVRM4/-) MICE: CHARACTERIZATION AND THERAPEUTIC APPROACH**
CLAUDIA GARGINI¹, ILARIA PIANO¹, ELENA NOVELLI², MARTINA BIAGIONI^{2,4}, FABIOLA BONEZZI³, GIUSEPPE CAMPISI³, RICCARDO GHIDONI³, CLAUDIA GARGINI¹ AND ENRICA STRETTO²
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25 MELATONIN SYNTHESIS IN THE HUMAN CILIARY BODY TRIGGERED BY TRPV4 ACTIVATION: INVOLVEMENT OF AANAT PHOSPHORYLATION

JESUS PINTOR, MARIA PEREZ DE LARA AND HANAN AWAD ALKOZI

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26 INTRAPERITONEAL INJECTION OF AN ANTI-APOPTOTIC PEPTIDE INHIBITS RETINAL GANGLION CELL DEATH IN ANIMAL MODELS OF GLAUCOMA

RAM H. NAGARAJ¹, RAGHU R. KRISHNAMOORTHY², SRUTHI SAMPATHKUMAR³

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27 MICROARRAY TRANSCRIPTOME ANALYSIS OF CORNEA AND LACRIMAL GLAND OF IL-22 KNOCK-OUT AND LYMPHATIC HYPOPLASIA TRANSGENIC MOUSE MODELS

EUN YOUNG CHOI, MD¹, HYUN GOO KANG, MD¹, AREUM YEO¹, SO YI JUNG², HYUNG KEUN LEE, MD¹,

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28 REGULATION OF INTRAOCULAR PRESSURE BY MICRORNA CLUSTER MIR-143/145

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29 ADVANCED ANTAGONIST OF RETINOL-BINDING PROTEIN 4 FOR TREATMENT OF THE ATROPHIC FORM OF AGE-RELATED MACULAR DEGENERATION

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30 UNIQUE HYDROGEL TECHNOLOGY - IN VITRO MODEL REPRESENTING CORNEAL LAYERS

AGNĖ ŽINIAUSKAITĖ, VYTAUTAS CĖPLA, RAMŪNAS VALIOKAS, GIEDRIUS KALESNYKAS AND

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31 HSP27 ADDITION INTENSIFIES AII AMACRINE CELL AND SYNAPSE DAMAGE INDUCED BY S100B IMMUNIZATION IN AN AUTOIMMUNE GLAUCOMA MODEL

STEPHANIE C. JOACHIM, SABRINA REINEHR, SANDRA KUEHN, CHRISTINA CASOLA,

DENNIS KOCH, GESA STUTE, H. BURKHARD DICK

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32 PEA-15 PHOSPHOPROTEIN MEDIATES OPTIC NERVE ASTROCYTE PHAGOCYTOSIS

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- 33 EPIGALLOCATEQUINGALLATE AND MELATONIN IN ORAL ADMINISTRATION IMPROVE VISUAL FUNCTION IN A RETINAL DEGENERATION MODEL, THE P23H RAT**
LORENA PERDICES¹, ISABEL PINILLA^{1,2}, LORENA FUENTES-BROTO^{1,3}, FRANCISCO J. SEGURA⁴, GEMA INSA SÁNCHEZ², ELVIRA ORDUNA², ANA ISABEL SÁNCHEZ-CANO^{5,2}, NICOLÁS CUENCA⁶
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- 34 OFF-LABEL DRUG USE AT THE POLICLINIC-UNIVERSITY HOSPITAL OF CATANIA, FROM 2012 TO 2015: FOCUS ON MITOMYCIN C**
LUCIA GOZZO¹, LAURA LONGO¹, SILVANA MANSUETO¹, FILIPPO DRAGO^{1,2}
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- 35 VITAMIN D IN SYSTEMIC SCLEROSIS PATIENTS WITH DRY EYE SYNDROME**
MIRIAM GALLO AFLITTO, CARLO RAPISARDA¹, ROBERTA AMATO^{1,2}, SALVO FICIL^{1,2}, DAVIDE SCOLLO¹ GIOVANNI PANTA¹, DANIELA ROCCA^{1,2}, AGATA MESSINA^{1,2}, ROSARIO FOTI³, TERESIO AVITABILE¹ ELISA VISALLI³, CATERINA GAGLIANO^{1,2}
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- 36 DESIGN, SYNTHESIS, AND CHARACTERIZATION OF A SELECTIVE INHIBITOR FOR RETINALDEHYDE DEHYDROGENASE (ALDH1A) ENZYMES**
ANGELICA HARPER¹, ANH LE², TIM MATHER³, ANTHONY BURGETT², JODY A. SUMMERS¹
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³Oklahoma Medical Research Foundation, Oklahoma City, OK, United States of America
- 37 NANOTECHNOLOGICAL SIRNA FORMULATIONS FOR THE TREATMENT OF DIABETIC RETINOPATHY**
SARHA CUPRI, MARIA LAURA AMADIO, ALESSIA PASCALE, CECILIA OSERA, VELIA D'AGATA, AGATA GRAZIA D'AMICO, GIAN MARCO LEGGIO, BARBARA RUOZI, STEFANO GOVONI, FILIPPO DRAGO CLAUDIO BUCOLO, ROSARIO PIGNATELLO
 Department of Drug Sciences, University of Catania, Italy
- 38 PROTECTIVE EFFECT OF ID PROTEIN ON TGF β 2 INDUCED FIBROSIS IN HUMAN TRABECULAR MESHWORK CELLS: IMPLICATION FOR DEVELOPING A GLAUCOMA THERAPY**
AVANI A. MODY, ROBERT J. WORDINGER, ABBOT F. CLARK
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 University of North Texas Health Science Center, Fort Worth, TX USA
- 39 ROLE OF GLUCOCORTICOID RECEPTOR GR β IN GLUCOCORTICOID-INDUCED OCULAR HYPERTENSION AND GLAUCOMA IN MICE**
GAURANG C. PATEL, YANG LIU, J. CAMERON MILLAR, AND ABBOT F. CLARK
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- 40 HUMAN-SPECIFIC LONG NON-CODING RNAS REGULATE OCULAR ANGIOGENESIS**
BO YU¹, QINBO ZHOU¹, CHASTAIN ANDERSON¹, JAKUB HANUS¹, FANGKUN ZHAO¹, JING MA¹, KUN ZHANG³ AND SHUSHENG WANG^{1,2}
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- 41 OCULAR TISSUE DISTRIBUTION OF ORALLY ACTIVE MULTIFUNCTIONAL ANTIOXIDANTS**
DAMIAN M. DASZYNSKI¹, THEODOR A. WOOLMAN¹, KAREN BLESSING¹, AND PETER F. KADOR^{1,2}
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²Department of Ophthalmology, University of Nebraska Medical Center, Omaha, NE, USA
- 42 TARGETING INFLAMMATION TO DELAY PHOTORECEPTOR DEGENERATION IN AN ANIMAL MODEL OF RETINITIS PIGMENTOSA**
MARTINA BIAGIONI¹, VIVIANA GUADAGNI¹, ELENA NOVELLI¹, ENRICA STRETTOI¹
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- 43 AGE-RELATED MACULAR DEGENERATION AND TGF- β 1: PHARMACODYNAMIC AND PHARMACOKINETIC PROFILE**
FRANCESCA LAZZARA, CLAUDIO BUCOLO, LEGGIO GIAN MARCO, VINCENZO FISICHELLA, GIURDANELLA GIOVANNI, CHIARA BIANCA MARIA PLATANIA, ANNAMARIA FIDILIO, FEDERICA GERACI, FILIPPO DRAGO
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- 44 ANTIOXIDANT AND OSMOPROTECTING ACTIVITY OF TAURINE IN DRY EYE MODELS**
ANNAMARIA FIDILIO, CLAUDIO BUCOLO, CHIARA BIANCA MARIA PLATANIA, FRANCESCA LAZZARA, FEDERICA GERACI, FILIPPO DRAGO
 Department of Biomedical and Biotechnological Sciences, School of Medicine
 University of Catania, Catania, Italy
- 45 IDENTIFICATION OF A GENE SIGNATURE REGULATED BY A LNCRNA ASSOCIATED WITH EXFOLIATION GLAUCOMA**
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- 46 MIRNAS IN VITREOUS HUMOR OF PATIENTS AFFECTED BY IDIOPATHIC EPIRETINAL MEMBRANE AND MACULAR HOLE**
MARIO D. TORO (PRESENTER)¹, ANDREA RUSSO¹, MARCO RAGUSA², ANTONIO LONGO¹, TERESIO AVITABILE¹, CINZIA DI PIETRO², DAVIDE BARBAGALLO², MICHELE REIBALDI¹
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- 47 INNER RETINAL REMODELING IN AN INDUCIBLE MOUSE MODEL OF RETINITIS PIGMENTOSA**
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48 RETINAL PK PROFILE OF CURCUMIN AFTER ORAL ADMINISTRATION IN RABBITS

¹CLAUDIO BUCOLO, ¹ANNAMARIA FIDILIO, ¹CHIARA BIANCA MARIA PLATANIA,
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49 NANOPARTICLE INTERACTION WITH VITREOUS HUMOR AND ITS EFFECT ON RETINAL PIGMENT EPITHELIAL CELL UPTAKE

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50 TRANSPALPEBRAL RHEOPHTHALMOGRAPHY EVALUATION OF THE IMPACT OF PROSTAGLANDIN ANALOGS ON OCULAR HEMODYNAMICS IN EARLY PRIMARY OPEN-ANGLE GLAUCOMA

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51 PRESENCE OF MELANOPSIN IN HUMAN CRYSTALLINE LENS EPITHELIAL CELLS AND ITS ROLE IN MELATONIN SYNTHESIS

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52 IMMUNOHISTOCHEMICAL CHARACTERIZATION OF NEUROTRANSMITTERS IN THE EPISCLERAL CIRCULATION IN RATS

ANJA LADEK¹, ANDREA TROST¹, CHRISTIAN RUNGE¹, FALK SCHRÖDL¹

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53 ROLE OF LACTOBIONIC ACID AND HYALURONIC ACID IN PROMOTION OF CORNEAL EPITHELIAL WOUND HEALING IN VITRO AND IN VIVO

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54 EFFICACY AND SAFETY ASSESSMENT OF LACTOBIONIC ACID FOR THE TREATMENT OF DRY EYE SYNDROME

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- 55 VEGF EXACERBATES HIGH-GLUCOSE-INDUCED DAMAGE IN HUMAN RETINAL ENDOTHELIAL CELLS**
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- 56 OCULAR PHARMACOKINETICS PROFILE OF PALMITOYLETHANOLAMIDE ENCAPSULATED IN NEW NANOSTRUCTURED LIPIDIC CARRIER**
FEDERICA GERACI¹, CLAUDIO BUCOLO¹, CHIARA BIANCA MARIA PLATANIA¹, GIOVANNI LUCA ROMANO¹, CARMELO PUGLIA², ROSARIO PIGNATELLO², EDUARDO MARIA SOMMELLA³, PIETRO CAMPIGLIA³, CARMINE OSTACOLO⁴, FILIPPO DRAGO¹
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- 57 GABAPENTIN NANOCARRIERS TO MANAGE OCULAR PAIN**
ROSARIO PIGNATELLO¹, SARHA CUPRI¹, CLAUDIO BUCOLO², FILIPPO DRAGO², DARIO RUSCIANO³, TERESA MUSUMECI¹, GIOVANNI PUGLISI¹
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- 58 GABAPENTIN NANOCARRIERS TO MANAGE OCULAR PAIN**
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- 59 P2X7 RECEPTOR AS PHARMACOLOGICAL TARGET IN DIABETIC RETINOPATHY**
CHIARA BIANCA MARIA PLATANIA, GIOVANNI GIURDANELLA¹, LUISA DI PAOLA², GIAN MARCO LEGGIO¹, SALVATORE SALOMONE^A, FILIPPO DRAGO^A, CLAUDIO BUCOLO^A
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- 60 STRUCTURAL DIFFERENCES BETWEEN P2X7 AND P2X4 RECEPTORS: A PROTEIN CONTACT NETWORK ANALYSIS**
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- 61 EFFECT OF DIETARY CHOLESTEROL ON OCULAR PATHOLOGIES IN AN AGE-RELATED MACULAR DEGENERATION MOUSE MODEL**
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- 62 TREATMENT WITH AN HDAC3 SELECTIVE INHIBITOR PREVENTS RETINAL GANGLION CELL NUCLEAR ATROPHY AND APOPTOSIS AFTER ACUTE AND CHRONIC OPTIC NERVE INJURY**
HEATHER M. SCHMITT^{1,2,4}, GUOJUN CHEN^{3,4}, YUYUANWANG^{3,4}, CASSANDRA L. SCHLAMP^{1,4}
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- 63 B2R SIGNALING IN NEO-ANGIOGENESIS**
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