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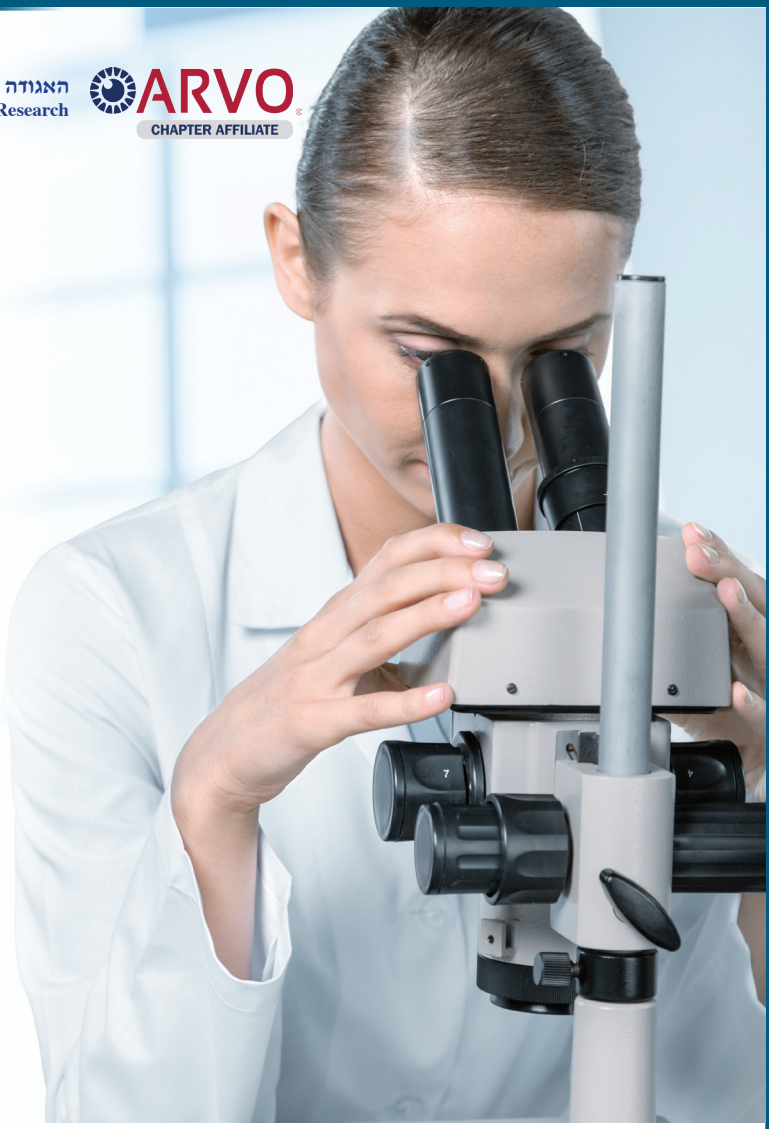

הכנס ה-37

של האגודה הישראלית לחקר העין והראיה

15-16 במרץ 2017 | מלון כפר המכביה

האגודה הישראלית לחקר העין והראיה
Israeli Society for Vision & Eye Research

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PROGRAM & ABSTRACTS

37th Annual Meeting

Kfar Maccabiah

15th-16th March, 2017

תכנית ותקצירים

הכינוס השנתי ה-37

כפר המכבייה

15-16 במרץ, 2017

עריכת התוכנית: פרופ׳ רות אשרי-פדן, פרופ׳ דויד צדוק, פרופ׳ עידי מצר, פרופ׳ דרור שרון

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עיצוב והבאה לדפוס: דבורה מרקס אוחנה ודרור שרון

ISRAELI SOCIETY FOR VISION AND EYE RESEARCH
The 37th Annual Meeting, March 15-16, 2017
Program at a glance

Wednesday, March 15, 2017

Session	Location	Time	Page
Coffee & Exhibition	Exhibition Hall	08:00 – 08:55	10
Opening remarks	Rayman Center	08:55 – 09:00	10
Therapy	Rayman Center	09:00 – 10:00	10-11
Cell biology	Rayman Center	10:00 – 11:00	12-13
Coffee & Exhibition	Exhibition Hall	11:00 – 12:00	13
Guest lecture- Michal Schwartz	Rayman Center	12:00 – 13:00	13
Lunch break	Dining Room	13:00 – 14:00	13
AMD- functional	Rayman Center	14:00 – 14:45	14-15
Option 1: Retina	Rayman Center	14:45 – 16:00	15-17
Option 2: Cornea	Rayman East	14:45 – 16:00	17-19
Coffee & Exhibition	Exhibition Hall	16:00– 16:30	20
Genetics	Rayman Center	16:30 – 17:05	20-21

Thursday March 16, 2017

Session	Location	Time	Page
Coffee & Exhibition	Exhibition Hall	08:00 – 08:50	22
Animal models	Rayman Center	08:50 – 09:45	22-23
Retinal genetics 1	Rayman Center	09:45 – 10:30	23-24
Coffee & Exhibition	Exhibition Hall	10:30 – 11:15	25
Retinal Genetics 2	Rayman Center	11:15 – 12:00	25-26
Awards & ISVER update	Rayman Center	12:00 – 12:30	26
Guest lecture- Alon Wolf	Rayman Center	12:30 – 13:00	26
Lunch break	Dining Room	13:00 – 14:00	26
Guest lecture- Alon Wolf	Rayman Center	14:00 – 14:30	26
Option 1: Glaucoma	Rayman Center	14:30 - 15:30	27-28
Option 2: Visual function	Rayman East	14:30 - 15:30	28-30
Coffee & Exhibition	Exhibition Hall	15:30 - 16:00	30
Oncology	Rayman Center	16:00 – 16:30	31
AMD	Rayman Center	16:30 – 17:00	32-33
Concluding remarks	Rayman Center	17:00 – 17:05	33

יושבי-ראש של האגודה הישראלית לחקר העין והראייה

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מרצים המקבלים השנה פרס על עבודות שהוצגו בכנס השנה שעברה (הכנס ה-36, 9-10 במרץ 2016)

Award Recipients for the Best Papers Presented at the Previous Annual Meeting (the 36th Meeting, March 9th-10th 2016)

מלגות נסיעה ל- ARVO ניתנות בעזרת מענקים שנתרמו באדיבות משפחת מרין לזכרו של פרופ' שאול מרין ז"ל, באדיבות משפחת דברת לזכרה של פרופ' אהובה דברת ז"ל, ובאדיבות עמותת "לראות".

1. Rana Hanna, Department of Ophthalmology, Hillel Yaffe Medical Center, Hadera

Lineage Tracing of Stem and Progenitor Cells of the Murine Corneal Epithelium in Hemostasis and after Limbal Chemical and Mechanical Injury

2. Michael Mimouni, Department of Ophthalmology, Rambam Health Care Campus, Technion- Israel Institute of Technology, Haifa

A Method for the Selection of Cataract Disintegrating Compounds and their use for Reversal of Crystalline Lens Opacification

3. Alon Skaat, Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University

Optic Nerve Head Drusen Prevalence in Normal-Appearing Eyes Using Enhanced Depth Imaging Optical Coherence Tomography

4. Elena Segal, Department of Pediatrics A, Meyer Children's Hospital, Rambam medical Center, Haifa

Mapping Protein-Protein Interactions of Bestrophin1 - a Potential Insight into the Development of Bestrophinopathies

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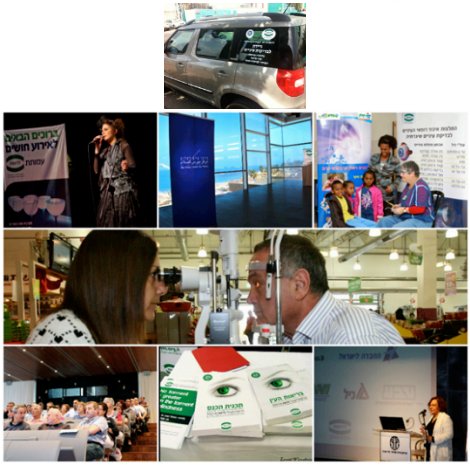
Lirot 10 years achievements

*16 million NIS financed tens of research projects in blindness prevention
*Providing annual scholarships for exceptional young researchers
*8 consecutive years promoting the Annual Eye Health Awareness Month
*Ophthalmology conferences for at risk populations
*Three Internet websites with live seminars and forums on eye diseases
*Vision screening for thousands of children in kindergartens to detect amblyopia and sight problems that can be cured by treatment by an ophthalmologist.
*11,000 eye checkups of senior citizens and Holocaust survivors all over Israel using the Eye Mobile facilities.
*30% of the elderly checked were saved from vision impairment or blindness.
*27,000 hours of volunteers, doctors and professionals supporting Lirot's activities in blindness prevention.

LIROT

THE ISRAELI RESEARCH ASSOCIATION FOR
EYE HEALTH AND BLINDNESS PREVENTION (R.A.)



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הרצאות אורח בכנס ה- 37

Keynote Speakers at ISVER 2017

Wednesday, March 15th 2017

Prof. Michal Schwartz

Department of Neurobiology, Weizmann Institute of Science

Title: Harnessing systemic immunity to combat neurodegenerative diseases

Thursday, March 16th 2017

Prof. Alon Wolf

Director, Biorobotics and Biomechanics Lab (BRML); Faculty of Mechanical Engineering; Technion Israel Institute of Technology

Title 1: On the effect of altering foot center of pressure on lower limb Biomechanics and clinical applications
Title 2: Human Machine Merger: Are we headed for the MMATRIX?

Wednesday, March15th 2017

Coffee and Exhibition 08:00 - 08:55

Opening remarks: Dror Sharon 08:55 - 09:00

Therapy

09:00 - 10:00

Moderators: Yossi Mandel and Ron Ofri

1 9:00

Differentiation of Human Embryonic Stem cells into Photoreceptor Precursors – In-Vitro and In-Vivo Study

Amos Markus (1), Yoav Chemla (1), Astar Shamul (1), Nairouz Farah (1), Ronald S. Goldstein (1), Yossi Mandel (1,2)
(1) Mina and Everard Goodman Faculty of Life Sciences, (2) Optometry and Visual Science, Faculty of Life Science. Bar-Ilan University, Ramat-Gan

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2 9:07 AC

Incorporation and Survival of Retinal Progenitors Derived from Human Embryonic Stem Cells (hESCs) in Rodent Eyes

Hamzah Aweidah (1), Alex Obolensky (1), Ayala Ejzenberg (1), Masha Idelson (2), Hanita Khaner (2), Benjamin Reubinoff (2), Eyal Banin (1)
(1) Department of Ophthalmology and (2) Gene Therapy Institute, Hadassah-Hebrew University Medical Center, Jerusalem

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3 9:14 AC

Retinal Transfection Efficacy of a Capsid Mutant Adeno-Associated Virus [AAV2-quad(Y-F)+T491V] Following Subretinal and Intravitreal Injection in Sheep

Maya Ross (1), Eyal Banin (2), Alexey Obolensky (2), Raaya Ezra-Elia (1), Hen Honig (3), Esther Yamin (2), Alexander Rosov (3), Edward Averbukh (2), William W Hauswirth (4), Elisha Gootwine (3), Ron Ofri (1)
(1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, (2) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (3) ARO, The Volcani Center, Rishon LeZion, (4) Department of Ophthalmology, University of Florida, Gainesville, FL, USA

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4 9:21 AC

Mobility and Tropism of Adeno - Associated Virus (AAV) Injected Subretinally or Intravitreally in Mice

Raaya Ezra-Elia (1), Alexey Obolensky (2), Ayala Ejzenberg (2), Dror Sharon (2), Eyal Banin (2), Ron Ofri (1)
(1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, (2) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

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5 9:28

A Novel Minimally Invasive Adjustable-Depth Blunt Injector for Delivery of Therapeutics into the Extravascular Spaces of the Choroid

Ygal Rotenstreich (1,2), Adi Tzameret (1,2), Sapir E. Kalish (1,2), Ettel Bubis (1,2), Michael Belkin (1,2), Iris Moroz (1), Mordechai Rosner (1,2), Itay Levy (3), Shlomo Margel (3), Ifat Sher (1)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Department of Chemistry, Bar-Ilan Institute of Nanotechnology and Advanced Materials, Ramat-Gan

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6 9:35

Active Sensing for Enhancement of Reading Capabilities in Prosthetic Vision

Chen Abraham (1), Nairouz Farah (2), Yuval Harpaz (3), Zeev Zalevsky (1), Yossi Mandel (2)
(1) Faculty of Engineering and the Bar-Ilan Institute of Nanotechnology & Advanced Materials, (2) Faculty of Life Sciences, Optometry Track and Bar Ilan Institute for nanotechnology and Advanced Materials (BINA), (3) Gonda Brain Research Center, Bar-Ilan University

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7 9:42

MetAp2 Inhibition for the Treatment of AMD

Ofra Benny
Institute of Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem

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9:49 **Discussion**

Cell biology

Moderators: Ruth Ashery-Padan and Tami Livnat 10:00 - 11:00

8 10:00 AC

Protective Effect of Intravitreal Administration of Exosomes derived from Mesenchymal Stem Cells on Retinal Ischemia

Elad Moisseiev (1), Johnathon Anderson (2), Sharon Oltjen (2), Mayank Goswami (2), Robert Zawadzki (2), Jan Nolta (2), Susanna Park (2)
(1) Tel Aviv Medical Center, Tel Aviv, (2) UC Davis, Sacramento, CA, USA

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9 10:07 AC

Characterization of Human Nonpigmented Ciliary Epithelium-Derived Exosomal miRNAs by Microarray Analysis

Natalie Lerner, Elie Beit-Yannai, Sofia Schreiber-Avissar
Ben-Gurion University of the Negev, Beer-Sheva

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10 10:14 AC

Bi-Modal Effect of Exosomes Dose Response in NPCE-TM communication in the Ocular Drainage System

Saray Tabak, Sofia Schreiber-Avissar, Elie Beit-Yannai
Ben-Gurion University of the Negev, Beer-Sheva

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11 10:21 AC

Possible Involvement of NETosis in Infectious and Inflammatory Processes in the Eye; Evidence from a Small Cohort of Patients

Tilda Barliya (1), Rima Dardik (2), Yael Nisgav (1), Mor Dachbash (1), Rita Ehrlich (3,4), Dov Weinberger (1,3,4), Tami Livnat (1,2,4)
(1) Laboratory of Eye research Felsenstein Medical Research Center (FMRC), Rabin Medical Center, Petah Tikva, (2) The Israeli National Hemophilia Center, Sheba Medical Center, Tel Hashomer, (3) Division of Ophthalmology, Rabin Medical Center- Beilinson campus, Petah Tikva, (4) Sackler School of Medicine, Tel-Aviv University

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12 10:28

Transcription Factors of the RPE Play a Role in Choroid Vascularization

Yamit Cohen-Tayar (1), Hadar Cohen (1), Ran Elkon (1), Pablo Blinder (1), Maria Idelson (2), Benjamin Reubinoff (2), Shalev Itzkovitz (3), Ruth Ashery-Padan (1)
(1) Tel-Aviv University, (2) Hadassah Medical Center, Jerusalem, (3) Weizmann Institute of Science, Rehovot

p. 48

13 10:35 **The Roles of Sip1 in Retinogenesis**

Yotam Menuchin-Lasowski (1), Pazit Oren-Giladi (1), Raaya Ezra-Elia (2), Ron Ofri (2), Ruth Ashery-Padan (1,3)
(1) Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, (2) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, (3) Sagol School of Neuroscience, Tel-Aviv University, Tel Aviv

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14 10:42 AC **Roles for MicroRNAs in Retinal Pigmented Epithelium Development and Function**

Benjamin Amram (1,2), Ohana Reut (1), Shaul Raviv (1), Ariel Rinon (1), Ruth Ashery-Padan (1,2)
(1) Department of Human Molecular Genetics & Biochemistry, Tel-Aviv University, Tel-Aviv, (2) Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv

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10:49 **Discussion**

Coffee and exhibition 11:00 - 12:00

Guest lecture- Prof. Michal Schwartz 12:00 - 13:00

Department of Neurobiology, Weizmann Institute of Science

Harnessing systemic immunity to combat neurodegenerative diseases

Lunch break 13:00 - 14:00

AMD- functional

Moderators: Anat Lowenstein and Zeev Dvashi

14:00 - 14:45

15 14:00 AC

Proteome of Aqueous Humor from Patients with Age-related Macular Degeneration

Batya Rinsky, Gala Beykin, Samer Khateb, Liran Tiosano, Shira Hagbi-Levi, Sarah Hayoun, Michelle Grunin, Itay Chowers

Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

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16 14:07 AC

Characterizing the Involvement of Macrophages in the Pathogenesis of Atrophic Age Macular Degeneration

Sarah Hayoun, Batya Rinsky, Shira Hagbi-Levi, Michelle Grunin, Itay Chowers

Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

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17 14:14 AC

Pro-Angiogenic Mechanism of Activated Macrophages from Patients with Age-related Macular Degeneration

Shira Hagbi-Levi, Michelle Grunin, Sarah Elbaz-Hayoun, Batya Rinsky, Itay Chowers

Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

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18 14:21 AC

The Contribution of Patient's Derived Factors, Disease State, and Microenvironment to Macrophage Function in the Context of Age-Related Macular Degeneration (AMD)

Shira Hagbi-Levi (1), Shai Carmi (2)*, Itay Chowers (1)*

* These two senior authors contributed equally to the work

(1) Department of Ophthalmology and (2) Braun School of Public Health and Community Medicine, Hadassah-Hebrew University Medical Center, Jerusalem

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19 14:28 AC

New Insight on the Autophagy Process as Key Therapeutic Target in Treating Dry Age Related Macular Denegation

Lior Shuster (1), Keren ben Yaakov (1), Shalom Lerrer (1), Zeev Dvashi (1), Ayala Pollack (1), Arieh S Solomon (2)
(1) Kaplan Medical Center, Rehovot, affiliated with Hadassah-Hebrew University of Jerusalem, Rehovot, Tel Hasomer, Ramat Gan, (2) Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer, Tel-Aviv University, Ramat-Aviv, Tel-Aviv

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14:35 **Discussion**

Retina (at Rayman Center)

Moderators: Eyal Banin and Ygal Rotenstreich 14:45 -16:00

20 14:45 AC

Visual Outcome of Cystoid Macular Edema in Pediatric Non-Infectious Uveitis

Maya Eiger-Moscovich (1), Oren Tomkins (2), Amer Radgonde (3), Zohar Habot-Wilner (4,6), Ahmed Kasb (2), Ronit Friling (5,6), Michal Kramer (1,6)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) Department of Ophthalmology, University College London, London, UK, (3) Department of Ophthalmology, Hadassah University Hospital, Hadassah medical School, Jerusalem, (4) Department of Ophthalmology, Tel Aviv medical center, Tel Aviv, (5) Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petach Tikva, (6) Sackler School of Medicine, Tel Aviv University, Tel Aviv

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21 14:52 AC

Adipose Tissue Derived Mesenchymal Stem Cells Differentiate Towards RPE and Rescue Apoptotic RPE under Oxidative Stress, in vitro and in vivo

Aya Barzelay (1, 2), Shira Wheisthal (1, 2), Anat Nitzan (1, 2), Mark Krauthammer (1, 2), Moshe Ben – Hemo (1, 2), Anat Loewenstein (1, 2), Adiel Barak (1, 2)
(1) Division of Ophthalmology, Tel Aviv medical center (2) Tel Aviv university

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22 14:59

ERG Oscillatory Potentials Frequency Domain Characteristics in Diabetic Retinopathy and CSNB Patients

Boris Rosin (1, 2), Maya Nitecki (1), Inbar Erdinest (1), Sarah Liss (1), Eyal Banin (1, 2)
(1) Department of Ophthalmology, Hadassah Hebrew University Medical Center, (2) Department of Medical Neurobiology (Physiology), Hadassah-Hebrew University School of Medicine, Jerusalem

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23 15:06

Synthetic 9-cis-beta-carotene Inhibits Photoreceptor Degeneration in Retinal Explants of rpe65rd12 Mouse Model of Retinoid Cycle Defect

Ifat Sher (1), Victoria Edelshtain (1,2), Adi Tzameret (1,2), Michael Ioffe (3), Alon Sayer (3), Ludmila buzhansky (3), Ehud Gazit (3), Ygal Rotenstreich (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) The Department of Molecular Microbiology and Biotechnology George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv

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24 15:13 AC

Clinical Characterization of Individuals with Achromatopsia Caused by Mutations in the *CNGA3* Gene

Alaa AlTalbishi (1,2), Tareq Jaouni (1), Devorah Marks Ohana (1), Shelly Stika (1), Moria Ben-Oliel (1), Inbar Erdinest (1), Gal Shoef (1), Alexey Obolensky (1), Dror Sharon (1), Eyal Banin (1)
(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (2) St. John Eye Hospital, Jerusalem

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25 15:20 AC

Retinitis Pigmentosa - Associated Cystoid Macular Edema Has Inflammatory Optical Density Characteristics

Tomer Batash (1), Hadas Newman (1,2), Adiel Barak (1,2), Shiri Zayit-Soudry (3,4), Eran Pras (2,5), Eyal Banin (6,7), Michael Politis (6,7), Anat Loewenstein (1,2), and Meira Neudorfer (1,2)
(1) Tel Aviv Sourasky Medical Center, Tel Aviv, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Rambam Health Care Campus, Haifa, (4) Rappaport Faculty of Medicine, Technion, Haifa, (5) Assaf Harofeh Medical Center, Zriffin, (6) Hadassah Medical Center, Jerusalem, (7) Hadassah-Hebrew University School of Medicine, Jerusalem.

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26 15:27 AC

Purification and Characterization of Human Dehydrodolychil Diphosphate synthase (DHDDS) Overexpressed in *E. Coli*: Implications for its Retinitis Pigmentosa-Causing Mutations

Moshe Giladi (1,2), Ilan Edri (1), Michal Goldenberg (1), Hadas Newman (1,2), Roi Strulovich (1), Yoni Haitin (1), Daniel Khananshvili (1), Anat Loewenstein (1,2)
(1) Sackler Faculty of Medicine, Tel Aviv University, (2) Tel Aviv Sourasky Medical Center

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27 15:34 AC

Multimodal *In-vivo* High Resolution Imaging of Gold Nanoparticle Labeled Photoreceptor Precursors

Yoav Chemla (1), Oshra Betzer (2), Amos Markus (1), Astar Shamul (1), Menachem Motiei (2), Nairouz Farah (1), Rachela Popovtzer (2), Yossi Mandel (1)
(1) Faculty of life Sciences, Optometry Track and Bar-Ilan Institute for nanotechnology and Advanced Materials (BINA), Bar-Ilan University, Ramat-Gan, (2) Faculty of Engineering and the Institute of Nanotechnology and Advanced Materials, Bar-Ilan University, Ramat Gan

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15:41 **Discussion**

Cornea (at Rayman East)

Moderators: Or Kaiserman and Abraham Solomon 14:45 -16:00

28 14:45

Stiffening of Posterior Rabbit Sclera using Bacteriochlorophyll Derivative (WST11) and Near Infrared Light (NIR) Through the Cornea

Alexandra Goz (1,2), Jurriaan Brekelmans (3), Alexander Brandis (1), Daniel Wagner (4), Xiaomeng Sui (4), Avigdor Scherz (1), Arie Marcovich (1,2)
(1) Departments of Plant Sciences, Weizmann Institute of Science, (2) Department of Ophthalmology, Kaplan Medical Center, Rehovot, (3) University Eye Clinic Maastricht, Maastricht, The Netherlands, (4) Department of Materials and Interfaces, Weizmann Institute of Science

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29 14:52 AC

Rho-Associated Kinase Inhibitor Decreases Human Corneal Endothelial Cell Apoptosis

Asaf Achiron (1,2), Anna Feldman (2,3), Lily Karmona (1,2), Haggay Avizemer (1,2), Elisha Bartov (1,2), Zvia Burgansky (1,2), Vicktoria Vishnevskia-Dai (2,4)
(1) Department of Ophthalmology, Edith Wolfson Medical Center, Holon, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) The Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, (4) The Goldschleger eye institute, Sheba Medical Center, Tel-Hashomer

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30 14:59

Corneal Stem Cell Niche and Dynamics in Health and Disease

Ruby Shalom-Feuerstein
Faculty of Medicine, Technion – Israel Institute of Technology, Haifa

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31 15:06 AC

The effect of Estrogen and Progesterone on Porcine Corneal Biomechanical Properties

Eyal Walter (1), Arie Marcovich (2,3), Joseph Levy (4), Xiaomeng Sui (5), Daniel Wagner (5), Boris Knyazer (1)
(1) Department of Ophthalmology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, (2) Department of Ophthalmology, Kaplan Medical Center, Rehovot, (3) Department of Plant and Environmental Sciences, The Weizmann Institute of Science, Rehovot, (4) Faculty of Health Science, Department of Clinical Biochemistry, Ben-Gurion University of the Negev, Beer-Sheva, (5) Department of Materials and Interfaces, The Weizmann Institute of Science, Rehovot

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32 15:13 AC

Long-Term Result of Corneal Cross-Linking by WST-D and Near Infra-Red (NIR) Light: biomechanical Results and Histologic Evaluation, 1, 4 and 8 Months After Treatment

Jurriaan Brekelmans (1,3), Alexandra Goz (2,3), Mor Dickman (1), Alexander Brandis (4), Xiaomeng Sui (5), Daniel Wagner (5), Rudy Nuijts (1), Avigdor Scherz (3), Arie Marcovich (2,3)
(1) University Eye Clinic Maastricht, Maastricht, the Netherlands, (2) Department of Ophthalmology, Kaplan Medical Center, Rehovot, Departments of (3) Plant and Environmental Science, (4) Biological Services, and (5) Materials and Interfaces, Weizmann Institute of Science, Rehovot

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33 15:20 AC

Corneal Cross-Linking in Patients Younger Than 18 Years Old with Progressive Keratoconus: Up to 7 Years of Follow-Up Results

Lior Or, Assaf Rozenberg, Adi Abulafia, Isaac Avni, David Zadok
Department of Ophthalmology, Assaf Harofeh Medical Center, Zerifin

p. 69

34 15:27 AC

The Efficacy of Vascular Endothelial Growth Factor-Trap (VEGF-trap) compared to Steroids for the Treatment of Corneal Neovascularization

Maya Eiger-Moscovich (1), Eitan Livny (1), Ruti Sella (1), Orly Gal-Or (1), Irit Bahar (1,2)
(1) Department of Ophthalmology, Rabin Medical Center, Petah Tikva, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

p. 70

35 15:34 AC

Treatment of Soft Tissue Expansion and Exophthalmos in Inactive Thyroid Eye Disease Patients using drops of Prostaglandin Analogues

Maya Eiger-Moscovich (1), Hadas Kalish (1,2), Inbal Avisar (1)
(1) Department of Ophthalmology, Rabin Medical Center, Petah Tikva, (2) Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv

p. 71

36 15:41 AC

Cytokine Profile, Environmental and Infectious Exposures of Patients with Dry Eye Syndrome, Sjogren's Syndrome and B-cell non-Hodgkin Lymphoma

Hadas Ben-Eli (1,2), Abraham Solomon (1), Martina Willhauck-Fleckenstein (3), Michael Pawlita (3), Geffen Kleinstern (2), Rania Abu Seir (4), Arava Kedar-Tirosh (2), Eldad Ben Chetrit (5), Dror Mevorach (6), Doron Aframian (7), Ora Paltiel (2,4)
(1) Department of Ophthalmology, (2) Braun School of Public Health, Hadassah-Hebrew University, (3) German Cancer Research Center, Heidelberg, Germany, (4) Department of Hematology, (5) Unit of Rheumatology, (6) Department of Internal Medicine and (7) Department of Oral Medicine, Hadassah Medical Center, Jerusalem

p. 72

37 15:48 AC

Risk Factors Predicting Steroid Induced Ocular Hypertension Following Photorefractive Keratectomy

Yumna Busool (1), Michael Mimouni (1), Igor Vainer (1), Tzahi Sela (3), Gur Munzer (3), Igor Kaiserman (2,3)
(1) Department of Ophthalmology, Rambam Health Care Campus, Haifa, (2) Department of Ophthalmology, Barzilai Medical Center, Ashkelon and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheba (3), Care-Vision Laser Centers, Tel-Aviv

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15:55 **Discussion**

Coffee and exhibition 16:00 - 16:30

Genetics

16:30 - 17:05

Moderators: Eran Pras and Libe Gradstein

38 16:30 AC

Polymorphism in Cytokine-Related Genes in Dry Eye Syndrome and Sjogren's Syndrome' Patients

Hadas Ben-Eli (1,2), Nir Gomel (3), Rania Abu Seir (4), Riki Geffen Perlman (4), Eldad Ben Chetrit (5), Dror Mevorach (6), Kleinstern (2), Doron Aframian (7), Ora Paltiel (2,4), Abraham Solomon (1)

p. 74

(1) Department of Ophthalmology, (2) Braun School of Public Health and Community Medicine, (3) School of Medicine, (4) Department of Hematology, (5) Unit of Rheumatology, (6) Department of Internal Medicine, (7) Department of Oral Medicine & Sjogten's syndrome Center, Hadassah-Hebrew University Medical Center, Jerusalem

39 16:37 AC

Molecular Genetic Analysis of Israeli Families with Idiopathic Infantile Nystagmus

Chen Weiner (1), Iris Nassie (1), Noam Shomron (2), Haike Reznik-Wolf (3), Eran Pras (1)

p. 75

(1) Matlow's Ophthalmogenetic Laboratory, Assaf Harofe Medical Center, Zerifin, (2) Functional Genomics Laboratory Tel Aviv University, (3) Danek-Gertner institute of Human Genetics, Sheba Medical Center, Tel Hashomer, (4) Department of Ophthalmology, Assaf Harofe Medical Center, Zerifin, affiliated to Tel Aviv University

40 16:44

Novel *PAX6* Mutation Causes Phenotypic Variability of Autosomal-Dominant Nystagmus and Foveal Hypoplasia

Libe Gradstein (1), Ohad Wormser (2), Regina Proskorovski (2), Juliana Habeeb (2), Ohad S. Birk (2,3)

p. 76

(1) Department of Ophthalmology, Soroka Medical Center and Clalit Health Services, Ben-Gurion University, (2) Morris Kahn Laboratory of Human Genetics, National Institute for Biotechnology in the Negev, Ben-Gurion University, (3) Genetics Institute, Soroka Medical Center, Ben-Gurion University, Beer Sheva

41 16:51 AC

Dissecting the Phenotypic Influence of Rare Genetic Variations among Patients with Age-Related Macular Degeneration

Nadav Shoshany (1,2), Chen Weiner (2), Ayala Kol (2), Noam Shomron (3), Eran Pras (1,2)
(1) Ophthalmology Department, Assaf Harofe Medical Center, Zeriffin, affiliated to Tel Aviv University, (2) Matlow's Ophthalmogenetic laboratory, Assaf Harofe Medical Center, Zeriffin, (3) Functional Genomics laboratory, Tel Aviv University

p. 77

16:58 **Discussion**

Coffee and Exhibition 08:00 - 08:50

Animal models

08:50 - 09:45

Moderators: Adi Inbal and Ruby Shalom-Feuerstein

42 8:50 AC **Changes in Retinal Genetic Profile of Dark Reared Albino Rats Predispose to Light Damage and may Mimics Aspects of Aging**
Amir Massarweh, Ido Perlman
Department of Physiology and Biophysics, the Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology and the Rappaport Institute, Haifa
p. 78

43 8:57 AC **Homozygous *CEP250* Knockout Leads to a Relatively Late-Onset Retinal Degeneration**
Alaa` Abu-diab(1), Ayat Khalaileh(1), Chen Matsevich(1), Alexey Obolensky(1), Marije de jong (2), Ayala Ejzenberg(1),Eyal Banin(1), Samer Khateb(1), Dror Sharon(1).
(1) Dept. of Ophthalmology and (2) Dept. of Otolaryngology, Hadassah-Hebrew University Medical Center, Jerusalem
p. 79

44 9:04 AC **Characterization of Retinal Function and Structure in *FAM161A* Knockout Mice**
Chen Matsevich (1), Avigail Beryozkin (2), Alexey Obolensky (1), Ayala Ejzenberg (1), Dror Sharon (2), Eyal Banin (1)
(1) Center for Retinal and Macular Degenerations, and (2) Molecular Ophthalmology Laboratory, Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem
p. 80

45 9:11 AC **A New Zebrafish Model for Studying Molecular Genetic Mechanisms Underlying Lens Epithelium Derived Cataract**
Kineret Taler (1), Ariel Rubinstein (1), Jeffery Gross (2), Adi Inbal (1)
(1) IMRIC, The Hebrew University of Jerusalem – Hadassah Medical School, (2) Department of Ophthalmology, Louis J. Fox Center for Vision Restoration, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
p. 81

46 9:18 AC **The Role of Nitric Oxide (NO) in Neuronal Adaptation in the Turtle Retina**
Reem Taha, Ido Perlman
Technion-Israel Institute of Technology, Haifa
p. 82

47 9:25 AC ***CEP78* Knockout Using CRISPR-Cas9 in Zebrafish**
Yael Kinarty (1,2), Samer Khateb (1), Dror Sharon (1), Adi Inbal (2)
(1) Dept. of Ophthalmology, Hadassah-Hebrew university Medical Center, Jerusalem, (2) Dept. of Medical Neurobiology, Institute for Medical Research Israel-Canada, The Hebrew University - Hadassah Medical School, Jerusalem
p. 83

48 9:32 AC **Evaluation of Retinal Degeneration in Royal College of Surgeons (RCS) Rats Using Blue Laser Fundus Autofluorescence and Optical Coherence Tomography**
Ettel Bubis, Adi Tzameret, Ifat Sher, Ygal Rotenstreich
Goldschleger Eye Institute, Sackler Faculty of Medicine, Tel Aviv University, Sheba Medical Center, Tel-Hashomer
p. 84

9:39 **Discussion**

Retinal genetics 1

09:45 - 10:30

Moderators: Tamar Ben-Yosef and Nitza Goldenberg-Cohen

49 9:45 AC **Nonsyndromic Retinitis Pigmentosa in the Ashkenazi Jewish Population: Genetic and Clinical Aspects**
Adva Kimchi (1), Samer Khateb (1), Rong Wen (2), Ziqiang Guan (3), Eran Pras (4,5), Shoshi Kurtzman (1), Samuel G. Jacobson (6), Hadas Newman (7,5), Tamar Ben-Yosef (8), Eyal Banin (1), Dror Sharon (1)
(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem. (2) Bascom Palmer Eye Institute, University of Miami, FL, USA, (3) Duke University Medical Center, Durham, NC, USA, (4) Department of Ophthalmology, Assaf Harofeh Medical Center, Zerifin, (5) Sackler Faculty of Medicine, Tel-Aviv University, (6) Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA, USA, (7) Department of Ophthalmology, Sourasky Medical Center, Tel-Aviv, (8) The Rappaport Faculty of Medicine, Technion, Haifa
p. 85

50 9:52 AC

Co-occurrence of CFH and PRDM13-Related Variants in a Family with Autosomal Dominant Maculopathy of Marked Variable Severity

Prasanthi Namburi (1), Segev Meyer (1), Tom Ben-Tovim (1), Rinki Ratnapriya (2), Samer Khateb (1), Ora Furman (3), Anand Swaroop (2), Eyal Banin (1), Dror Sharon (1)
(1) Ophthalmology Hadassah Department, -Hebrew University Medical Center, Jerusalem, (2) Neurobiology-Neurodegeneration & Repair Laboratory, National Eye Institute, National Institutes of Health, Bethesda, MD, USA, (3) School of Medicine-IMRIC-Microbiology and Molecular Genetics, Hebrew University of Jerusalem

p. 86

51 9:59 AC

Analyzing the Genetic Basis for Inherited Retinal Dystrophy in a Cohort of Israeli Patients by Targeted Next Generation Sequencing

Yasmin Tatour (1), Muhammad Imran Khan (2), Frans P.M. Cremers (2), Tamar Ben-Yosef (1)
(1) Rappaport Faculty of Medicine, Technion, Haifa, (2) Radboud University Medical Center, Nijmegen, The Netherlands

p. 87

52 10:06 AC

Molecular Inversion Probes (MIPs) Analysis of 108 Genes Associated with Inherited Retinal Diseases in 410 Israeli Index Cases

Samer Khateb (1), Muhammad Imran Khan (2), Mor Hanani (1), Ephrat Brill (1), Prasanthi Namburi (1), Eyal Banin (1), Frans P.M. Cremers (2), Dror Sharon (1)
(1) Hadassah-Hebrew University Medical Center, Jerusalem, (2) Department of Human Genetics and Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands

p. 88

53 10:13 AC

Clinical Characteristics of Patients with Retinitis Pigmentosa due to Biallelic *FAM161A* Mutations

Avigail Beryozkin (1), Samer Khateb (1), Carlos Idrobo (1), Alexey Obolensky (1), Tamar Ben-Yosef (2), Dror Sharon (1), Eyal Banin (1)
(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (2) Rappaport Faculty of Medicine, Technion, Haifa

p. 89

10:20 **Discussion**

Coffee and Exhibition 10:30 - 11:15

Retinal genetics 2 11:15 - 12:00

Moderators: Hadas Newman and Ido Perlman

54 11:15
Identification of a Novel Gene Involved in Syndromic Retinitis Pigmentosa
Tamar Ben-Yosef (1), Elana Chervinsky (2), Yasmin Tatour (1)
(1) Rappaport Faculty of Medicine, Technion, Haifa, (2) The Genetic Institute, Emek Medical Center, Afula
p. 90

55 11:22 AC
The Genetics of Inherited Retinal Dystrophies in the Palestinian Population
Alaa AlTalbishi (1,2), Yahia AlSweity (1), Fathiya Abu Turky (2), Prasanthi Namburi (2), Frans Cremers (3), Muhammad Imran Khan (3), Eyal Banin (2), Dror Sharon (2)
(1) St John Eye hospital, Jerusalem, (2) Hadassah-Hebrew University Medical Center, Jerusalem, (3) Department of Human Genetics, Radboud University Nijmegen Medical Center, the Netherlands
p. 91

56 11:29 AC
EYS Mutations can be Associated with Widespread Retinal Degeneration with Early Macular Involvement
Gilad Allon (1,2), Shiri Zayit-Soudry (2), Dror Sharon (3), Hamzah Aweidah (3), Eyal Banin (3), Tamar Ben-Yosef (1)
(1) Rappaport Faculty of Medicine, Technion, Haifa, (2) Department of Ophthalmology, Rambam Health Care Campus, Haifa, (3) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem
p. 92

57 11:36 AC
Two Different novel *EYS* Mutations Cause Retinitis Pigmentosa in a Single Bedouin Kindred
Ohad Wormser (1), Libe Gradstein (2), Soltan Khalaila (2), Lena Mashkit (3), Khalil Elbedour (3), Barak Markus (4), Jaime Levy (2), Tova Lifshitz (2), Ohad S. Birk (1,3)
(1) The Morris Kahn Laboratory of Human Genetics, Ben-Gurion University, (2) Department of Ophthalmology and (3) Genetics Institute, Soroka Medical Center and Clalit Health Services, Faculty of Health Sciences, Ben-Gurion University, Beer Sheva, (4) Weizmann Institute of Science, Rehovot
p. 93

58 **Carrier Frequency Analysis of Mutations Causing Recessive Inherited Retinal Diseases in the Israeli Population**

11:43

AC

Mor Hanany (1), Gilad Allon (2,3), Adva Kimchi (1), Anat Blumenfeld (1), Eyal Banin (1), Tamar Ben Yosef (2), Dror Sharon (1)
(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (2) Rappaport Faculty of Medicine, Technion, Haifa, (3) Department of Ophthalmology, Rambam Health Care Campus, Haifa

p. 94

11:50 **Discussion**

Awards and ISVER update

12:00 - 12:30

Guest lecture 1– Prof. Alon Wolf

Director, Biorobotics and Biomechanics Lab (BRML); Faculty of Mechanical Engineering; Technion Israel Institute of Technology

12:30 - 13:00

On the effect of altering foot center of pressure on lower limb Biomechanics and clinical applications

Lunch

13:00 - 14:00

Guest lecture 2– Prof. Alon Wolf

Director, Biorobotics and Biomechanics Lab (BRML); Faculty of Mechanical Engineering; Technion Israel Institute of Technology

14:00 - 14:30

Human Machine Merger: Are we headed for the MMATRIX?

Glaucoma (at Rayman Center)

14:30 - 15:30

Moderators: Hani Levkovitch-Verbin and Orna Geyer

59 14:30
The Microarchitecture of Schlemm's Canal Before and After Selective Laser Trabeculoplasty
Alon Skaat (1), Sung Chul Park (2), Jeffrey M. Liebmann (3)
(1) Goldschleger Eye Institute, Sheba Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (2) Department of Ophthalmology, Manhattan Eye, Ear and Throat Hospital, New York, NY, USA, (3) Harkness Eye Institute, Columbia University Medical Center, New York, NY, USA
p. 95

60 14:37 AC
Intra Ocular Injection of Plastic Microspheres Induces Glaucoma in Mice
Amir Sternfeld (1), Yaniv Barkana, Ron Ofri (2), Tamar Azrad-Leibovitch (3), Moran Friedman (3), Nitza Goldenberg-Cohen (3,4,5)
(1) Departments of Ophthalmology, Rabin Medical Center – Beilinson Hospital, Petach-Tikva, (2) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, (3) The Krieger Eye Research Laboratory Felsenstein Medical Research Center, Petach-Tikva, (4) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (5) Department of Ophthalmology, Bnai Zion Medical Center, Haifa
p. 96

61 14:44 AC
High Intensity Focused Ultrasound (Hifu) as a Novel Treatment for Moderate-Advanced Glaucoma Patients
Ari Leshno, Alon Skaat, Shlomo Melamed
The Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer
p. 97

62 14:51 AC
Visual Field Testing, 15 Year Trends in a Large Health Maintenance Organization
Elad Ben-Artsi (1), Modi Goldenfeld (1), Asaf Cohen (2), Avi Porath (2), Hani Levkovitch-Verbin (1)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, (2) Maccabi Healthcare Services
p. 98

63 14:58 **Measuring Contrast Sensitivity with SPARCS in Specific Areas of Vision – A Meaningful Way to Assess Quality of Life and Ability to Perform Daily Activities in Glaucoma Patients**

Michael Waisbourd (1,2), Priyanka Gogte (2), Hamoon Eshraghi (2), Daniel Lee (2), Remy S. Manzi (2), Sheryl S Wizov (2), Lisa A. Hark (2), George L. Spaeth (2)
(1) Tel-Aviv Medical Center, Tel-Aviv, Israel (2) Wills Eye Hospital, Philadelphia, PA, USA

p. 99

64 15:05 **Philadelphia Telemedicine Glaucoma Detection and Follow-up Study: Methodology and Year 1 Results**

Michael Waisbourd (1,2,5), Lisa A. Hark (2,5), L. Jay Katz (2,5), Deiana Johnson (2), Laura Pizzi (4), Thien Dan V. Bui (5), Jane Lee (6), Jonathan S. Myers, (2,5), Benjamin E. Leiby (6), Scott J. Fudemberg, (2,5) Anand V. Mantravadi (2,5), Jeffrey Henderer (7), Jeanne Molineaux (2), Arthur Resende (2), Archana Srinivasan (3), Shae Reber (3), Anna P. Murchison (2,5), Julia A. Haller (2,5)
(1) Tel-Aviv Medical Center, Tel-Aviv, Israel, (2) Wills Eye Hospital, Glaucoma Research Center, Philadelphia, USA, (3) Wills Eye Hospital, Department of Telemedicine, Philadelphia, USA, (4) Thomas Jefferson University School of Pharmacy, Philadelphia, USA, (5) Sidney Kimmel Medical College, Thomas Jefferson University Philadelphia, USA, (6) Thomas Jefferson University Division of Biostatistics, Philadelphia, USA, (7) Temple University School of Medicine, Department of Ophthalmology, Philadelphia, USA

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15:12 **Discussion**

Visual function (at Rayman East)

14:30 - 15:30

Moderators: Ariela Gordon-Shaag and Yoram Gutfreund

65 14:30 **Comparison Between the amounts of Accommodation Activated by Printed Text vs. Text Displayed on a Computer Screen**

Hadas Eichenstein, Avigail Hazut, Mayan Zarbiv, Bat Sheva Bernstein, Einat Shneor
Hadassah Academic College, Jerusalem

p. 101

66 14:37 AC

Association of Myopia with Cognitive Function among One Million Israeli Adolescents

Jacob Megreli (1,2,4), Adiel Barak (2,3), Dana Bez (1,4), Hagai Levine (4)
(1) Tzameret Military Medical Program, Hebrew University-Hadassah Medical School, Jerusalem, (2) Tel Aviv Sourasky Medical Center, (3) Sackler Faculty of Medicine, Tel Aviv University, (4) Hebrew University-Hadassah Braun School of Public and Community Medicine, Jerusalem

p. 102

67 14:44

Head-Mounted Projection System for Visual Stimulation and Cortical Recordings as a Novel Method for Studying Natural and Artificial Vision in Behaving Animals

Tamar Arens-Arad, Nairouz Farah, Zeev Zalevsky, Yossi Mandel
Faculty of life Sciences, Optometry Track and Bar-Ilan Institute for nanotechnology and Advanced Materials (BINA), Bar-Ilan University, Ramat-Gan, Faculty of Engineering, Bar Ilan University, Ramat Gan

p. 103

68 14:51 AC

Perceptual Grouping of Moving items in the Barn Owl (*Tyto alba*) - Behavioral and Neural Study

Tidhar Lev-Ari, Yael Zahar, Yoram Gutfreund
Department of Neuroscience, The Ruth and Bruce Rappaport Faculty of Medicine and Research Institute, Technion, Haifa

p. 104

69 14:58

Binocular Summation and the Correlation Between Spatial and Temporal Visual Functions in Normal and Amblyopic Subjects

Auria Eisen (1), Nairouz Farah (1), Zvia Burgansky-Eliash (2), Uri Polat (1), Yossi Mandel (1)
(1) Faculty of life Sciences, Optometry Track, Bar-Ilan University, Ramat-Gan, (2) E. Wolfson Medical Center, Holon

p. 105

70 15:05 **Chromatic Multifocal Pupillometer for Objective Diagnosis of Neurodegeneration in the Eye and the Brain**

AC

Daniel Ben Ner (1,2), Ifat Sher (1), Maya Gurevich (1,2), Ron Chibel (1,2), Mohamad Mahajna (1,2), Alon Skaat (1,2), Zachary Weinerman (1,2), Anat Achiron (2,3), Inbal Sharvit-Ginon (4,5), Ramit Ravona-Springer (4), Michal Beeri (4), Eran Pras (2,6), Hadas Newman (2,7), Jaime Levy (8), Samer Khateb (9), Eyal Banin (9), Dror Sharon (9), Ygal Rotenstreich (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, (4) Sagol Neuroscience Center, Sheba Medical Center, Tel Aviv University, (5) Department of Psychology, Bar Ilan University, Ramat-Gan, (6) The Matlow's Ophthalmo-Genetics Laboratory, Department of Ophthalmology, Assaf-Harofeh Medical Center, Zerifin, (7) Ophthalmology Department, Tel Aviv Sourasky Medical Center, (8) Department of Ophthalmology, Soroka University Medical Center, Ben Gurion University of the Negev, Beer Sheva, (9) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

p. 106

71 15:19 **A Method for Rapid Objective Strabismus Angle Measurement**

AC

Oren Yehezkel (1), Abraham Spierer (2), Dan Oz (1), Ran Yam (1), Michael Belkin (3)
(1) Novasight Ltd, Airport city, (2) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (3) Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer

p. 107

15:26 **Discussion**

Coffee and Exhibition 15:30 -16:00

Oncology

16:00 - 16:30

Moderators: Shahar Frenkel and Mordechai Rosner

72 16:00 AC **Use of Sonic Hedgehog Pathway Gene expression to predict Response to Vismodegib in Advanced BCC of Eyelid**

Amir Sternfeld (1), Gur Ben-Yehuda (2), Iftach Yassur (1), Gil Tauber (3), Yoav Vardizer (4), Dean Adel (2), Nitza Goldenberg-Cohen (4,5)
(1) Department of Ophthalmology, Rabin Medical Center – Beilinson Hospital, Petach-Tikva, (2) Department of Plastic, Rabin Medical Center – Beilinson Hospital, Petach-Tikva, (3) Department of Dermatology, Rabin Medical Center – Beilinson Hospital, Petach-Tikva, (4) Department of Ophthalmology, Bnai Zion Medical Center, Haifa, (5) The Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Petach-Tikva

p. 108

73 16:07 **Ntravitreal Chemotherapy for Treating Vitreoretinal Lymphoma – 20 Years Experience**

Jacob Pe'er, Ron Kaufman, Shahar Frenkel
Hadassah-Hebrew University Medical Center, Jerusalem

p. 109

74 16:14 **Leaky Choroidal Nevi: A Clinical, Imaging and Therapeutic Analysis**

Shahar Frenkel, Gustavo A. Gutierrez-Vargas, Jacob Pe'er
Department of Ophthalmology, Hadassah-Hebrew University Hospital, Jerusalem

p. 110

75 16:21 **The Mechanism of the Toxicity of Intravitreal Carboplatin Injection in a Rabbit Model**

p. 111

Vicktoria Vishnevskia-Dai (1,4), Ofira Zloto (1,4), Dana Loberman (1,4), Ido Didi Fabian (1,4), Lea Twito (2,4), Ifat Sher (2,4), Ygal Rotenstreich (2,4), Arieh Solomon (4), Hani Verbin Lekovitz (3,4), Mordechai Rosner (1,4)
(1) Ocular Oncology research laboratory, (2) Retinal research laboratory, (3) Glaucoma research laboratoy, (4) Goldschleger Eye Research Institute Tel Aviv University Tel Hashomer

16:28 **Discussion**

AMD

16:30 - 17:00

Moderators: Itay Chowers and Ayala Pollack

76 16:30 AC

Genome Wide Association Analysis for Sub Retinal Drusenoid Deposits

Gala Beykin*, Michelle Grunin*, Shira Hagbi-Levi, Batya Rinsky, Sarah Elbaz-Hayoun, Itay Chowers
* equal contribution
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

p. 112

77 16:37 AC

The Association of Demographic Factors with Visual Acuity of Neovascular Age-Related Degeneration under anti-VEGF Therapy

Gala Beykin, Edward Averbukh, Diego Almeida, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

p. 113

78 16:44 AC

Whole-Genome Association Study of Age-Related Macular Degeneration in the Israeli Population

Michelle Grunin (1), Gala Beykin (1), Elior Rahmani (2), Regev Schweiger (2), Liran Tiosano (1), Samer Khateb (1), Shira Hagbi-Levi (1), Batya Rinsky (1), Shai Carmi (3), Eran Halperin (4), Itay Chowers (1)
(1) Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (2) Molecular Microbiology and Biotechnology, Tel-Aviv University, (3) Public Health, Hadassah-Hebrew University Medical Center, Jerusalem, (4) Computer Science and Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, CA, USA

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79 16:51 **Phase I/IIa Clinical Trial of Human Embryonic Stem Cell (hESC)-Derived Retinal Pigmented Epithelium (RPE, OpRegen®) Transplantation in Advanced Dry Form Age-Related Macular Degeneration (AMD): Interim Results**

Eyal Banin (1), Yitzchak Hemo (1), Tareq Jaouni (1), Devora Marks Ohana (1), Shelly Stika (1), Svetlana Zheleznykov (1), Alexey Obolensky (1), Maria Gurevich (2), Charles S. Irving (2), Benjamin Reubinoff (3)
(1) CRMD, Department of Ophthalmology, and (3) Center for Embryonic Stem Cells and the Department of Gynecology and Obstetrics, Hadassah-Hebrew University Medical Center, Jerusalem. (2) Cell Cure Neurosciences Ltd, Jerusalem

p. 115

16:58 **Discussion**

Concluding Remarks 17:00 - 17:05

Dror Sharon

תקצירים

Abstracts

Differentiation of Human Embryonic Stem cells into Photoreceptor Precursors – In-Vitro and In-Vivo Study

Amos Markus (1), Yoav Chemla (1), Astar Shamul (1), Nairouz Farah (1), Ronald S. Goldstein (1), Yossi Mandel (1,2)

(1) Mina and Everard Goodman Faculty of Life Sciences, (2) Optometry and Visual Science, Faculty of Life Science. Bar-Ilan University, Ramat-Gan

Purpose: Several protocols for the generation of photoreceptors with variable efficacy have been published recently. Herein, we compare the efficacy of and optimize two photoreceptor differentiation protocols. In addition, we explore various strategies for cell labeling for in-vivo studies.

Methods: Human embryonic stem cells (hESC line H9) were differentiated into photoreceptor precursors using two protocols. In the first protocol, differentiation was induced by a combination of Dkk1, Noggin and IGF1 (DKK1 protocol); while the second protocol used different combinations of molecules: eIWR 1, SAG, CHIR 99021 (eRIW1 protocol). In both protocols sized-controlled spheres were generated using agarose microwell dishe. Differentiation was characterized by mRNA expression (CRX, NRL, VSX2, PAX6), immunostaining and FACS analysis (CRX). Two different strategies for cell labeling for in-vivo imaging, at two different stages of the protocols, were explored. The first was transduction of cells with GFP-expressing AAV of multiple serotypes, transfection efficiency was determined by FACS. The second strategy, was to differentiate hESC constitutively-expressing GFP to photoreceptor precursors. The differentiated cells were injected into the subretinal space of Long-Evans rats (100,000 cells/5 µl) and tracked by a rodent imaging fluorescence camera over a month.

Results: FACS analysis revealed that over 80% of the cells were positive for CRX in both differentiation protocols. NRL and CRX expression levels were similar for both protocols although the expression of the early markers, VSX2 and PAX6 was higher for the DKK1 protocol. Notwithstanding, the CRX fluorescent intensity in FACS of DKK1 induced cells appeared less intense. in the cell labelling experiments, AAV2 was the only serotype that efficiently infected the cells. About 70% of the transplanted cells' fluorescence was detected by fluorescent imaging 4 weeks post sub-retinal transplantation.

Conclusions: This study is progress on the important goals of photoreceptor precursor generation and in vivo detection for transplantation. Further studies will evaluate the cell integration and synapse formation with the host retina.

Incorporation and Survival of Retinal Progenitors Derived from Human Embryonic Stem Cells in Rodent Eyes

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Purpose: Cell therapy is considered a potential therapeutic approach that may delay, halt or reverse retinal degeneration. In this study we evaluated the ability of Human Embryonic Stem Cells (hESCs) to give rise to retinal progenitor cells *in-vitro*, and examined their survival and fate *in-vivo* following subretinal transplantation into rodent eyes.

Methods: GFP expressing hESCs were grown and expanded *in vitro* with a combination of nicotinamide, basic fibroblast growth factor and CHIR for 4-5 weeks. Between 1-2ul of progenitor cells at a concentration of 75,000 cells/ul were injected transsclerally into the subretinal space of either RCS rats or immune-deficient NSG mice. Survival of engrafted cells was verified *in vivo* by fundus imaging using Spectralis OCT and a Micron III Retinal Microscope equipped for GFP visualization. Survival, differentiation and integration of transplanted cells were then evaluated by histology and immunohistochemistry.

Results: GFP-filtered fundoscopy revealed strong green fluorescence in treated areas of transplanted eyes. In some eyes, GFP+ fibers emanating from the transplanted regions towards the optic disc were observed. Formation of subretinal grafts was confirmed *in vivo* by OCT. Histologically, GFP+ grafts were found in treated eyes. 1 month post-injection, the majority of cells in subretinal grafts expressed the photoreceptor-specific marker Rhodopsin. At 7 weeks, subretinal cells began to express Recoverin and Synapsin. Engrafted cells were also observed in the inner retinal layers, where their morphology differed: GFP+ cells in the ganglion cell layer extended neurites towards the optic nerve, and other cells in the inner retina demonstrated morphology typical for the layer in which they were located. In RCS rats, in-vivo GFP expression attenuated over time and was lost all together 7-8 weeks post injection. Histologically, human-derived cells were no longer present at this time, and CD3 staining showed infiltration by host T-cells in the treated regions, suggesting rejection of the grafts. To explore the survival of the retinal progenitors on an immune-deficient background, transplantation in NSG mice were performed. Following intraocular transplantation, cells survived and were present in intraviteal and subretinal grafts up to 11 week post-injection.

Conclusions: hESCs can give rise to retinal progenitors *in-vitro* which demonstrate expression of photoreceptor-specific markers. Following subretinal transplantation, the cells survived 7-8 weeks in RCS rats and for 11 weeks in NSG mice. Transplanted cells demonstrate morphology and markers that correlate with the retinal layer in which they integrate.

Retinal Transfection Efficacy of a Capsid Mutant Adeno-Associated Virus [AAV2-quad(Y-F)+T491V] Following Subretinal and Intravitreal Injection in Sheep

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Purpose: Recently we reported that subretinal delivery of an AAV5 vector carrying the CNGA3 gene results in long-term recovery of photopic vision in CNGA3-mutant day blind sheep. However, subretinal injections can cause severe complications, require anesthesia, limit the area of retina that can be treated and require advanced surgical techniques and a specialized operating room. Intravitreal delivery of the vector would overcome most of these disadvantages.
The aim of the current study was to evaluate whether AAV2-quad(Y-F)+T491V vector carrying a GFP fluorescent marker under the control of a red/green opsin promoter can transfect cone photoreceptors following subretinal and intravitreal injections.

Methods: Viral vectors carrying GFP were injected in five eyes of three normal sheep. The vector was delivered subretinally in two eyes, epiretinally (using a subretinal cannula) in two more eyes, and intravitreally using a 30G needle in the fifth eye. GFP expression was evaluated *in vivo* by serial fundus photography with fluorescein angiography lens every three weeks. Eleven weeks post-surgery the sheep were sacrificed and GFP expression was evaluated by immunohistochemistry.

Results: Imaging of the two eyes injected subretinally revealed detectable GFP expression three weeks post-treatment in one eye, and six weeks post-treatment in the second eye. GFP expression seemed to be confined to the area of the bleb formed during surgery. The eyes injected epiretinally and intravitreally did not show evidence of GFP expression throughout the duration of follow up. Immunohistochemistry revealed high GFP expression in two subretinally-injected eyes, but not in eyes treated with epiretinal or intravitreal injections.

Conclusions: AAV2-quad(Y-F)+T491V shows high transfection efficacy following subretinal delivery. However, epiretinal and intravitreal injections did not result in GFP expression in the retina. It is possible that in these eyes the vector was neutralized by the ocular immune system, or was unable to penetrate the retina and reach the photoreceptors.

Mobility and Tropism of Adeno - Associated Virus (AAV) Injected Subretinally or Intravitreally in Mice

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Purpose: Recently our group reported successful gene insertion, protein expression and functional improvement of photopic function in CNGA3-deficient day blind sheep treated with subretinal injections of an AAV5 vector carrying CNGA3 under red/green promoter control (Banin *et al*, 2015).

The purposes of the present study were to investigate the nature of AAV5 mobility and tropism, and to determine whether the route and site of injection can influence the migration of the virus in the eye and in other organs.

Methods: Five mice were injected subretinally with Adeno virus and served as a control group. AAV5 was injected intravitreally (n=5) or subretinally in the peripheral (n=14) or central (n=5) sub-retinal space. All injections were performed unilaterally.

Both viruses carried a luciferase gene under control of the ubiquitous cytomegalovirus promoter. In vivo bioluminescent imaging of the entire body, including the eyes, was performed using an in vivo imaging system (IVIS) after a systemic injection of the enzyme's substrate, luciferine.

Results: Eleven days after injection, IVIS showed expression of luciferase in 4/5 of five Adeno injected eyes. Lucifrerase expression was also seen in all subretinally-injected, and 2/5 of invtravitreally-injected eyes, and remained positive for up to 28 weeks (n=3) post injection.
In animals in which luciferase was expressed, it was confined to the injected eye only and was not demonstrated in any other organ including optic nerve.

Conclusions: As gene therapy becomes a potential curative treatment for patients with inherited retinal diseases, questions regarding mobility and tropism of viral vectors, such as AAV5, within the mammalian host have important implications for the safety and long-term efficacy of this therapeutic modality. Our results demonstrate long-term expression that is confined to the eye, validating the safe nature of the vector.

A Novel Minimally Invasive Adjustable-Depth Blunt Injector for Delivery of Therapeutics into the Extravascular Spaces of the Choroid

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Purpose: To investigate the feasibility and safety of a novel minimally-invasive adjustable-depth blunt injector for pharmaceuticals and cell therapy delivery into the extravascular spaces of the choroid (EVSC).

Methods: An adjustable-depth blunt injector for delivery of therapeutics into the EVSC was developed. Two hundred and fifty microliters containing Indocyanine Green (ICG), sodium fluorescein, iron oxide nanoparticles (IONPs) or 15 million human bone marrow mesenchymal stem cells (hBMSCs) were injected into the EVSC of New Zealand rabbits using the novel injector, 3.5 mm posterior to the limbus. No immunosuppressants were used. Spectral Domain Optical Coherence Tomography (SD-OCT), fundus imaging, electroretinography (ERG) and histology analysis were performed for assessment of injection safety and efficacy.

Results: ICG, fluorescein, IONPs and stem cells were detected across the EVSC in rabbit eyes, covering over 80 percent of the posterior eye surface. Injected IONPs were retained in the EVSC for at least two weeks following injection. Stem cells were retained in the EVSC for 10 weeks following transplantation. No retinal detachment, choroidal hemorrhage or inflammation were detected in any of the injected eyes or contralateral control eyes. No reduction in retinal function was recorded by electroretinogram up to 10 week following cell transplantation.

Conclusions: This novel minimally invasive delivery system may be used to safely inject large volumes of pharmaceuticals and cell therapies into the EVSC from the same location used for intravitreal injections. Therapeutics are introduced into a new treatment reservoir compartment -the EVSC which can serve as a depot, in close proximity to the retinal pigment epithelium (RPE), throughout the surface of the RPE. This system is predicted to enhance the therapeutic effects of treatments for posterior eye disorders. Furthermore, this study demonstrates the safety of hBMSC transplantation in the EVSC compartment and is expected to directly lead to phase I/II clinical trials for hBM-MSC transplantation in retinal degeneration patients.

Active Sensing for Enhancement of Reading Capabilities in Prosthetic Vision

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Purpose: Current retinal prostheses offer a promising solution to people with retinal degenerative diseases. Notwithstanding, the obtained visual acuity is still severely limited for various reasons. In this work, we studied the enhancement of simulated prosthetic reading through "active sensing".

Methods: To simulate prosthetic vision we converted images to low resolution gray-level images (2 bit), where the pixels' intensities are represented by Gaussian phosphenes. To investigate reading capabilities, various phosphenes pixilated word images were displayed at different phosphene densities (0.75-2 cycles per degree (CPD)) and contrasts to young healthy subjects (N=11) with normal vision. The size of the characters was set to the font size matching 1.6 degrees of the letter 'x'. We investigated the effect of both passive and active sensing on reading performance. To implement an "active sensing" modality, we enabled the subject to actively scan words presented on a computer monitor using the mouse with an additional option to zoom and control letter size, while passive scanning was produced by horizontal movements of words at 1/8 phosphene size or 0.2-0.5 degrees (corresponding to 0.75-2 CPD). We measured recognition rates and reading speed for various phosphene densities and contrasts with active sensing, passive scanning or no scanning. In addition, we analyzed the scanning path.

Results: Reading accuracy increased with increasing contrast and phosphene density, reaching a plateau at CPDs higher than 1.25. Reading accuracy was increased by a factor of up to 1.3 with active scanning as compared to no scanning or passive scanning; the effect was most significant at pixel densities between 0.8 to 1 CPD. Moreover, zooming significantly enhanced recognition rate by a factor of up to 14. Interestingly, in the same set of investigations the reading speed was not affected. Scanning path analysis revealed characteristic horizontal and axial movements at an average amplitude of 3 and 1.5 degrees respectively.

Conclusions: We have shown that active scanning increases reading performances in simulated prosthetic vision. These results highlight the importance of an interactive interface with patients and shed light on techniques that can greatly enhance the quality of prosthetic vision.

MetAp2 inhibition for the treatment of AMD

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Purpose: The gold standard of therapy for "wet" Age-related Macular Degeneration (AMD) includes almost exclusively anti-VEGF (vascular endothelial growth factor) drugs, however, VEGF is only one amongst several other critical effectors of angiogenesis. Our research goal was to validate a molecular target, Methionine Aminopeptidase 2 (MetAp2) as a downstream target to VEGF and develop novel therapy based on slow release formulation for inhibiting ocular neovascularization.

Methods: Biodegradable nanoparticles were loaded with MetAp2 to obtain a stable slow-release treatment for AMD. Biological efficacy was demonstrated in different in vitro and in vivo angiogenesis assays as well as the laser induced Choroidal Neovascularization (CNV).

Results: Nanoparticle loaded with MetAp2 inhibitor was characterized. In the laser induced CNV experiments performed in C57/Bl mice (10 mice per group) we detected between 30-45% inhibition in vessel area using oral administration or intravitreal injections. Fluorescein Angiography showed significant reduction in vessel permeability (6 mice per group). Importantly, the treatment led to regression of CNV lesions and not only growth arrest as with anti-VEGF therapy (5 mice per group).

Conclusions: MetAp2 is a valid target for CNV therapy and its inhibition leads to broad spectrum anti-angiogenic effect in the retina.

Protective Effect of Intravitreal Administration of Exosomes derived from Mesenchymal Stem Cells on Retinal Ischemia

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Purpose: Exosomes are small intracellular vesicles, which contain and transport a variety of proteins and RNAs from their cell of origin to neighboring cells. Exosomes derived from human mesenchymal stem cells (hMSCs) cultured under hypoxic conditions contain proteins and growth-factors that promote angiogenesis. This study investigated the effect of intravitreal administration of these exosomes on retinal ischemia using a murine model.

Methods: Oxygen-induced-retinopathy (OIR) was induced by exposing one-week-old male C57BL/6J mice to 5 days of 75% hyperoxic conditioning, and then returned to room air. After hyperoxic conditioning (at 12 days of age), the right eye of each mouse was injected intravitreally with saline (Group 1) or exosomes derived from hMSCs (Group 2) and compared to control mice of the same age raised in room air (no OIR) and injected intravitreally with saline (Group 3). Two weeks post-injection, fluorescein angiography (FA) and phase variance optical coherence tomography angiography (pvOCTA) were used to assess retinal perfusion. Retinal thickness was determined by OCT. The eyes were harvested after euthanasia for histologic analysis. The extent of retinal neovascularization was quantitated histologically by counting vascular nuclei on the retinal surface as a measure of retinal ischemia.

Results: Exosomes derived from hMSCs induced vascular preservation in a mouse model of OIR, as determined in vivo by FA and pvOCTA. Retinal thickness was reduced in OIR eyes when compared to eyes without OIR; exosome treatment partially preserved retinal thinning in OIR eyes (111.1±7.4 μm in Group 1; 132.1±11.6 μm in Group 2; $p<0.001$). Histological analysis demonstrated reduced neovascularization in OIR eyes treated with exosomes when compared to saline-treated OIR eyes (7.75±3.68 neovascular nuclei per section in Group 1; 2.68±1.35 neovascular nuclei per section in Group 2, $p<0.001$). No immunogenicity was detected and no ocular/systemic adverse effects were noted during the follow-up.

Conclusions: Intravitreal injection of exosomes derived from hMSCs was well tolerated without immunosuppression and decreased the severity of retinal ischemia in this murine model. This is the first study using intravitreal administration of exosomes in ophthalmology, an appealing novel non-cellular therapeutic approach warrants further exploration.

Characterization of Human Nonpigmented Ciliary Epithelium-Derived Exosomal miRNAs by Microarray Analysis

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Purpose: Exosomes are Nano-sized vesicles secreted from *different cell* types into the extracellular space. Exosomes from various cell sources contain both mRNAs and miRNAs that could be *transferred to target cells*. miRNAs have been discovered in aqueous humor *(AH)* and seem to have unique functions in the eye, which poorly understood. Our goal is to determine whether exosomal RNA could play a role in the signaling communication between Human Nonpigmented Ciliary Epithelium (NPCE) and the Trabecular Meshwork (TM) cells.

Methods: Exosomes were isolated from NPCE cell culture *media* through ultracentrifugation and characterized by TRPS method and exosome-specific surface markers. Exosomal RNAs were extracted and profiled using microarray technology. To determine the uptake of the NPCE RNA by TM cells, NPCE derived exosomes were red fluorescent RNA dye labelled and added to TM cells.

Results: The NPCE cell derived exosomes were mostly 100±10 nm in diameter as measured by TRPS with typical exosomal surface markers. We identified approximately 584 miRNAs per sample. Many of the miRNAs detected by the microarray analysis were previously found in human AH. Over one third of the most prevalent miRNA detected in AH were also presented in exosomes. Several of the miRNAs identified in NPCE exosomes samples have been previously described to regulate some pathways which are important in IOP control and glaucoma, such as the PI3K-AKT, Wnt signaling, focal adhesion-dependent cell-matrix interactions, the mTOR and TGF-β pathways. Furthermore, Image Stream Flow Cytometry experiments revealed that exosomes have the capacity to transfer their RNA to TM cells.

Conclusions: In this study, we showed that exosomes from NPCE cell line contain RNA that could be delivered to TM cells. Profiling of the exosomal miRNAs of NPCE cells provided new insights into the characteristics of miRNAs in NPCE derived exosomes. Exosomal miRNAs may mediate the communication between AH inflow and outflow tissues and modulate the intraocular pressure in *glaucoma disease*.

Bi-Modal Effect of Exosomes Dose Response in NPCE-TM communication in the Ocular Drainage System

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Purpose: Exosomes are small membranous vesicles, 30-120nm in diameter, secreted by most cell types in culture, carrying mainly mRNA, miRNA and proteins. These native biological nanoparticles are found in several biological fluids and also in aqueous humor (AH). Exosomes physiological functions include intercellular communication between the exosome-producing cells and target cells. The role of exosomes in the ocular drainage system in health and glaucoma disease remains obscure. Hence, the understanding of the exosomal pathway and its role in IOP control may reveal therapeutic targets for treatment of ocular hypertension and glaucoma. Our purpose is To investigate the effect of various exosomes concentrations from non-pigmented-ciliary-epithelium cells (NPCE) on the expression of signaling molecules participating in the communication between NPCE and Trabecular-meshwork cells (TM), via the ocular AH, by tracking the Wnt-AKT-TGFβ2 signaling pathway in TM cells. Retinal-pigment-epithelium (RPE) derived exosomes were used as control.

Methods: Exosomes were isolated by PEG 8,000 method from NPCE and RPE cells conditioned media. Concentrations were determined by TRPS method. Various exosomes concentrations were incubated with TM cells. mRNA (β-Catenin, Axin2 and LEF1) and protein (β-Catenin, GSK-3β) expression were determined using Western blot and real-time quantitative PCR respectively.

Results: Exposure of confluent TM cells for 8h to various concentrations of exosomes, lead to significant changes in the expression of the measured proteins. Exposure to low exosome concentration was associated with decreased expression of β-Catenin, GSK-3β, as compared to exposure to high exosomal concentrations ($p < 0.01$). When exosomes were incubated with TM cells for 2h, a tendency of decrease was found in β-catenin, Axin2 and LEF1 mRNA levels in low concentrations of exosomes compared to high ones.

Conclusions: Our findings suggest that exosomes concentration plays a major role in the NPCE-TM communication in-vitro. Furthermore, a bimodal TM response to exosome concentration exposure was found.

Possible Involvement of NETosis in Infectious and Inflammatory Processes in the Eye; Evidence from a Small Cohort of Patients

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Purpose: To evaluate whether NETosis is involved in infectious and inflammatory processes in the eye and track NET-complexes in patients with proliferative diabetic retinopathy (PDR).

Methods: Animal model; Eyes of C57BL/6J mice were intravitreally injected with lipopolysaccharide (LPS), Interleukin 8 (IL-8) , Tumor Necrosis Factor α (TNFα) or saline. Histology and immunofluorescence staining for CD11b, neutrophil elastase (NE), myeloperoxidase (MPO) and citrullinated histone 3 (H3Cit) were performed. Human subjects: Vitreous samples were collected from patients with PDR and divided to mild (PDR1) and severe (PDR2) according to the severity of the disease and compared to control samples. Levels of MPO, H3Cit-MPO and NE-MPO complex were measured by ELISA.

Results: Massive influx of CD11+ inflammatory cells, involving both the anterior and posterior chambers, was observed in the murine eyes 24 hours post LPS, IL-8 or TNFα injections. Cells excreted to their surroundings an extracellular net-like structure positive for NE, MPO and H3Cit. H3Cit staining was abolished by DNase I treatment, indicating presence of extracellular DNA in the net-like structures. PDR2 patients' vitreous samples contained significantly higher levels of MPO (173±230) as compared to PDR1 (12 ±33, $p<0.05$) or controls (0, $p<0.01$). The levels of H3Cit-MPO and NE-MPO complexes were also significantly higher in PDR2 patients (776±1274, 573±911, respectively) compared to PDR1 (0, $p<0.05$) and controls (0, $p<0.05$).

Conclusions: Our study illustrates existence of NETosis in cytokine - induced ocular inflammation in a mouse model and human samples. Furthermore, the extent of NET complex formation was higher in a subset of patients exhibiting more complicated PDR.

Transcription Factors of the RPE Play a Role in Choroid Vascularization

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Purpose: Haploinsufficiency of Pax6 leads to a pan-ocular syndrome termed aniridia. Neovascularization of the cornea and choroid has been reported in patients with aniridia, yet Pax6 involvement in this pathogenesis remained elusive. Somatic mutagenesis of Pax6 in the specified retinal pigmented epithelium (RPE) resulted in a phenotype of aniridia and further transcriptomic analysis revealed an up-regulation in Sox9, a factor related to late stages of RPE differentiation. Both Pax6 and Sox9 are key transcription factors (TF) in organogenesis, however their regulatory interaction and influence on angiogenesis are yet to be determined.

Methods: To this purpose, conditional mutations are induced in mice and quantitative expression levels are measured in situ using the novel method of single molecule FISH (smFISH). The choroidal phenotype is analyzed using a tool we developed which uses a BDT machine learning algorithm and automatically classifies between arteries and veins and the choriocapillaries following cardiac perfusions of the mice with Albumin conjugated to FITC.

Results: To this purpose, conditional mutations are induced in mice and quantitative expression levels are measured in situ using the novel method of single molecule FISH (smFISH). The choroidal phenotype is analyzed using a tool we developed which uses a BDT machine learning algorithm and automatically classifies between arteries and veins and the choriocapillaries following cardiac perfusions of the mice with Albumin conjugated to FITC.

Conclusions: This is the first time a specific TF is shown to play a role in the common pathology of choroidal neovascularization. Moreover, this Study demonstrates regulatory relation between two master regulators of the RPE. This regulation dictates tissue maturation and thus may contribute to the highly studied field of developing differentiation protocols from stem cells to RPE cells for transplantations.

The Roles of Sip1 in Retinogenesis

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Purpose: The transcription factor Sip1 (Zeb2) plays multiple roles during the nervous system development from early acquisition of neural fate to cortical neurogenesis and gliogenesis. In humans, SIP1 (ZEB2) haploinsufficiency leads to Mowat-Wilson syndrome, a complex congenital anomaly characterized by intellectual disability, epilepsy and Hirschsprung disease. Several studies also link Sip1 to eye development and disease, yet its roles in retinal development were never studied before. In this work we uncover the role of Sip1 in retinogenesis.

Methods: To study the functions of Sip1 in the developing retina we employed Cre/loxP mutagenesis for somatic deletion of Sip1 in the embryonic retina. We determined changes in morphology, cell fate, cell-cycle dynamics, differentiation dynamics and cell survival by detection of gene and protein expression in situ. Chromatin immune-precipitation and Luciferase assay were used in order to identify direct transcriptional targets of Sip1.

Results: The expression of Sip1 is initially detected in retinal progenitor cells (RPC) and is later restricted to horizontal and subtypes of amacrine cells. Sip1 deletion from RPCs resulted in a delay in the generation of retinal interneurons leading to a reduction in their number and in retinal width. Chromatin immune-precipitation and luciferase assay experiments suggest that Sip1 supports the generation of amacrine and horizontal interneurons through activation of the transcription factor Ptf1a.

Conclusions: The study documents, for the first time, the dynamic expression pattern and temporal activities of Sip1 during mammalian retinogenesis and uncovers novel roles for Sip1 in the differentiation dynamics of retinal interneurons.

Roles for MicroRNAs in Retinal Pigmented Epithelium Development and Function

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Purpose: Dysfunction of the retinal pigmented epithelium (RPE) results in degeneration of photoreceptors and loss of vision and is correlated with common blinding disorders in humans. Although many protein-coding genes are known to be expressed in the RPE and to be important for its development and maintenance, virtually nothing is known about the in vivo roles of non-protein coding transcripts in The RPE.

Methods: Herein, through RPE specific conditional mutagenesis of Dicer1 or Dgcr8, the importance of miRNA for RPE differentiation was uncovered. To Analyze the phenotype we used histological staining, in-situ and antibody labeling. To uncover the transcriptomic phenotype the deferential expression of miRNA and mRNA in control and mutant RPEs was examined using microarray and validated with qPCR and antibody staining.

Results: Here we show that conditional Knock out (cKO) of miRNAs from the RPE, does not lead to trans-differentiation of the RPE. As the RPE preserves gross morphology and express key RPE markers. In addition, we do not see an effect on RPE cell survival. However, we did find that miRNAs are crucial for normal RPE development; 1) Cell size, we found that in cKO there is a 2 fold higher cell density. 2) Melanogenesis, We see a drastic reduction in pigmentation in the cKO 3) Function, we see dramatically reduced expression of the visual cycle genes. Interestingly, the depletion of miRNAs from the RPE prevented maturation of the adjacent, genotypically normal, photoreceptor. Specifically we show that miRNA of the RPE are required for normal outer segment morphogenesis and photoreceptor survival.

Conclusions: This study reveals specific miRNAs that are essential for maintaining the differentiation state, adhesive properties and physiology of the RPE cells and indicates that they play non-cell autonomous roles in RPE-retinal communication.

Proteome of Aqueous Humor from Patients with Age-related Macular Degeneration

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Purpose: Age related macular degeneration (AMD) is associated with marked altered gene and protein expression in the retina. We wished to assess the aqueous humor (AH) proteome in AMD patients as compared to age-matched controls in order to gain insight into the pathogenesis of the disease and identify potential biomarker for it.

Methods: AH was collected during cataract surgery from 10 neovascular AMD (nvAMD) patients (mean age 81.8±5.69, Female / Male =5/5) and 10 age-matched controls (mean age 78.3±6.22, Female/male =5/5). 10µl of AH was taken per sample and pooled together to create two samples (nvAMD and controls). Intensity-based label-free quantification (MS1) was then performed (Weizmann Institute of Science). Functional analysis was performed via DAVID 6.8. Proteins were classified to 6 functional groups and compared to random proteins known via $\chi 2$. A validation set was evaluated via multiplex ELISA for proteins that were differentially expressed in nvAMD. The validation set included 50 additional samples: 20 controls (mean age 74.8±7.14, Female/ Male=10/10), 15 atrophic AMD (aAMD) (mean age 77.3±10.47, Female/male==5/10) and 15 nvAMD (mean age 78.6±7.45, Femake/male=9/6).

Results: A total of 674 proteins were identified in AH by MS1 via appropriate filtering. 239 proteins were upregulated in nvAMD (nvAMD/Control>2, peptide tags>2), and 5 were expressed only in nvAMD. 86 proteins were upregulated in controls (nvAMD/Control<0.5, peptide tags>2). Functional analysis demonstrated enrichment for 6 group: platelet degranulation (enrichment score (ES): 28.1, GO:0002576), negative regulation of endopeptidase activity (ES:18.82 GO:0010951), cellular protein metabolic process (ES: 11.78, GO:0044267), Epidermal growth factor-like domain (ES: 10.34, IPR000742), Sushi/SCR/CCP (ES:10.14, IPR000436) and Complement and coagulation cascades (ES:9.16, hsa04610). AMD proteins expressed were upregulated for 3/6 protein clusters ($\chi 2<0.05$ compared to randomized data). Multiplex ELISA on the validation set for confirmed the MS1 results in 4/9 proteins tested ($p<0.05$).

Conclusions: Comparison between the AH proteomic profiles of AMD patients in different stages of the disease and controls provided insight to the pathogenesis of AMD. Several genes and functional classes show altered expression in AH from AMD patients. Further research should confirm if these proteins may serve as biomarkers of AMD.

Characterizing the Involvement of Macrophages in the Pathogenesis of Atrophic Age Macular Degeneration

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Purpose: Recent studies implicated macrophages in age-related macular degeneration (AMD) through both the atrophic (aAMD) and neovascular (nvAMD) stages. Here, we aim to investigate the effect of distinct subtypes of macrophages from AMD patients on photoreceptor cell survival, and their involvement in aAMD progression

Methods: Monocytes were isolated from AMD patients and polarized into four subtypes of macrophages: M0 (MCSF), M1 (LPS+IFN-ɣ), M2a (IL-13, IL-4), and M2c (IL-10). An in vivo model of photic retinal injury that recapitulates features of aAMD was established. To that end, albino mice (n=7) were exposed to 8000 lux of white light for 3 hours leading to photoreceptor degeneration and oxidative stress. Light-injured mice were injected intravitreally with each subtype of Dio stained macrophage, along with a PBS-injected contralateral eye as control. 7 days later, electroretinogram (ERG) analysis was recorded and outer nuclear layer (ONL) thickness was measured in order to evaluate visual function and photoreceptor survival in each group. We also developed an in vitro model, in which retinal explants from pigmented mice were incubated with each subtype of macrophages via a membrane for 16 hours. Afterwards, the retinal explants were evaluated for photoreceptor apoptosis using a TUNEL assay.

Results: Monocytes from 7 patients were evaluated (female=3, male=4, mean age=69.6). In the in vivo model of photic retinal injury, ERG results showed a mean reduction of 50% (p=0.02) of b-wave amplitudes in eyes injected with M2a macrophages as compared to control. Histological analysis revealed a trend towards ONL nuclei loss with a mean reduction of 40% (p=0.3) and 20% (p=0.3) in eyes injected with M2a and M1 macrophages, as compared to control, respectively. In the in vitro retinal explant model, M2a and M1 macrophages were associated with a mean photoreceptor cell death of 57 % (p=0.04) and 22 % (p=0.7) as compared to control, respectively

Conclusions: Among all types of macrophage phenotypes tested, the M2a macrophages showed a neurotoxic effect on photoreceptors in-vitro and in-vivo. Such an effect may potentially be involved in photoreceptor loss during aAMD progression. Further investigation as to the M2a phenotype and its effects on aAMD may lead to possible new avenues of treatment for the disease.

Pro-Angiogenic Mechanism of Activated Macrophages from Patients with Age-related Macular Degeneration

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Purpose: Monocytes/macrophages may exert a pro-angiogenic effect in the context of neovascular age-related macular degeneration (nvAMD). We have previously found a pro-angiogenic effect of polarized M(IFNγ and LPS) human macrophages from nvAMD patients as compared to age-matched controls. This effect was identified in-vivo in the rat model of laser-induced choroidal neovascularization (LI-CNV), with a correlation to the ex-vivo choroid sprouting assay (CSA) findings. We now aim to explore the mechanism which mediates the pro-angiogenic effect of the activated macrophages from nvAMD patients.

Methods: Monocytes were isolated from nvAMD patients and were differentiated into Mo, M(IFNγ and LPS), and M(IL-13+IL-4) macrophages. Protein levels of candidate cytokines for mediation of angiogenic effects were assessed in the macrophages' cell culture supernatants using ELISA. To assess the macrophages' pro-angiogenic mechanism, we performed CSA, initially with macrophages' supernatants, and then with the addition of candidate cytokines which were differentially secreted by the activated macrophages.

Results: A higher CSA sprouting area (SA) was identified following addition of media from M(IFNγ and LPS) cells as compared to non-treated wells (mean of ratios±SEM 3.62±0.52, P =0.0001; t-test; n=19). Mo and M(IL-13+IL-4) cells' supernatant had no effect on SA (1.57±0.34, p=0.11; n=19, and 1.55±0.5, p=0.28; n=14, respectively). TNFα (5.4-fold, p=0.0001), VEGFa (1.5-fold, p=0.007), and IL-6 (11.2-fold, p=0.0001) were up-regulated in the pro-angiogenic M(IFNγ and LPS) macrophage phenotype as compared to Mo. Cytokines at their levels in the M(IFNγ and LPS) culture media per ELISA, were added to the CSA culture. VEGFa (0.86±0.08, p=0.16; n=9), and IL1β (0.8±0.2, p=0.34; n=10) showed no effect on the SA as compared to control wells, while TNFα was associated with enlarged SA (1.6±0.2, p=0.01; n=8,), and IL-6 (0.64±0.1, p=0.01; n=9) and IL-8 (0.47±0.14, p=0.007; n=8) with decreased SA.

Conclusions: These data further supports the putative role of macrophages and their cytokine products in modulating CNV. It also suggests that factors other than VEGF may also mediate such a pro-angiogenic macrophage effect, while other cytokines may suppress CNV. Thus, targeting multiple cytokines simultaneously may potentially serve as a therapeutic strategy for the disease.

The Contribution of Patient's Derived Factors, Disease State, and Microenvironment to Macrophage Function in the Context of Age-Related Macular Degeneration (AMD)

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Purpose: Macrophages were implicated in the pathogenesis of AMD. Such macrophage pathogenic effect is the sum of the genetic and environmental factors that determine the cell's phenotype, as well as specific microenvironment that can modulate macrophage function and their response to treatment. Assessing the contribution of such factors in determining macrophage pathogenicity may provide important insights on the etiology of AMD, with potential relevance for personalized medicine applications.

Methods: Monocytes derived from nvAMD patients and controls were differentiated and activated into three macrophage subtypes: MO (M-CSF), M1 (M-CSF, LPS, IFNγ) and M2 (M-CSF, IL-13, IL-4) as part of a previous study. These activated macrophages were characterized in terms of their angiogenic properties in a rodent model of laser-induced choroidal neovascularization (LI-CNV) via assessment of the CNV area following isolectin staining in an unbiased fashion. For the purpose of the current research, these results were analyzed via a mixed design ANOVA model with repeated measures, using the statistical software R, to quantify factors which affect macrophage function.

Results: Variability of macrophage function in vivo (LI-CNV area) was assessed in 8 nvAMD patients and 9 aged matched controls. Overall, macrophage effect on LI-CNV area was explained by inter-subject factors (genetic, demographics, disease state, environment; 16.92% of the variance in the LI-CNV area), macrophages subtype (a lab manipulation that mimics the effect of microenvironment; 19.55%), and by the interaction of inter-subject and cell subtype (35.46%). These factors did not explain 28.05% of macrophage phenotype variation. Interestingly, the interaction of disease status (nvAMD vs. Age-matched-controls) and macrophage subtype explained 16% of LI-CNV area variation.

Conclusions: These findings suggest that inter-patient variability has a moderate but important contribution to macrophage function. The microenvironment may also affect macrophage function in context relevant to nvAMD. Thus, genetic and environmental factors may assist in predicting important characteristics of macrophage function and nvAMD progression, while to a large extent, manipulation of macrophage phenotype may affect their angiogenic function in a patient specific manner.

New Insight on the Autophagy Process as Key Therapeutic Target in Treating Dry Age Related Macular Denegation

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Purpose: Age-related macular degeneration (AMD) is a neurodegenerative disease characterized by loss or damage of photoreceptors and retinal pigment epithelium (RPE) cells, resulting in the accumulation of aggregate-prone proteins. Autophagy is a cellular mechanism that removes damaged organelles and protein, and has been implicated in process of degeneration, senescence and cellular death of RPE cells. Recently, several publications have suggested that autophagy might also be involved in the onset and progression of AMD. Mammalian target of rapamycin (mTOR) is a major negative regulatory axis of autophagy. Hence, direct inhibitors of mTOR, like Rapamycin, are known to induce autophagy. However, the effect of Rapamycin on the RPE cells was rarely investigated. Our study assessed the proliferation rate of RPE cells depending on Rapamycin concentration.

Methods: The effect of Rapamycin was examined in ARPE-19 cell line. Cells were treated with Rapamycin at three different concentrations: 50nM, 100nM and 150nM. The proliferation rate of RPE cells treated with rapamycin was determined by XTT analysis**.**

Results: We have found that increasing concentration of Rapamycin reduces the proliferation of RPE cells, reaching to about 20% of untreated cells with the 150nM Rapamycin three days after treatment.

Conclusions: In contrast to others publications, in this work Rapamycin did not prevent cells death. This work suggests that additional mechanism is activated at different concentrations of Rapamycin. So far Very little is known regarding the roles of the autophagy process during the onset and progression of dry AMD. This study aims to elucidate the roles of autophagy in the development of dry AMD.

Visual Outcome of Cystoid Macular Edema in Pediatric Non-Infectious Uveitis

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Purpose: Cystoid macular edema (CME) is a major complication of non-infectious uveitis in children, often causing significant visual loss. CME is usually chronic, and may persist despite control of inflammation. This study investigated the visual outcome of CME in pediatric uveitis, with relation to treatment modalities.

Methods: In a retrospective study, the medical records of children treated for uveitis-related CME in four tertiary uveitis clinics in Israel and London between 2005-2015 were reviewed. Data included demographics, diagnosis, visual acuity, clinical and imaging findings and treatment given specifically for CME, and at 3,6,12 and 24 months thereafter.

Results: The study cohort included 28 eyes of 21 children (9 females and 12 males, mean age 8.2±3.6 years). Median follow-up duration was 22 months (minimum four months). The most common diagnosis were pars planitis (n= 9) and idiopathic anterior uveitis (n=6). Uveitis and CME were diagnosed simultaneously in 16 eyes (57%). Uveitis was active at CME diagnosis in 25 eyes (89%). Median time to resolution was 11 months (IQR 6-17), with complete resolution in 18 eyes (64%) by 24 months. Structural causes that limited CME resolution included epiretinal membrane, retinal vasculitis with neovascularization and vitreal traction. Baseline VA was ≥20/40 in 7 eyes (25%), increased to 61.6% at 3 months (p=0.007), and remained stable thereafter. Treatment included corticosteroids (systemically and/or locally), immunosuppression and biologic therapies. No correlation was found between outcome and specific treatment strategy.

Conclusions: Prognosis of CME is favorable despite its chronic course. Larger cohorts are needed to define differences between treatment regimens.

Adipose Tissue Derived Mesenchymal Stem Cells Differentiate Towards RPE and Rescue Apoptotic RPE under Oxidative Stress, in vitro and in vivo

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Purpose: Oxidative stress leads to degeneration and apoptosis of Retinal pigment epithelial cells (RPE) in age related macular degeneration (AMD). Subcutaneous adipose derived mesenchymal stem cells (ASCs) may serve a therapeutic tool for regenerating RPE. Here we evaluated ASCs' protective effect on apoptosis of RPE, the differentiation potential of ASCs towards RPE, and the efficacy of sub-retinal transplantations of ASCs in a mouse model of AMD.

Methods: Human ASCs were harvested from subcutaneous fat of patients undergoing abdominoplasty. A co-culture of ASCs and human RPE, or human RPE alone, was subjected to oxidative stress by exposure to 1.5mM hydrogen peroxide (H2O2). H2O2 induced RPE apoptosis was measured by Annexin V/ propidium iodide staining and flow cytometry analysis. The differentiation potential of ASCs towards RPE was evaluated using td-tomato marked RPE and GFP marked ASCs seeded in a co-culture. GFP marked ASCs were then isolated by FACS sorter and analyzed for RPE and eyefield markers (BF1, Rx, MITF, PAX6, RPE65) by qRT-PCR and immunostaining. Finally, GFP marked ASCs were transplanted in the subretinal space of sodium iodate (NAIO3) treated mice compared to controls of subretinal saline injection. Evaluation of transplanted ASCs and endogenous RPE was studied by immunostaining for GFP and RPE65 of frozen sections at day 0, 7, 14, and 21 days post injection.

Results: Treatment of RPE with ASCs prevented H2O2 induced apoptosis (70% decrease, $p < 0.05$). After 7 days in co-culture, ASCs upregulated RPE and eyefeild markers (BF1 1.9+ 0.2 Rx 4.5+0.8 MITF 1.9+0.17 PAX6 5.5+0.2 RPE65 7.7+2.6, folds of control). In vivo, transplanted ASCs were located in the subretinal space of NAIO3 mice at days 0, 7, 14, and 21 post injections. Level of RPE65 was higher in ASCs treated mice at day 14 (4 folds increase in mean florescence of RPE65 compared to controls).

Conclusions: Treatment of apoptotic RPE with ASCs reduced RPE apoptosis in vitro. ASCs demonstrate a differentiation potential into RPE, evident by upregulation of RPE and eye field markers. Transplantation of ASCs in the subretinal space of NAIO3 mice resulted in an increase in RPE cell count compared to controls. ASCs may have therapeutic potential in regenerating RPE.

ERG Oscillatory Potentials Frequency Domain Characteristics in Diabetic Retinopathy and CSNB Patients

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Purpose: The Oscillatory Potentials (OPs) of the electroretinogram (ERG), composed of 3-6 waves superimposed on the ascending limb of the b-wave, have been shown to be attenuated in several disorders, including those entailing ischemic damage (e.g., Diabetic Retinopathy - DR) and Congenital Stationary Night Blindness (CSNB). However, their attenuation was demonstrated exclusively in the time domain, while their frequency domain properties were not extensively studied.

Methods: We examined the frequency domain properties of OPs of normal versus DR and CSNB patients using wavelet analysis. Retrospective analysis of 42 normal, 32 DR and 44 CSNB patients was performed, and further data collection is ongoing. We assessed the frequency domain activity of the OPs at various frequency bands using wavelet analysis employing real Morlet wavelet functions. The Frequency Separation Ratio (FSR) was defined as the mean normalized power of frequency above 250Hz divided by that between 100 and 250 Hz. The results were compared using the student's t-test. All analyses were performed using Matlab 2015b (The MathWorks Inc., Natick, MA).

Results: The average values for the oscillatory activity normalized power above 250 Hz was 0.093 (SEM 0.04, n=42) in the normal vs 0.71 (SEM 0.14, n=32) in the DR group vs 2.3 (SEM 0.19, n= 44) in the CSNB group, with the difference proving to be significant ($p < 0.01$, one-way ANOVA, Bonferroni corrected for multiple comparisons). Notably, all normal subjects had a FSR of < 0.2, and all diabetic subjects and CSNB subjects had an FSR of > 0.2.

Conclusions: Frequency domain analysis of the OPs provides additional information not revealed by the traditional time domain analysis techniques. In particular, wavelet analysis is well suited for this goal due to high resolution in both time and frequency domains. The frequency properties of the OPs provide a reliable means to asses for presence of Diabetic Retinopathy and CSNB as indicated by our study, with the FSR providing a means to separate the normal from the DR groups. This parameter, and perhaps additional measures of frequency domain activity above 250 Hz, may provide a means to identify and perhaps assess DR severity.

Synthetic 9-cis-beta-carotene Inhibits Photoreceptor Degeneration in Retinal Explants of rpe65rd12 Mouse Model of Retinoid Cycle Defect

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Purpose: To examine the biological effects of synthetic 9-cis-beta-carotene prepared from inexpensive building materials.

Methods: Animal research. Retinas from RPE65/Rd12 mice were incubated in media supplemented with 1mM synthetic 9-cis-beta carotene or vehicle for 18 hours. Retinas were fixed and sections were stained with antibodies directed against S-cone opsin and M-cone opsin. Number of positively stained cells per retinal section was determined.

Results: A novel practical cost-effective synthetic route for 9-cis-beta carotene was developed. Significantly higher number of cells expressing M-opsin and S-opsin were identified in retinal cultures incubated with synthetic 9-cis-beta carotene (mean ± SE: 24±9 and 15.5±4.5, respectively) as compared with control cultures (mean ± SE: 5±0 and 7.5±2.5, respectively).

Conclusions: Biologicaly active 9-cis-beta-carotene was synthesized from inexpensive building materials. Synthetic 9-cis beta carotene rescued M- and S-cones from degeneration in retinal explants of mice with a defect in the retinoid cycle, suggesting that synthetic 9-cis-beta-carotene may possibly be an effective treatment for retinal dystrophies involving the retinoid cycle.

Clinical Characterization of Individuals with Achromatopsia Caused by Mutations in the *CNGA3* Gene

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Purpose: To clinically characterize a population of individuals with achromatopsia due to mutations in the cone cyclic nucleotide-gated ion channel alpha-subunit (*CNGA3)* gene.

Methods: Fifteen individuals with genetically-verified *CNGA3* achromatopsia participated in this study, which was sponsored by AGTC and approved by the local IRB. Visual function and retinal structure was examined using a variety of non-invasive tests including a full routine ophthalmic examination, ETDRS visual acuity, color vision using the Ishihara and D-15 tests, reading speed, perimetry, degree of nystagmus (as measured by visual fixation stability on a MAIA microperimeter), light sensitivity testing (light discomfort), optical coherence tomography (OCT), electroretinography (ERG), fundus photography and completion of quality of life questionnaires.

Results: Eight males and seven females with a mean age of 31 years (range 21-42y) were enrolled. All had biallelic mutations in the CNGA3 gene (12 homozygous). Visual acuity was significantly reduced in all individuals, ranging from 20/125 to 20/250. Nystagmus assessment showed unstable fixation in most patients. Anterior segment slitlamp exam was unremarkable in all patients, but most manifested a blunt foveal reflex on fundoscopy. Macular microperimetry testing showed an average threshold of 21.7 decibels, which is reduced as compared to normal values of healthy individuals (26-36 dB). Color vision was severely impaired, with most patients showing scotopic lines on the D-15 test. Full field ERG showed absence of cone flicker response in all individuals while rod function was within normal range in the majority of patients (13/15), with a mean dark-adapted b-wave of 263μV microvolt (normal >200μV). Spectral domain OCT showed an optically empty space in the foveal region of eight of the patients while four showed loss or disruption of the ellipsoid zone of photoreceptors. Three subjects had a normal OCT.

Conclusions: Achromatopsia causes severe visual impairment and photophobia which affects the daily life of individuals with the disease. The present study provides information on retinal function and structure in this disease, in preparation for application of gene augmentation therapy which has recently been developed for this condition.

Retinitis Pigmentosa - Associated Cystoid Macular Edema Has Inflammatory Optical Density Characteristics

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Purpose: Cystoid macular edema (CME) is reported in 10-15% of patients with retinitis pigmentosa (RP). The pathogenesis of CME in RP is not entirely understood, and both inflammatory and tractional mechanisms have been suggested. The purpose of this study was to evaluate intraretinal/intracystic fluid optical density (OD) of eyes with RP-associated CME in order to determine the more likely pathogenesis.

Methods: A retrospective multicenter study was conducted. Spectralis SD-OCT (Heidelberg, Germany) was used to evaluate intraretinal-intracystic OD in 12 treatment-naive eyes with RP as the sole ophthalmic pathology. OD in the vitreous and the CME cystic spaces was measured using imageJ software (NIH) from exported raw scan data. OD ratios (ODR) were calculated by dividing the mean pixel intensity of the CME by the mean pixel intensity of the vitreous. An ODR cutoff value (1.0489, p=0.0001) was used to differentiate between an inflammatory (>1.0489) versus a tractional etiology (<1.0489), as determined in an earlier study by our group (93.6% sensitivity and 62.5% specificity). Level $P < 0.05$ was assumed to denote significance in all tests.

Results: The mean ODR value of the RP patients was 1.32, suggestive of a dominant inflammatory process (i.e., >1.0489). No significant difference was found between the RP eyes and the inflammatory ODR values (p=0.5), whereas RP ODR values differed significantly from the tractional ODR values (p=0.02), revealing a dominant inflammatory process in the pathogenesis of CME secondary to RP.

Conclusions: Our findings indicate a dominance of inflammatory processes in the CME of RP eyes. The higher reflectivity of the intraretinal fluid might reflect the presence of inflammatory proteins and acute-phase serum reactants. Understanding the pathogenesis of CME in RP may support a potential anti-inflammatory therapeutic approach for this ailment.

Purification and Characterization of Human Dehydrodolychil Diphosphate synthase (DHDDS) Overexpressed in *E. Coli*: Implications for its Retinitis Pigmentosa-Causing Mutation

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Purpose: Among Ashkenazi Jews, a missense mutation (K42E) in *DHDDS*, encoding the enzyme dehydrodolichyl diphosphate synthase involved in *N*-linked protein glycosylation, results in autosomal recessive RP. Although the genetic basis is well established, the underlying molecular mechanisms leading to the clinical phenotypes remain poorly understood due to lack of structural and functional information.

Methods: Codon-optimized full-length human DHDDS was cloned into pET-32b as a thioredoxin fusion protein. The K42E mutation was introduced using the QuickChange methods. DHDDS-WT and DHDDS-K42E were overexpressed in *E. coli* and purified using immobilized metal affinity chromatography and size-exclusion chromatography. The thioredoxin fusion protein was removed using TEV protease. Oligomeric state of the overexpressed proteins was assessed using analytical size-exclusion chromatography and activity of the overexpressed proteins was assessed using a radioactive assay.

Results: The proteins were produced in quantity and purity suitable for structural and functional studies. The purified proteins form stable homodimers and show time- and substrate-dependent activity. DHDDS-K42E is ~30% less active compared to DHDDS-WT.

Conclusions: The protocol we developed is suitable for obtaining recombinant DHDDS and mutants thereof in sufficient quantities and quality, thereby providing new opportunities for future structural and functional studies. These studies will shed light on the mechanisms underlying DHDDS-related retinitis pigmentosa and may lead to novel therapeutic approaches.

Multimodal *In-vivo* High Resolution Imaging of Gold Nanoparticle Labeled Photoreceptor Precursors

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Purpose: Imaging of transplanted cells in the retina is an important research area and a valuable clinical tool. The use of gold nanoparticles (GNPs) for imaging and drug carrying was recently introduced for various purposes and applications. In this study, we investigated the use of GNPs as a potential novel imaging modality for ocular cell therapy in a rat model.

Methods: GFP-expressing human embryonic cells (hESC) were differentiated into photoreceptor precursors (PRPs) in a 24 days protocol, recently optimized at our lab. Twenty nm diameter GNPs conjugated to a PEG7 (Polyethylene glycol) linker and coated with glucose, were synthesized and characterized using transmission electron microscopy (TEM), dynamic light scattering (DLS) and ultraviolet-visible (UV-vis) spectroscopy. PRPs, and a cancer cell line (MeWo expressing GFP) uptake of the GNPs was verified using TEM and dark field microscopy. The toxic effect of the GNPs on the cells was evaluated by cell morphology and MTT cell viability and proliferation assay. The GNPs-labelled cells were transplanted into the sub-retinal space of the rats (n=4) and monitored *in-vivo* using a rodent fundus camera, equipped with fluorescence (GFP tracking) and Optical Coherence Tomography imaging OCT capabilities for retinal structure visualization (Phoenix Research Laboratory, Micron IV). In addition, the GNP-labeled cells were imaged *in-vivo* using a micro-CT scanner (Skyscan 1176, Bruker, Belgium).

Results: The PRPs marker cone-rod Homeobox (CRX) revealed that hESC were efficiently differentiated into PRPs (approximately 80% yield). TEM and dark field microscopy demonstrated the successful uptake of the GNPs by the cells. Results revealed no toxic effect of GNPs on the cells. Cell migration was visualized by CT imaging of the labelled cells. The fluorescent cells were further visualized by a fluorescence fundus camera revealing no fluorescence quenching effect caused by the GNPs.

Conclusions: GNPs cell labeling has low toxicity and could be imaged by CT following transplantation to the rat retina. This method of cell labeling with GNPs offers a valuable tool for molecular imaging in retinal cell therapy and diagnostics.

Stiffening of Posterior Rabbit Sclera using Bacteriochlorophyll Derivative (WST11) and Near Infrared Light (NIR) Through the Cornea

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Purpose: To demonstrate that WST11 /NIR through the cornea increases scleral stiffness and resistance to stretch on enucleated rabbit eyes for the treatment of progressive myopia

Methods: Thirteen paired rabbit eyes were enucleated post mortem. One eye of each pair was randomly chosen for treatment. Tropicamide 1% eye drops were instilled on the treated eye for pupil dilation and the episcleral tissue was removed. The back of the eye was immersed in a cup with WST11 in saline 2.5 mg/ml for 20 minutes. After impregnation the eye globes were placed upside down on a Goldmann 3 mirror retinal lens. In all cases, the posterior sclera inferior to the optic nerve was used as scleral target area. Scleral illumination was performed by NIR laser at 755nm with 50 mW through the pupillary entrance for 10 minutes. A light meter detected an intensity of 10 mW/cm2 outside the illuminated sclera. After the treatment, the eye was dissected and the retina and choroid were removed. A 4 X10mm scleral strip was dissected horizontal from the treatment area using a self- constructed double-blade cutter. A control strip was taken from the contralateral eye at the same position. The scleral thickness of the strips was determined using a mechanical micrometer caliper (Baker DMM25 0-25mm Digital Micrometer).The samples were immediately transferred to the biomechanical tester (Minimat, Rheometric Scientific GmbH, Germany) and stress-strain measurements were performed.

Results: The maximal stress increased by 86.37 % after treatment from 7.12 MPa to 13.27 MPa ($p<0.01$). Young's modulus increased by 64.38 %, after treatment from 33.72 MPa to 55.43 MPa ($p<0.001$).

Conclusions: This novel treatment with WST11 and NIR illumination through the pupillary entrance induced scleral stiffening in ex vivo eyes and may be utilized to halt the progression of degenerative myopia.

Rho-Associated Kinase Inhibitor Decreases Human Corneal Endothelial Cell Apoptosis

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Purpose: Corneal endothelial cells (CEC) are essential for corneal function and clear vision. As human CEC are non-proliferative and cannot regenerate after injury, preservation of CEC is of utmost importance. Several recent studies have demonstrated that selective Rho-associated kinase inhibitor (ROCKi) decreased apoptosis and promoted migration and of both primate- and human-cultured CEC. Our aim in this study was to evaluate whether exposure to ROCKi will effect human CEC tissue survival in a commercial storage medium

Methods: Human-donor corneo-limbal rings were divided into fragments which were randomly stored in commercial storage media with or without addition of 10μM ROCKi (AdooQ Bioscience,CA) ROCKi for one week. Samples were dissociated into single cells by 0.25% trypsin digestion. CEC were targeted using the Anti-Human CD31 antibody. CEC survival were evaluated in paired samples for early and late apoptosis rate with flow cytometric analysis of Annexin-V and propidium iodide (PI) double staining.

Results: Nine corneoscleral rings from seven donors were studied. Following 1 week of incubation with ROCKi, CEC demonstrated reduced early apoptosis rate (19.37%±6.7 vs. 36.75%±9.9, p=.004, mean difference = 17.4%, 95% CI of the difference= 7.2% to 27.4%) and late apoptosis rate (11.3%±6.7 vs. 26.14%±14.49, p=.006, mean difference = 14.8%, 95% CI of the difference= 5.7% to 23.9%), compared to control

Conclusions: This is the first report to study the effect of ROCKi on CEC loss in human tissue stored in storage media. ROCKi prevented endothelial loss and thus, might be used to limit or slow down CEC loss in donor corneal tissue during eye banking. This may be beneficial for promoting future graft survival.

Corneal Stem Cell Niche and Dynamics in Health and Disease

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Purpose: The purpose of this study is to explore the regenerative capacity of cell populations in the ocular surface in homeostasis and in injury

Methods: We used a transgenic mouse model for corneal lineage tracing (ConfettiR26R;K14-CreERT) that allows by Tamoxifen induction to label K14+ limbal and corneal basal cells irreversibly and stochastically with one our of four fluorescent genes and track clonal fate over time. To study the response to injury we performed alkali burn or algerbrush wounds of the limbus or corneal center. Living animals were and followed for up to 6 months, at each time point mice were anesthetized and eyes were imaged by bright field and fluorescent microscopy.

Results: Small clusters of cells were identified throughout the entire cornea and limbus shortly after induction. After long term chase, limbal Confetti-labelled stripes were developed very slowly, reaching the corneal center within 4 month. Limbal and corneal surgical removal did not lead to corneal opacification within 2 months of experimental follow up but corneal clusters showed increased size compared to control. Alkali limbal injury resulted in severe corneal opacification and conjunctivalization that coincided with lateral Confetti stripe development. Albino mice showed a high sensitivity to all types of injuries, as compared to pigmented littermates.

Conclusions: These results indicate that the limbus provides the major if not only source for corneal epithelial stem cell regeneration. Confetti lineage tracing can provide a useful platform for answering key questions in limbal stem cell biology, identifying different cell populations in the cornea in homeostasis and in pathology.

The effect of Estrogen and Progesterone on Porcine Corneal Biomechanical Properties

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Purpose: To investigate the effect of the hormones estrogen and progesterone on the biomechanical properties of porcine corneas.

Methods: Thirty fresh porcine corneas were acquired from an abattoir. The corneas were equally divided into three groups that were incubated for one week in Optisol GS solution containing supra-physiologic concentrations of the hormones estrogen or progesterone, or no added substance as control. After the incubation period central corneal thickness of each cornea was measured using an electronic caliper, and corneas were then cut into strips measuring 10mm by 4mm. The strips were clamped between 2 pneumatic jaws of a computer controlled biomaterial tester (Instron 4502) and stretched at a constant rate of 1 mm/min until tissue rupture, while constantly recording the stress and strain of the tissue. Stress-strains curves were plotted and Young's modulus was calculated for each corneal strip.

Results: Average corneal thickness was 873.5±143.1µm for the control group 928.0±97.7µm for the estrogen group and 922.0±116.7.1µm for the progesterone group. There was no statistically significant difference between the groups (p=0.89). The average Young modulus was 17.00±3.46 MPa for the control group, 16.95±6.83 MPa for the progesterone group and 12.33±3.24 MPa for the estrogen group. There was a statistically significant difference between the control and estrogen groups (p= 0.018), while the difference between control and progesterone groups was non-significant (p=0,72).

Conclusions: Estrogen has a relaxing effect on the porcine cornea, causing a reduced stiffness of the tissue as expressed in a reduced Young's modulus. Progesterone has no significant effect on the bio-mechanical properties of porcine corneas. As many properties are common between human and porcine corneas, these findings may be applicable to human corneas.

Long-Term Result of Corneal Cross-Linking by WST-D and Near Infra-Red (NIR) Light: biomechanical Results and Histologic Evaluation, 1, 4 and 8 Months After Treatment

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Purpose: To determine long-term follow up safety and efficacy of WST-D/NIR treatment for corneal stiffening in an in vivo New-Zealand-White (NZW) rabbit model.

Methods: Twenty-three left eyes of NZW rabbits were de-epithelialized and treated topically with WST-D for 20 minutes (2.5mg/mL WST11 [Steba-Biotech, France] combined with dextran-500kD). WST-D impregnated corneas were illuminated by a NIR laser (755nm) at 10mW/cm2 for 30 minutes. Fellow eyes served as controls and were left untreated. One (n=6), 4 (n=9), or 8 (n=4) months after treatment a 4mm wide strip was cut and its elastic modulus was determined by extensometry. Histological and haematoxylin and eosin stained sections were prepared from corneas one week (n=4), and 8 months after treatment (n=4). Five 300µm wide areas were randomly selected in each cornea for manual keratocyte counting.

Results: Elastic moduli were significantly higher in all treated eyes of all groups compared to their paired controls (16.0±2.3MPa vs. 9.6±3.6MPa, p=0.008; 18.1±4.5MPa vs. 12.6±2.3MPa, p=0.003; 18.6±3.6MPa vs. 14.2±3.6MPa, p=0.01; respectively 1, 4 and 8 months after treatment). A gradual increase in elastic modulus was seen over time in the contralateral eyes.
A significant (p=0.002) decrease in keratocytes was seen in the anterior third of the stroma, one week after treatment. Eight months after treatment repopulation had occurred in the anterior third of the stroma. Keratocyte counts were comparable between control and treated eyes (p=0.562). Both one week and 8 months after treatment, there was no significant difference in the number of keratocytes in the middle (p=0.640 and p=0.810) and posterior third (p=0.463 and p=0.355) of the stroma.

Conclusions: A significant corneal stiffening, persisting after full maturation, is achieved in rabbits by WST-D/NIR cross-linking. WST-D/NIR might thus provide a treatment option to arrest keratoconic progression by means of safe NIR light that allows treatment of corneas of any thickness without endangering deeper ocular structures. Keratocyte apoptosis in the anterior stroma is seen immediately after treatment, however full repopulation of keratocytes has occurred 8 months after treatment.

Corneal Cross-Linking In Patients Younger Than 18 Years Old with Progressive Keratoconus: Up to 7 Years of Follow-Up Results

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Purpose: To evaluate the long-term visual, refractive, topographic and safety outcomes of corneal cross-linking (CXL) in the management of progressive keratoconus in patients younger than 18 years old.

Methods: A retrospective case analysis was performed on 92 eyes of 46 patients 18 years or younger, with progressive keratoconus, who underwent CXL from August 2007 to August 2016 in at least one eye.

Follow-up measurements taken up to 7 years after treatment were compared with baseline values. Preoperative and 1-year to 7-year postoperative data were collected for the treated and untreated eye-pair. Parameters included uncorrected visual acuity (UCVA), Best spectacle-corrected distance visual acuity (BCVA), manifest refraction, pachymetry and corneal topography.

Results: Mean age of patients was 15.6±2.1 years (11–18 years). Follow-up was up to 7 years. The mean UCVA did not change after the procedure and stayed stable during all years of follow up (0.7±0.1 logMAR). BCVA improved at all follow-up times, (from 0.3±0.1 logMAR to 0.2±0.03 logMAR) though not to the level of statistical significance. There was no significant change in mean keratometry or max keratometry. Stability of measurements of corneal aberration was demonstrated. There were no complications noted.

Conclusions: Our long-term follow-up suggests that CXL is a safe and effective procedure when used to prevent keratoconus progression in pediatric patients at all 7-year follow-up.

The Efficacy of Vascular Endothelial Growth Factor-Trap (VEGF-trap) compared to Steroids for the Treatment of Corneal Neovascularization

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Purpose: To examine the effectiveness of Aflibercept, a relatively new and very potent anti VEGF agent, in comparison to the steroid Celestone, for the treatment of established corneal blood vessels in a rabbit model.

Methods: Corneal neovascularization was induced in the right eye of 24 New Zealand albino rabbits by means of corneal chemical burn creation. Four weeks later they were randomly assigned to four treatment groups and received a subconjunctival injection of either Aflibercept, Celestone, combination of Aflibercept and Celestone or saline. Digital photographs taken on weekly intervals were evaluated by two masked observers for extent, centricity, and density of corneal neovascularization. The change in extent, centricity and density of corneal neovascularization from before treatment initiation to 28 days later was assessed in each of the treatment groups and compared to the control group. Four weeks after treatment initiation the rabbits were anesthetized and their eyes were enucleated and processed for Histopathology.

Results: In all comparisons performed between the digital photographs of the three treatment groups and the control group the change in corneal neovascularization amount wasn't statistically significant ($P>0.18$). Hematoxylin and Eosin dye also didn't demonstrate a statistically significant difference in neovascularization amount ($P>0.08$).

Conclusions: Treatment of corneal neovascularization is extremely challenging, with no widely accepted treatment modality. According to our study results Aflibercept and Celestone weren't proven effective for the treatment of formed corneal neovascularization. More research is needed in order to evaluate the role of those agents in the clinical setting.

Treatment of Soft Tissue Expansion and Exophthalmos in Inactive Thyroid Eye Disease Patients using drops of Prostaglandin Analogues

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Purpose: To describe the results of our interventional phase 3 study regarding the treatment of orbital and periorbital fat proliferation and exophthalmos in inactive thyroid eye disease (TED) patients using drops of Prostaglandin Analogues.

Methods: Five patients suffering from periorbital fat proliferation and exophthalmos due to inactive TED were treated by Prostaglandin Analogues drops once daily for 6 months. Soft tissue volume and exophthalmos were assessed by digital photographs, Hertel exophthalmometry and MRD at treatment initiation, after 3 and 6 months of treatment and 3 months post treatment cessation. The digital photographs taken at each follow-up were compared by two masked oculoplastic surgeons who were asked to evaluate which photograph was taken before treatment and which after 6 months of treatment based on observation of the periorbital fat.

Results: Exophthalmos measurement on Hertel exophthalmometry improved mildly in 3 out of 5 patients and remained unchanged in the others. No difference was observed on MRD measurements. On the digital photographs' assessment both observers correctly identified which of the photographs was taken after treatment in 2 patients. One of the observers also correctly identified 2 of the other 3 patients while the second observer was undecided. Four of the five patients also reported a subjective improvement in their appearance.

Conclusions: In this phase 3 study we found mild objective improvement in periorbital fat and exophthalmos as assessed by digital photographs and by Hertel exophthalmometry as well as subjective improvement in most of the treated patients. More research is needed in order to evaluate the role of this treatment in the clinical setting.

Cytokine Profile, Environmental and Infectious Exposures of Patients with Dry Eye Syndrome, Sjogren's Syndrome and B-cell non-Hodgkin Lymphoma

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Purpose: Dry eye syndrome (DES) is a manifestation of Sjogren's syndrome (SS), an autoimmune disease (AID) with a high lifetime risk of B-cell non-Hodgkin lymphoma (B-NHL). We aimed to explore whether an etiologic continuum exists from DES through SS to B-NHL by assessing environmental and infectious exposures and cytokine levels in these disorders.

Methods: In a clinic-based case-control study 702 participants: 91 SS, 120 DES, 211 controls (age and sex-matched), and 280 B-NHL cases were recruited and interviewed regarding exposures. Antibody titers to HCV, HBV, EBV, CMV, *H. pylori*, and *C. trachomatis* were tested by multiplex serology. Serum cytokines IL4, IL6, IL10, IL12, IL17, TNFα, INFγ and IL1β were tested on SS and DES participants using multiplex ELISA.

Results: SS showed a female predominance (9.2:1). Factors inversely associated with NHL, DES and SS include alcohol consumption (OR=0.47, 95%CI: 0.32-0.71; OR=0.54, CI: 0.33, 0.88; OR=0.27, CI: 0.15, 0.49, respectively) and East European ancestry for SS (OR=0.43; CI: 0.23-0.79), compared to controls. Self-reported infection requiring hospitalization was more common in NHL (OR=1.91; CI: 1.22-2.98), DES (OR=3.22; CI: 1.93-5.35) and SS (OR=4.58; CI: 2.56-8.18) than in controls. NHL cases were more likely to report 1st degree relatives with hematologic cancer (OR=1.91; CI: 1.00-3.62), while 1st degree relatives with AID were more common among SS (OR=5.23; CI: 2.58-10.58) and DES patients (OR=3.56; CI: 1.84-6.89). IL10 and IL12 levels were higher in SS than in DES, while controls had intermediate levels (P<0.001). A higher proportion of SS patients had antibodies to HCV, EBV-EA-D and CMV (P=0.02, 0.02, 0.01, respectively) than NHL, DES or controls. CMV seropositivity was more common in SS patients (OR=3.56; CI: 1.14-11.04), while that of *C. trachomatis* was decreased in DES (OR=0.40; CI: 0.19-0.84) compared to controls.

Conclusions: While some factors appear to be associated with all 3 conditions, some were specific to one or two of them. Cytokine activation does not show a continuum from controls→DES→SS. Patients with DES and SS appear distinct in terms of infectious exposures. Further work is required to understand events leading to B cell NHL in autoimmune disease.

Risk Factors Predicting Steroid Induced Ocular Hypertension Following Photorefractive Keratectomy

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Purpose: To assess the risk factors for steroid induced ocular hypertension (OHT) following photorefractive keratectomy (PRK).

Methods: A retrospective study. A total of 3566 eyes of 1783 patients following PRK, between January 2000 and December 2015. Patients were followed up for at least 3 months. Intraocular pressure (IOP) was measured using Goldman applanation tonometer after 1 week, 3 and 6 months. Steroid induced ocular hypertension was defined as IOP elevation of 25% while on topical steroid treatment (minimum 24 mm Hg), followed by an IOP drop of 25% when steroid treatment was discontinued.

Results: Overall, 3566 eyes of 1783 subjects were included in the final analysis of this study. The mean age of the participants was 26.9 ± 7.5 years and 54.85% were males. A total of 106 eyes (2.97%) were steroid responders. The responder group had a higher proportion of males (70.7% versus 29.2%, respectively, $p<0.001$), higher central corneal thickness (531.9 ± 40.2 versus 521.2 ± 40.9, $p=0.008$), lower mean keratometric power (43.3 ± 1.8 versus 44.0 ± 1.8, $p<0.001$), higher proportion of high myopia (>6D) (31.1% versus 22.1%, $p=0.03$), a higher rate of post surgical corneal haze (16.9% versus 4.2%, $p<0.001$), and were treated post operatively with more potent steroids. In multivariate analysis male gender (OR=1.18, P=0.005), central corneal thickness (OR=1.01, p=0.02), mean Keratometric power (OR=0.90, P=0.01), high myopia (OR=1.33, P=0.04), postoperative corneal haze (OR=3.26, P=0.03) and treatment regimen remained significant (P=0.02).

Conclusions: Significant factors associated with post PRK OHT are: male gender, high CCT, low mean keratometry reading, high myopia, corneal haze and stronger steroids such as dexamethasone.

Polymorphism in Cytokine-Related Genes in Dry Eye Syndrome and Sjogren's Syndrome' Patients

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Purpose: Cytokine-related genes are assumed to be key players in dry eye syndrome (DES) and Sjogren's syndrome (SS) pathogenesis. However the association between specific genes variants and both DES and SS are unclear, and comparisons between these two diseases has not yet been performed. In this study we compared single nucleotide polymorphism (SNP) variation in genes encoding cytokine levels among SS and DES patients in Israel.

Methods: A total of 180 subjects were recruited, 82 with SS and 98 with DES. Using a candidate gene approach and allele-specific PCR technique for genotyping, the proportions of risk alleles in TNFα (rs1800629), IL10 (rs1800896) and TNFAIP3 (rs2230926) SNPs were compared between study groups.

Results: The allelic distribution of the study groups was found to be very similar and match to Caucasians (CEU – Northern Europeans from Utah) population distributions in these SNPs. While none of the SNPs variants were found to be statistically significant associated to SS or DES in a recessive model, in an additive model the TNFα (rs1800629)-G risk allele was found among a higher proportion of SS patients compared to DES (Homozygote-G: 70.8% vs. 64.7%; Heterozygote: 26.9% vs. 11.2%, respectively, p=0.02). After adjusting for possible confounders, none of the tested SNPs were associated with SS compared to DES.

Conclusions: The frequency of IL10 (rs1800896-A) and TNFAIP3 (rs2230926-G) alleles was not found differ significantly between SS and DES patients. These findings may be due to limited power of the sample size of 180 participants. The TNFa (rs1800629-G) SNP seems to be associated with SS in an additive model. TNFa protein levels are known to be associated with inflammation, outcome of infection, and susceptibility to autoimmune diseases such as SS. The gene has also been associated with non-Hodgkin lymphoma, a serious complication of SS. Further comparison to healthy controls is required, as well as exploring other SNPs variants relating to the immune pathway in order to understand the genetic basis of DES and SS etiology.

Molecular Genetic Analysis of Israeli Families with Idiopathic Infantile Nystagmus

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Purpose: To characterize and identify the molecular cause of Idiopathic Infantile Nystagmus (IIN) in three families.

Methods: Three non-related IIN families were recruited. Clinical data including slit-lamp and funduscopic examination were obtained. Blood samples were collected from participants for DNA extraction. Molecular assessments included exclusion of candidate loci using STS polymorphic markers, whole exome sequencing (WES), and comparative genomic hybridization (CGH) on selected samples.

Results: All patients had involuntary oscillations of the eyes starting in the first few months of life. Except mild-moderate refractive errors, no other underlying ocular or systemic diseases were identified. Family-1 comprised thirty three members of whom seventeen affected manifested autosomal dominant (AD) inheritance. Families-2 (eleven members) and 3 (six members) included six affected participants manifested autosomal recessive (AR) inheritance.
Molecular analysis mapped Family-1 members (lod scores>3.0) to a small chromosomal deletion on chromosome -1q31. WES on eleven participants of families 2 and 3 is underway.

Conclusions: We demonstrate genetic heterogeneity in three Israeli IIN families. The disorder links to a small chromosomal deletion on chromosome 1p31 in one large AD family, while two other families exhibit AR inheritance with unidentified yet molecular cause.

Novel *PAX6* Mutation Causes Phenotypic Variability of Autosomal-Dominant Nystagmus and Foveal Hypoplasia

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Purpose: To investigate the clinical presentation and molecular basis of congenital nystagmus in an extended family in south Israel.

Methods: Large kindred of Moroccan Jewish ancestry presented with apparently autosomal-dominant congenital nystagmus. All affected individuals underwent a thorough ophthalmologic examination. Blood samples were collected, and genomic DNAs were extracted. Whole exome sequencing data of two affected individuals were filtered using Ingenuity Variant Analysis™.

Results: Affected individuals demonstrated large array of phenotypic variability, from being totally asymptomatic to having severe visual handicap. Visual acuity ranged from 6/10 to counting fingers. All but one patient had nystagmus, and 3 patients had strabismus. Anterior segment abnormalities were found in 3 patients, and one had presenile cataract. Foveal hypoplasia was detected in 2 individuals and anomalous optic nerve appearance in 4. Most patients had significant refractive errors ranging from high myopia to high hyperopia. Only a single mutation with relevant biological context, in *PAX6*, segregated within the family as expected for autosomal dominant heredity. The mutation was not found in open access databases (dbSNP147, HGMD™, ExAC, HapMap, and 1000 genomes) or in our in-house database of whole exome sequences of over 100 ethnically matched healthy controls. This heterozygous c.383G>A (NM_001127612.1) p.Arg128His missense mutation in *PAX6* affects an amino acid that is well conserved throughout evolution, and is predicted by SIFT and PolyPhen-2 to be damaging or possibly damaging, and by Ingenuity™ to cause loss of gene function.

Conclusions: Our results suggest that a novel *PAX6* mutation underlies the disease in this family. This mutation was found to cause less penetrant and more phenotypically variable disease than the previously reported mutation in the same codon, p.Arg128Cys, which was associated with nystagmus and foveal hypoplasia in all affected individuals. Our study describes the phenotypic variability in the family, and highlights the importance of unraveling the specific ophthalmic defects underlying congenital nystagmus.

Dissecting the Phenotypic Influence of Rare Genetic Variations among Patients with Age-Related Macular Degeneration

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Purpose: Age-related Macular Degeneration (AMD) is a complex disorder whose phenotype results from interplay of many genetic and environmental factors. We aimed to identify rare genetic variations among patients with distinct phenotypic characters of AMD.

Methods: We performed Whole Exome Sequencing (WES) on four patients manifesting distinct phenotypic characters of AMD, and searched for influencing genetic variants in previously identified macular degeneration related genes. Validation studies of the variants included bioinformatics tools, segregation analysis of mutations within the families, and an estimate on variant prevalence in ethnically matched cohorts of AMD patients and controls.

Results: All index patients were in their 6^{th} to early 7^{th} decade when diagnosed. Approximately, 400,000 genomic variants for each DNA sample were included in the downstream bioinformatics analysis, which ended in the discovery of a rare *BEST1* 3'UTR change (rs195155) in a patient with adult onset foveo-macular vitelliform dystrophy (AFMVD); a null *RPL1* mutation (p.Gln1987X) in a patient with drusen and focal outer-segments abnormalities; and a rare PLEKHA1 mutation (p.Ser177Asn) in two sibs with severe visual impairment due to extensive geographic atrophy and/or choroidal-neovascularisation.

Conclusions: By WES we identified rare genetic variants in genes with significant relevance to AMD. Learning their pathogenic contribution to disease phenotype is yet to be defined.

Changes in Retinal Genetic Profile of Dark Reared Albino Rats Predispose to Light Damage and may Mimics Aspects of Aging

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Purpose: Our quantitative findings on the effects of dark rearing on light induced retinal damage are consistent with our assumption that increased photon absorption by the increased rhodopsin content in the dark reared retina does not explain the increased light induced retinal damage. The purpose of the study was to explore if there is a change in the genetic profile of the dark reared rats that can explain the susceptibility of their retinas to light induced damage.

Methods: Whole genome search using microarray technology were used. High-quality RNA samples were evaluated for genome-wide transcript expression using Agilent Rat gene expression microarrays. We had three biological repeats of each group, dark for 2 weeks (Dark) versus light and dark cycles (Cycle). Samples were labeled, hybridized to microarray slide, washed and scanned according to manufacture protocols. The two-color microarray images were extracted with the aid of Feature Extraction 11.0 (Agilent Technologies Inc.). The RDyeNormSignal and GDyNormSignal were imported into JMP-Genomic from raw data set, transformed to log2 scale, normalized using quantile normalization and batch normalization, and filtered for transcripts with less than 5% variation between samples. Principal component analysis and variance component analysis were performed and followed by one-way analysis of variance (ANOVA).

Results: At adjusted p-value of less than 0.05 and difference in expression of 0.7 (about 1.6 fold changes), a list of 31 differentially genes was obtained, 27 of them coding for known proteins. Apex2, Cdc7, Lin9, Bdnf, Pcdhga8, Etv4, Capn3, Bmf, C-jun, Npw, Slc38a2, Gpr20, Rmnd1, Tlr10, Myh6, Zbtb1, Usp25 and Mbnl1 were down-regulated. While Egr1, Wnt7a, Apoa2, Slpi, Sppl2c, Mroh5, Hoxa4l, Aph-1b and Boc were up-regulated. Genes related to DNA maintenance\repair are down regulated, while expression of genes coding proteins associated with cell survival and oxidative stress is altered to assure cell survival. Moreover, genes which were related to aging and\or senescence (eg: Cdc7, Bdnf, Egr1) were altered in a manner that may mimic an aged-like condition.

Conclusions: Taking all together, two weeks dark changes the genetic profile of the retina of albino rats which can explain the increased susceptibility to light damage and may mimics aspects of aging.

Homozygous *CEP250* Knockout Leads to a Relatively Late-Onset Retinal Degeneration

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Purpose: We have previously reported that a nonsense mutation in the centrosome-associated protein *CEP250* (C-Nap1) gene causes atypical Usher syndrome (USH) in patients of Iranian Jewish origin. In addition, the patient carriers a nonsense *C2orf71* mutation either heterozygously or homozygously. Retinal degeneration in patients who were homozygous for the *CEP250* mutation only had a relatively late age of onset. The aim of the current study was to generate and clinically characterize a knockout (KO) mouse model for Cep250.

Methods: Heterozygous mice for a conditional non-activated construct were generated by an outsource company and shipped to the animal facility, they were used to produce an activated-homozygous cep250 KO mice by breeding them with Cre–recombinase homozygous mice. The mice were genotyped by PCR and Sanger sequencing. Retinal function was evaluated by electroretinography (ERG) at different ages (6 and 12 months) and retinal structure by histological analysis. If retinal dysfunction and/or retinal degeneration will be revealed in the KO animals, further immunohistochemistry and gene expression analysis will be applied on KO and control mice.

Results: We generated a KO mouse model for Cep250 by activating a construct with a deletion of exons 6 and 7. 33 homozygous animals were bred thus far and raised up to the age of 18 months. DNA and RNA analysis verified that the mutation leads to frameshift NM_001130000 p.(Asp200Argfs*7). ERG analysis at the age of 6 months did not revealed any clear evidence for retinal degeneration. A subsequent analysis at the age of 12 months showed a 50% decrease in the a- and b-wave amplitudes comparing to WT. In some of the KO mice, cone ERG in light adapted conditions did not reveal any response.

Conclusions: Homozygous KO for Cep250 affected rod and cone function at a relatively late age. Other models usually show no ERG function by the age of 6 months. Additional tests, including hearing test, will be performed to examine the mice phenotype mimics the atypical USH phenotype in humans.

Characterization of Retinal Function and Structure in *FAM161A* Knockout Mice

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Purpose: *FAM161A* mutations are the most common cause of ARRP in Israel. Our purpose was to characterize retinal function and structure in *Fam161a* knockout (KO) mice and compare it to wild type (WT) mice.

Methods: 83 *Fam161a* KO mice and 43 WT mice were used. Retinal function was evaluated by measuring the optokinetic response to assess visual acuity (VA) as well as by electroretinography (ERG). Retinal structure was studied *in-vivo* by OCT and histological analysis (H&E staining), including quantitative measurement of retinal layers thickness. Immunohistochemical staining (IHC) and western blot (WB) were performed to verify that the FAM161A protein was not expressed in KO mice.

Results: Optokinetic response measurements revealed deterioration of VA in KO mice over time, while VA in WT mice remained stable: Mean of 0.452c/d in WT mice versus 0.427c/d at age 1m, 0.351c/d at age 3m, and 0.201c/d at age 6m in KO mice ($P<0.01$). ERG analysis showed progressive decrease of amplitudes in KO animals over time, and by the age of 6m responses in KO mice became undetectable. OCT imaging showed thinning of the outer nuclear layer (ONL) in affected animals over time and this was verified by quantitative histology: Mean of ONL thickness was 46.2μm at age 1m and 41.1μm at 6m in WT mice versus 35.4μm at age 1m, 17.03μm at age 3m, and 9.0μm at age 6m in KO mice. At 8m of age, only sparse photoreceptor nuclei remained. IHC revealed Fam161a expression in the ganglion cell, inner and outer nuclear layers in WT retina, while there was no expression in KO mice. WB confirmed lack of *Fam161a* protein expression in KO animals.

Conclusions: *FAM161A* KO mice demonstrate progressive retinal degeneration between the ages of 1-8 months, as demonstrated by various indicators of retinal function and structure. Gene augmentation therapy is now being examined in this model, as a possible first step to future application of such treatment in humans with *FAM161A* disease.

A New Zebrafish Model for studying Molecular Genetic Mechanisms Underlying Lens Epithelium Derived Cataract

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Purpose: We have identified a novel model for fibrotic cataract formation in zebrafish, caused by reduced Lysyl hydroxylase 3 (Lh3) function. We propose to use this model to study, in vivo, the molecular mechanisms leading to spontaneous development of cataract derived from the lens epithelium.

Methods: In a forward genetic screen we identified a mutant with abnormal eye development. We used whole genome sequencing and RNA-Seq to identify the mutant gene. To analyze the phenotype we used several tissue labeling techniques, including immunohistochemistry, in-situ hybridization and histological staining. We used small molecule inhibitors to evaluate the contribution of TGFβ-signaling to the phenotype and transmission electron microscopy (TEM) to analyze the phenotype at subcellular level.

Results: We identified the mutant gene as *plod3*, which encodes Lh3 and found that the mutation leads to generation of a cellular mass that develops from the lens epithelium. In addition, *plod3* mutants have dislocated lenses (ectopia lentis) and several other body dimorphisms. Immunohistochemical labeling showed increased proliferation of lens epithelial cells and loss of their epithelial features.
TGFβ signaling plays a critical role in formation of the cellular mass as evidenced by increased pathway activity and rescue of the cataract phenotype by a specific inhibitor of TGFβ signaling.

Conclusions: Loss of Lh3 activity results in lens epithelium abnormalities, leading to the formation of a cellular mass and cataract and to ectopia lentis. The lens epithelium-derived cataract shows some resemblance to fibrotic reactions and hence could contribute to the search of new preventative treatments of fibrosis, a common complication of cataract surgeries.

The role of Nitric Oxide (NO) in neuronal adaptation in the turtle retina

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Purpose: Adaptation to changing conditions of illumination is one of the unique properties of the vertebrate visual system. A human observer with normal vision can function visually from star light to very bright light. Visual adaptation mechanisms were attributed to the retina, and divided into two major categories; receptoral and neuronal (post-receptoral) adaptation. While receptoral adaptation is well understood, little attempts have been directed into the understanding of the mechanisms underlying neuronal adaptation. Nitric Oxide (NO) was suggested to act as a neuromodulator in the vertebrate retina that was synthesized by Nitric Oxide Synthase (NOS) in the retina as the background illumination is increased. This study tested the working hypothesis that NO plays a role in neuronal adaptation.

Methods: Electroretinogram (ERG) recordings from turtle eyecups were done under different background illumination conditions while raising retinal NO level with L-arginine (NOS substrate) or lowering it with L-NAME (a competitive NOS inhibitor). Small-amplitude ERG responses were used to derive sensitivity to light. P-III and P-II components of the ERG were isolated in order to assess the function of photoreceptors (PRs) and ON-center bipolar cells (ON-BCs) respectively.
Similar experiments were conducted on horizontal cells by intracellular recordings.

Results: With bright light stimuli, eliciting large-amplitude ERGs, raising NO increased the amplitude of P-III and P-II while lowering NO reduced these responses. In contrast, raising/lowering NO increased/decreased light sensitivity of PRs (P-III), and decreased/increased that of ON-BCs (P-II) respectively. When we measured light sensitivity for dark-adapted state and different background lights, we found that background desensitization of ON-BCs started at lower background levels compared to PRs. This is the manifestation of neuronal adaptation. When NO level was raised, this difference between ON-BCs and PRs was eliminated, while lowering NO made the difference more pronounced, indicating that neuronal adaptation is affected by NO. NO effects upon horizontal cells light sensitivity were similar to those of PRs.

Conclusions: We show that NO may play a role in neuronal adaptation. The opposing effects of NO upon light sensitivity of PRs and ON-BCs probably reflect NO-dependent increase in guanylate cyclase activity in the PRs and additional effect of NO on post-synaptic signal transduction pathway in ON-BCs. This latter NO effect needs further studies, but may involve S-nitrosylation, and not activation of guanylate cyclase.

CEP78 Knockout Using CRISPR-Cas9 in Zebrafish

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Purpose: *CEP78* encodes a centrosomal protein that is expressed in the cilia of photoreceptors. We recently reported that *CEP78* mutations cause cone-rod degeneration with sensorineural hearing loss in humans. *CEP78* has only one homologue in zebrafish with about 50% similarity. Aiming to study the function of CEP78, we generated *cep78* mutations using the CRISPR-Cas9 system.

Methods: Primers targeting two different regions (in exons 2 and 3) of *cep78* in zebrafish were designed using the online tool CHOPCHOP. A Guide-RNA was injected together with Cas9 protein into single-cell stage WT embryos. Screening for mutations was performed by restriction enzyme analysis followed by Sanger sequencing.

Results: We injected 165 single-cells embryos and raised 150 fish that are potentially- chimeras for different *cep78* sequence alterations. Mutation analysis revealed 7 out of 9 fish with suspected mutations that were outcrossed to generate heterozygous fish. Sequencing analysis of their offspring revealed 5 different variants at the expected CRISPR site, including a +9-2 bp indel causing a frameshift and a deletion of 4 bp. Fish that were heterozygous for these mutations were crossed aiming to obtain homozygous *cep78* knockout fish. The analysis of the homozygous fish is in progress and will be reported at the meeting.

Conclusions: Zebrafish can serve as a quick and relatively easy animal model for studying function of genes of interest. In combination with the novel CRISPR-Cas9 system, it provides a powerful tool for analysis of retinal disease genes, such as CEP78. We anticipate that the zebrafish model we develop will aid to understand the function of CEP78 and hopefully to develop gene therapy for CEP78 disease.

Evaluation of Retinal Degeneration in Royal College of Surgeons (RCS) Rats Using Blue Laser Fundus Autofluorescence and Optical Coherence Tomography

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Purpose: To evaluate the correlation between blue light laser autofluorescence (BAF) fundus imaging, multicolor fundus imaging, optical coherence tomography (OCT), histology and electroretinography (ERG) findings of retinal degeneration in Royal College of Surgeons (RCS) rats

Methods: Nine pigmented RCS rats were subjected to a bi-weekly, BAF and multicolor fundus imaging as well as spectral domain OCT imaging using the Heidelberg SPECTRALIS® Imaging platform at ages 4-12 weeks. Imaging results were correlated with our previously obtained data of 69 RCS rats documenting retinal function (measured by electroretinogram, ERG) and histopathology analysis.

Results: Rats exhibited two distinct forms of dystrophy by BAF imaging, starting at the age of 8 weeks and up until 12 weeks. Highly hypoflourescent, contained patches accompanied by hyperfluorescent foci were observed in BAF fundus images most frequently located in close proximity to blood vessels. These lesions could also be identified using the multicolor fundus imaging using the green and blue laser reflectance analysis but not using the infrared (IR) imaging. When examined using SD-OCT these lesions corresponded to an abrupt disappearance of a section of the Debris Zone (DZ) layer, that may allude to micro bleeding or other vascular stress taking part in the dystrophy process. The second type of aberrant findings was an amorphic pattern of smaller, lighter patches radiating from the optic disc towards the periphery of the retina. This aberration could not be detected using any of the multicolor channels and corresponded in the SD-OCT to a gradual thinning and eventual disappearance of the DZ layer. Our ERG and histology analysis demonstrated a significant degeneration of photoreceptors at the age of 8 weeks. The maximal ERG b-wave was lower than 20 microvolts, and the outer nuclear layer (ONL) degenerated and contained a single cell layer.

Conclusions: BAF imaging provided new observations regarding the degeneration process in dystrophic RCS rats. The combination of BAF fundus imaging and SD-OCT scanning allows for a noninvasive, efficient monitoring of DZ clearance and vascular changes that occur in parallel to retinal photoreceptor degeneration.

Nonsyndromic Retinitis Pigmentosa in the Ashkenazi Jewish Population: Genetic and Clinical Aspects

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Purpose: Nonsyndromic retinitis pigmentosa (RP) is the most common inherited retinal disease, with a prevalence of 1:5,000 in Europe and USA and 1:2,230 in the Jewish population in Israel. This difference is mainly due to intra-community marriages. We analyzed the genetic and clinical findings in RP patients of Ashkenazi Jewish (AJ) descent, aiming to identify genotype-phenotype correlations.

Methods: 230 RP patients who reported AJ origin were included. Sanger sequencing was performed to detect specific founder mutations. Ophthalmologic analysis included visual acuity (VA), visual field, electroretinography (ERG), and imaging.

Results: The causative mutation was identified in 37% of families. The most prevalent RP-causing mutations are the previously described Alu insertion (c.1297_8ins353, p.K433Rins31*) in *MAK* (39% of families with a known genetic cause for RP) and c.124A>G (p.K42E) in *DHDDS* (33%). Additionally, disease-causing mutations were identified in the following genes: *BBS2, CNGB1, EYS, FAM161A, HGSNAT, NR2E3, PRPH2, RHO, RP2, RPE65 and RPGR*. Analysis of clinical parameters (VA and cone-flicker ERG) of patients with the most common founder mutations revealed that on average patients with biallelic *MAK* mutations had a later age of onset and a milder retinal phenotype, compared to patients with biallelic *DHDDS* mutations.

Conclusions: Our AJ cohort of RP patients is the largest reported to date, and shows a substantial difference in the genetic causes for RP compared to cohorts of other populations, mainly a large proportion of AR cases and a unique composition of causative genes. The most prevalent RP-causing genes in our cohort, *MAK* and *DHDDS*, were not described as major causative genes in other (non-Jewish) populations. The clinical data analysis shows that the phenotype of the *MAK* group of patients is less severe than that of *DHDDS* patients.

Co-occurrence of CFH and PRDM13-Related Variants in a Family with Autosomal Dominant Maculopathy of Marked Variable Severity

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Purpose: North Carolina macular dystrophy (NCMD) is an autosomal dominant macular dystrophy, considered as a non-progressive developmental disorder with variable expressivity. Our study was aimed to clinically characterize and genetically identify the cause of disease in a multigeneration family including six affected individuals with a highly variable maculopathy phenotype.

Methods: The study was approved by the Institutional Review Board and the Declaration of Helsinki. All participants (except of MOLI1154 IV:3) underwent a series of ophthalmic examinations including comprehensive ophthalmic examination and ocular imaging. Whole exome sequencing (WES) analysis was performed in two individuals from family MOL1154 using Nextera Rapid Capture Expanded Exome kit on a HiSeq2500 platform (Illumina, San Diego, CA, USA).

Results: Clinical analysis of affected individuals revealed an extremely large clinical variability which is independent of age. WES revealed a heterozygous deletion of six nucleotides (c.2247_2252delACTTAA; p.L750_K751del) in the *CFH* gene in the index case. Subsequent segregation analysis revealed this variant in five out of the six affected individuals. The non-carrier individual had a relatively mild macular phenotype compatible with age-related macular degeneration (AMD). In addition, we used Sanger sequencing analysis to screen the upstream region of *PRDM13* that has been reported recently to be associated with NCMD. The analysis revealed a heterozygous transversion (chr6: 100040974A>C) located within the previously described suspected control region in all six affected individuals. Since the two genes are located on different chromosomes, they are expected to segregate independently along generations. However, coinheritance analysis of the two variants showed that all affected individuals carried both variants (likelihood of 1 in 1024).

Conclusions: As NCMD has a wide spectrum of clinical phenotypes that can overlap with early-onset maculopathy and age-related macular degeneration (AMD) which is a relatively common aging disorder, diagnosis is a challenging task. The co-inheritance pattern resembles digenic inheritance, however a larger number of families will need to be studied to verify this hypothesis.

Analyzing the Genetic Basis for Inherited Retinal Dystrophy in a Cohort of Israeli Patients by Targeted Next Generation Sequencing

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Purpose: To identify the genetic basis for Inherited Retinal Dystrophy (IRD) in a cohort of Israeli patients.

Methods: This study was part of the ERDC4000 project. Targeted Next Generation Sequencing of 108 genes associated with nonsyndromic IRDs was performed to analyze ~4,000 probands, including 91 of our patients. Bioinformatic analysis of sequencing results was performed based on minor allele frequency, variant location, and variant type. For missense variants pathogenicity was evaluated with the following prediction tools: Mutation Taster, polyphen2, SIFT and CADD. Each putative mutation was validated by Sanger sequencing, and segregation in the family was tested (if possible).

Results: Disease-causing mutations in 25 genes were identified in 41/91 patients (45%), similar to the percent obtained in our lab using whole exome sequencing. The most common inheritance mode was autosomal recessive (56%), followed by autosomal dominant (14%) and X-linked (3%). The most common causative genes were *ABCA4* and *USH2A* (10% of solved cases each). In 16 patients the molecular diagnosis led to a change in the definition of the inheritance mode. In 13 patients the molecular diagnosis led to re-evaluation of clinical data, and to a change in the definition of the clinical phenotype. Five unsolved patients were eventually solved by other strategies, including whole exome sequencing and Sanger sequencing of novel IRD genes which were not included in the original ERDC4000 panel.

Conclusions: Targeted Next Generation Sequencing proved to be a cost-effective diagnostic approach for IRD patients. These results are important for molecular diagnosis, carrier screening and genetic counseling, in the relevant populations. In addition, they have a putative value for future development of novel therapeutic strategies for IRDs.

Molecular Inversion Probes (MIPs) Analysis of 108 Genes Associated with Inherited Retinal Diseases in 410 Israeli Index Cases

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Purpose: Non-syndromic inherited retinal diseases (IRDs) display an enormous allelic and genetic heterogeneity as ~140 genes have been implicated. The purpose of this study was to use the molecular inversion probes (MIPs) technique to screen a large number of unsolved Israeli patients for variants in 108 IRD-associated genes.

Methods: The target enrichment procedure was based upon 6,200 MIPs that captured ~1,600 exons and flanking intronic regions of 108 IRD-associated genes as well as selected deep-intronic variants and deletion-breakpoints. The individual captured targets were bar-coded, pooled (on average 120 samples), and sequenced on a NextSeq500 apparatus. The paired end reads were mapped to genomic reference; thereafter variant calling and annotation was performed using an in-house pipeline. An SQL database was created to efficiently analyze the MIPs results. All probands were previously prescreened for known founder IRD mutations in the Israeli population.

Results: Sequencing data was obtained for 410 IRD Israeli probands, mainly with retinitis pigmentosa (257 probands) and Stargardt disease (60 patients), as well as cone-dominated disease and Leber congenital amaurosis. Disease-causing mutations were identified in 34% (n=140) of cases. Interestingly, a few unusual findings were identified in the MIPs data. First, we identified a substantial proportion of patients who carry an IRD disease-causing mutation in addition to the one that is responsible for the disease. In addition, in three isolated female probands we identified heterozygous *RP2* variants, inherited in an X-linked pattern. Finally, in two families with autosomal dominant RP, we identified a heterozygous frameshift mutation towards the end of the reading frame of *RDH12*, a gene known to cause autosomal recessive RP.

Conclusions: Employing MIPs technology, we were able to provide a genetic diagnosis for a large number of previously unsolved cases. In total, about 50% of the 1500 families in our cohort are genetically solved. The results of our study suggest that use of gene panels will facilitate gene-defect identification in IRDs. In populations harboring a common founder mutations, a prescreening of these mutations is recommended.

Clinical Characteristics of Patients with Retinitis Pigmentosa due to Biallelic *FAM161A* Mutations

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Purpose: *FAM161A* mutations are currently the most common cause of autosomal recessive retinitis pigmentosa (ARRP) in the Israeli population, and were reported in only a few families elsewhere. In the present study we explored the clinical phenotype of patients harboring FAM161A mutations in order to provide information on the clinical spectrum of this RP-subtype.

Methods: Data were collected retrospectively from medical records of 85 patients harboring biallelic *FAM161A* pathogenic mutation/s. Clinical information included, when available: best-corrected visual acuity (BCVA), refractive error, full-field electroretinography (ERG), Goldmann visual fields, ocular coherence tomography (OCT), color, infrared and fundus autofluorescence imaging.

Results: The most frequent initial symptom was night blindness. BCVA was largely preserved in the majority of patients through the first three decades of life, and often severely deteriorated by the 5th and 6th decades. In advanced cases, ophthalmoscopy revealed the classic signs of RP including waxy pallor of the optic discs, attenuated retinal vessels, and bone spicule-like pigmentation accompanied by retinal atrophy in the mid-periphery. Interestingly, pigmentary changes were relatively late to appear, and in older patients (ages 50+), nummular pigmentation observed. ERG recordings revealed non-detectable rod responses at time of first testing (mean age 36) in 40 of 43 patients, while cone flicker was below detection in 33 patients. FAF images showed a hyper-autofluorescent ring around the fovea in all patients at young ages (third decade of life). Macular OCT showed thinning of the outer nuclear layer (ONL) around the fovea, with relative preservation of the fovea. In 42 of 46 patients which has OCT data available, an epiretinal membrane (ERM) was observed, but frank cystoid macular edema (CME) was rare, appearing in only 4 patients.

Conclusions: Mutations in *FAM161A* cause ARRP with symptoms usually manifesting in the 3rd or 4th decade of life. The clinical phenotype largely falls within the spectrum often described in RP caused by other genes. Interestingly, pigmentary changes seem to appear relatively late in the course of disease, ERMs are relatively common, but CME is quite rare. The data collected can assist in evaluation of *FAM161A* patients, provide information on the course of disease and may be relevant for future application of novel therapies.

Identification of a Novel Gene Involved in Syndromic Retinitis Pigmentosa

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Purpose: To identify the cause for syndromic retinitis pigmentosa (RP), in a consanguineous Israeli Muslim Arab family.

Methods: Patients underwent complete physical and ophthalmic evaluation, including best-corrected visual acuity, biomicroscopic examination, fundus autofluorescence and electroretinography (ERG) testing. Patients' DNA was subjected to whole exome sequencing (WES). Reverse transcription followed by PCR analysis was used to test for gene expression.

Results: The two patients had mild intellectual disability and hyperactivity. In addition, they suffered from night blindness and mildly reduced visual acuity. At the ages of 14 and 15 years, funduscopy revealed optic disc pallor with diffuse RPE changes. Fundus autofluorescence showed macular blocked fluorescence, stapled staining of the peripheral retina with late perifoveal leakage. WES revealed no mutations in any of the known genes involved in inherited retinal dystrophy. However, both patients were found to be homozygotes for a splice-site mutation in the *SCAPER* gene, encoding S-phase Cyclin A-associated Protein in the Endoplasmic Reticulum. RT-PCR analysis revealed that *SCAPER* is expressed in both retina and brain.

Conclusions: Our findings place *SCAPER* as a novel causative gene for RP with intellectual disability.

The Genetics of Inherited Retinal Dystrophies in the Palestinian Population

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Purpose: To identify the common genes and mutations which are causing different types of inherited retinal dystrophies (IRDs) in the Palestinian population.

Methods: Retrospective analysis of Palestinian families who were recruited at Hadassah and St. John Eye Hospital between the years 1999 and 2016. All recruited patients signed a consent form and were diagnosed clinically using imaging modalities as well as electrophysiological exam. Genetic analysis was performed by Sanger sequencing of founder mutations, molecular inverted primers (MIPs) analysis, and whole exome sequencing (WES).

Results: 315 Palestinian families with inherited retinal dystrophies were recruited for the study: 282 of whom (90%) showed an autosomal recessive inheritance pattern. The most common clinical diagnosis was retinitis pigmentosa (RP) accounting for 29.5% of families, followed by Stargardt disease (14%), cone rod dystrophy (10.8%), and leber congenital amaurosis (9.2%). Genetic analyses revealed 88 mutations (8 of which are novel) in 42 genes identified in 168 (53%) of the families. Only 19 of the identified mutations are founder, the most common ones are p.K294* in the TRPM1 gene and p.V529M in CNGA3. While for some diagnoses we were able to identify the cause of disease in a low fraction of families (e.g. CRD with 38%), other phenotypes yielded much higher rates (including Stargardt with 61% all with ABCA4 mutations, CSNB with 85%, mainly due to a founder mutation in TRPM1, and achromatopsia and Best disease with 81% and 89% respectively).

Conclusions: To the best of our knowledge, this is the first clinical and genetic report of a Palestinian cohort with IRDs. The analysis revealed a large genetic heterogeneity with a relatively high level of private mutations, therefore a thorough genetic analysis using different methods and advanced techniques is needed for an efficient analysis.

EYS Mutations can be Associated with Widespread Retinal Degeneration with Early Macular Involvement

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Purpose: To characterize the retinal phenotype associated with *EYS* mutations.

Methods: Genetic analysis included Next-Generation Sequencing and direct Sanger sequencing. Patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity, electrophysiological assessment including full-field ERG and VEP, either Humphrey or Goldman visual field examination, color vision testing using the Farnswarth D-15 test, and spectral domain optical coherence tomography (SD-OCT).

Results: Most patients with a mutation in the *EYS* gene had a typical Retinitis Pigmentosa (RP) phenotype, with a rod>cone disease process. However, some patients had early and extensive cone involvement presenting as macular degeneration, which subsequently progressed into widespread retinal degeneration. Both inter- and intra-familial phenotypic variability were observed.

Conclusions: *EYS* mutations are associated with a spectrum of retinal phenotypes, ranging from classic RP, to a phenotype which might resemble Cone-Rod Dystrophy.

Two Different novel *EYS* Mutations Cause Retinitis Pigmentosa in a Single Bedouin Kindred

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Purpose: To investigate clinical presentation and molecular basis of severe early-onset retinitis pigmentosa (RP) in a Bedouin clan in southern Israel.

Methods: Affected individuals underwent thorough ophthalmologic examination, visual fields testing and electroretinography (ERG). Blood samples were collected, and genomic DNAs were extracted. Molecular analysis included whole-exome sequencing (WES) analyses for 2 probands, and 750k SNP array for all family members in the study. Haplotype reconstruction was done using data from SNP arrays. Copy number variation (CNV) analysis was done for another patient using 250k SNP array. WES variants which passed a filtering cascade were screened in our in-house 100 ethnically-matched controls. RFLP was used to test the identified disease-associated variants both in 100 ethnically matched controls and in affected individuals of different kindreds yet of the same Bedouin clan.

Results: All affected individuals of two apparently unrelated consanguineous families, exhibited severe disease with an onset in the second or third decade of life, marked constriction of visual fields and severely reduced and delayed ERG responses under photopic and scotopic conditions. Combining CNV analysis with WES we identified in this kindred two different mutations in EYS (RP25): a deletion mutation encompassing 10 of the 43 exons and a p.W1817* nonsense mutation. Segregation analysis of both mutations demonstrated that all affected individuals were either homozygous for either one of the mutations, or compound heterozygous for both mutations. Both mutations are predicted to cause loss of function of the encoded protein and were not present in 200 ethnically-matched controls.

Conclusions: We demonstrate pseudo-dominant heredity of RP in a consanguineous Bedouin clan caused by homozygosity and compound heterozygosity for two different EYS mutations: a nonsense mutation and a microdeletion. Our findings of two different mutations in the same gene in a single inbred kindred highlight the limitations of homozygosity mapping in disease-gene identification in inbred kindreds. Identification of the novel RP-causing mutations will facilitate early diagnosis, screening, and genetic counseling in the Bedouin population.

Carrier Frequency Analysis of Mutations Causing Recessive Inherited Retinal Diseases in the Israeli Population

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Purpose: Inherited Retinal Diseases (IRDs) are a group of diseases caused by mutations in >226 genes. Previous carrier frequency calculations based on mathematical analysis and a limited number of control individuals revealed relatively high frequencies (1 of 5 individuals). The main purpose of this study is to calculate carrier frequency for the different autosomal recessive (AR) IRD mutations and genes in the Israeli population.

Methods: We created an SQL database including information from the following sources: 1. Genotype of a large number (>5000) of Ashkenazi Jewish (ASH) controls deposited in gnomAD. 2. In-house genotyping data of specific mutations in controls. 3. Hardy-Weinberg (HW) calculations of carrier frequency based on the number of affected individuals in each ethnic group, as represented in our cohort of >1500 families with IRDs.

Results: We identified 262 IRD-causing mutations in 65 genes in Israeli patients. For the ASH subpopulation, gnomAD and HW-based data were available for 26 mutations and showed high correlation (r-0.61, $p<0.00002$), therefore allowing one to use HW-based data as a reliable estimate. For the remaining subpopulations, only HW-based data were available. Overall carrier frequency per subpopulation ranges from 1 of 2.7 to 14 individuals, with the highest value obtained for the Arab-Muslim subpopulation in Jerusalem reaching an extremely high carrier rate of 37%, mainly due to founder mutations in *TRPM1, CNGA3*, and *ABCA4*. Carrier frequency per gene ranges from 1 of 29 to 2,500 individuals in the different subpopulations with *ABCA4, USH2A* and *MYO7A*, being the most common ones with average carrier frequency of 1/29, 1/71 and 1/90 respectively. We estimate the total carrier frequency for at least one of the AR-IRD mutations in the Israeli population to be 25%. This value is likely to increase as additional mutations are identified.

Conclusions: The carrier frequency of IRD mutations in the Israeli population is relatively high with marked variability among subpopulations, and therefore these data are highly important for more reliable genetic counseling and gene screening. The high carrier frequency in some subpopulations is not surprising since the prevalence of RP in Israel (1:2200) is much higher than worldwide reports (1:4500).

The Microarchitecture of Schlemm's Canal Before and After Selective Laser Trabeculoplasty

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Purpose: Selective laser trabeculoplasty (SLT) is a safe and effective procedure for lowering intraocular pressure (IOP) in open angle glaucoma (OAG) patients. Despite its widespread use, its mechanisms of action is not yet fully understood. This study aims to characterize the in vivo effect of SLT on the structure of Schlemm's canal (SC) in OAG eyes.

Methods: Prospective, cross-sectional, interventional study. Eighteen eyes of 18 OAG patients were enrolled and underwent a complete ophthalmologic examination). Eighty-one serial horizontal enhanced depth imaging (EDI) OCT B-scans (interval between B-scans, ~35 µm) of the nasal corneoscleral limbal area were obtained before and 4 weeks after the SLT procedure. The EDI OCT B-scans in the overlapping area between the two sets of serial scans (before and after SLT) were selected for analysis based on the structures of aqueous and blood vessels in each EDI OCT scan as landmarks. The cross-sectional area of SC was measured in each selected EDI OCT B-scan. After 3-dimensional reconstruction, SC volume was calculated using commercially available 3-dimensional reconstruction software.

Results: Among 18 eyes of 18 OAG patients, SC was imaged successfully before and after SLT in 13 eyes. Fifty overlapping EDI OCT B-scans from before and after SLT were selected for analysis. Following SLT, mean intraocular pressure was significantly reduced from 19.8±7.6 mmHg to 14.4±3.8 mmHg (p=0.003), the mean SC cross-sectional area increased by 8%, from 2478±550 µm2 to 2682±598 µm2 (p=0.03), and SC volume increased significantly from 4304592± 954777µm3 to 4658250± 1039956µm3 (p=0.03).

Conclusions: SLT expands SC in OAG patients and is consistent with increased trabecular outflow. Whether specific preoperative SC anatomic features are correlated with the amount of IOP reduction remains to be determined. An improved understanding of the SLT effect on microarchitecture of the trabecular outflow pathway in vivo in glaucoma patients, using EDI-OCT, may help better explain the SLT mechanism of action and might help in the prediction which patients might best benefit from the procedure.

Intra Ocular Injection of Plastic Microspheres Induces Glaucoma in Mice

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Purpose: To establish and characterize a glaucoma model in mice through the injection of plastic microspheres into the anterior chamber (AC) and measurement of intraocular pressure (IOP), retinal thinning and loss of retinal ganglion cells (RGC).

Methods: Plastic microspheres were injected into the AC of the right eye (OD) in 17 wild type (WT) mice. The left eye (OS) served as a control. IOP was measured pre-injection and weekly post-injection, and mice were sacrificed 4 weeks post-injection. Histological analysis included measurement of retinal thickness and RGC count. Calculations were made based on 3 consecutive areas measuring 10µm each, every 5-10 sections, to a total of 20-25 sections per eye. Mean values were compared between the study and control eyes. Optic nerve (ON) fibers density of injected and control eyes was compared using Luxol Fast Blue (LFB) staining. ON were evaluated for inflammatory reaction anti-CD45 antibodies.

Results: Mean IOP in the WT mice prior to injection was 11.1±2.5mmHg OD and 12.2±2.9mmHg OS. Four weeks post injection, prior to sacrifice, mean IOP was 14.5±3.3mmHg OD and 13.2±2.9mmHg OS. There was a significant increase in mean IOP in OD from pre-injection to the end of follow-up (P=0.003). Six (35.3%) study eyes had IOP of 17mmHg or more at the last follow-up compared with 2 (11.8%) control eyes. Mean retinal thickness was 193.7±15.5µm in the study eyes compared with 223.9±15.5µm in the control eyes (P=0.03) and mean RGC count was also reduced to 16.0±0.5 in the study eye compared with 17.6±0.7 in the control eye (P=0.005), per X20 field. Decreased fibers density using LFB staining, and inflammatory reaction were identified in the study eyes' ONs.

Conclusions: Microspheres injection into the AC induces elevated IOP, thinning of retina, and loss of RGC and ON axons as expected in glaucoma. The IOP differences were mild yet induced these changes, apparently by obstruction of the trabecular meshwork. Inflammatory response may play a role in the process. This glaucoma model might be of future use for examining neuroprotective therapy.

High Intensity Focused Ultrasound (Hifu) as a Novel Treatment for Moderate-Advanced Glaucoma Patients

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Purpose: To evaluate the safety and efficacy of the ultrasonic circular cyclo-coagulation procedure using high intensity focused ultrasound (HIFU) in moderate glaucoma patients.

Methods: A prospective interventional non-comparative study. Sixteen eyes (of 16 patients) with uncontrolled moderate-advanced glaucoma were enrolled. All eyes were treated with high intensity focused ultrasound (HIFU), which contains 6 activated transducers operating at 21 MHz. A thorough ophthalmic examination and intra ocular pressure (IOP) measurements (using Goldman tonometer) were performed before the procedure and at 1 day, 1, 4 and 12 weeks after the procedure. Primary outcome was defined as a surgical success (defined as ≥20% IOP reduction and IOP >5 mm Hg) at the last follow-up visit. Secondary outcomes were mean IOP at each follow-up visit, number od medications use, complications profile, and re-interventions

Results: IOP was significantly reduced from a mean preoperative pressure of 27.6±5.8 mm Hg to a mean postoperative pressure of 15.2±5.2 (P<0.001), 15.3±5.2 (P<0.001), 17.1±2.7 (P=0.018), and 17.3±2.9 (P=0.012) mm Hg at 1 day, 1, 4 and 12 weeks, respectively. A mean IOP reduction of 12.3±5.8 mm Hg was achieved. Surgical success was achieved in 14 of 16 eyes (87.5%). No major intraoperative or postoperative complications were noted.

Conclusions: Ultrasonic circular cyclo-coagulation using high-intensity focused ultrasound is an effective and well-tolerated method to reduce IOP in patients with moderate glaucoma.

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Visual Field Testing, 15 Year Trends in a Large Health Maintenance Organization

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Purpose: Visual field (VF) testing is a fundamental testing modality in ophthalmology and particularly in diagnosis and follow up of glaucoma patients. We performed a retrospective cohort study to identify VF testing trends over the past 15 years in a large health care organization.

Methods: The eligible study population consisted of all Maccabi Healthcare Services members between January 2000 and December 2014. We performed statistical analysis of our longitudinal electronic medical charts. Approximately 2 million patients were analyzed with regard to presence of glaucoma or glaucoma suspect diagnoses, registered antiglaucoma medications and number of VF tests performed.

Results: Between the years 2000-2014, 198,864 VF tests were performed by 93,637 patients. Of all VF tests, 47.5% were not related to patients with any glaucoma/ glaucoma suspect diagnosis nor to patients who received antiglaucoma medications. This fraction demonstrated an increasing trend and in 2014, 74% of all tests were as such. Normal tension glaucoma patients performed the highest number of tests with a mean of 3.5±3.4 VF per patient. Pigmentary dispersion, pseudoexfoliation and open angle glaucoma patients performed more tests than others with means of 3.2±3.2, 2.7±3.1 and 2.6±3.1 VF per patient respectively. The mean time interval between first glaucoma related diagnosis to first VF was 26.5±6.3 months. Once a patient performed his first VF, the annual mean of VF performed was 1.0±0.4. In most Israeli regions the average numbers of annual VF tests ranged between 0.9+0.4 to 1.1±0.5 tests per patient. In the peripheral northern region only 0.4±0.2 annual tests were performed per patient.

Conclusions: There is a growing trend of VF tests performed on indications other than glaucoma. Approximately half of the patients were sent to VF tests due to headaches, unspecified visual disturbances, neurologic or neuro-ophthalmologic suspected conditions. On average, suspected glaucoma and glaucoma patients were sent to their first VF test more than 2 years after diagnosis. This relatively long primary interval is opposed to an average once-a-year VF assessment that begins after the first VF test was performed. A possible explanation is that only after a VF damage is demonstrated, do ophthalmologist tend to monitor its progression. Regional differences in access to VF affect the annual performances.

Measuring Contrast Sensitivity with SPARCS in Specific Areas of Vision – A Meaningful Way to Assess Quality of Life and Ability to Perform Daily Activities in Glaucoma Patients

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Purpose: To investigate in patients with glaucoma: 1) correlations between measurements of contrast sensitivity (CS) in specific areas of vision and corresponding visual field (VF) areas, and 2) the impact of reduced CS in these areas on subjective assessment of vision-related quality of life (VRQoL) and objective performance-based measures.

Methods: The Spaeth-Richman Contrast Sensitivity Test (SPARCS) measured CS in the inferior, superior, and central areas and the Pelli-Robson test measured central CS. VFs were tested in all patients using standard automated perimetry and the mean deviation (MD) average scores for the corresponding areas were calculated. The National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) assessed VRQoL, and the Compressed Assessment of Ability Related to Vision (CAARV) assessed vision-related performance.

Results: Three hundred twenty-two eyes of 161 patients were included in our analysis. Significant correlations were found between CS and VF scores in the inferior, central, and superior areas ($P<0.0001$ for all). Significant correlations were found between SPARCS scores in the inferior areas in both eyes and most CAARV scores ($P<0.05$). Significant correlations were also found between SPARCS scores in the inferior and superior areas in the worse eye and most NEI-VFQ-25 scores ($P<0.05$).

Conclusions: CS and VF scores significantly correlated in all tested areas. Reduced CS in the inferior areas of both eyes affected most performance-based measures. Measurement of CS areas by use of SPARCS is a meaningful way to assess VRQoL and the ability to perform daily activities in patients with glaucoma.

Philadelphia Telemedicine Glaucoma Detection and Follow-up Study: Methodology and Year 1 Results

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Purpose: To evaluate an innovative, community intervention using fundus photography to improve access and utilization of eye care to detect, treat, and manage high-risk subjects with previously undiagnosed eye pathology.

Methods: Approximately 2,500 subjects at risk for glaucoma are being recruited to this twofold study. Phase 1 consists of detecting eye disease at primary care offices and Health Centers using telemedicine (Visit 1) followed by a comprehensive eye exam in the same setting (Visit 2). Phase 2 involves randomizing 300 subjects to either Intervention group (n=150) or Usual Care group (n=150) and scheduling follow-up eye exams with a local ophthalmologist (Visit 3). The Intervention consists of using patient navigators and a social worker to reduce barriers to eye care. A comprehensive cost analysis is being conducted.

Results: During Visit 1, 42% of the telemedicine screening results were normal, 37% were abnormal, 16% were unreadable, and 5% had OHTN. Satisfaction survey results showed that 99.7% (n=642/644) of the subjects screened were satisfied or very satisfied with Visit 1.

Conclusions: Investigating telemedicine as a way to diagnose whether or not an individual has glaucoma demonstrated that telemedicine allows off-site glaucoma specialists to effectively evaluate and view digital images of optic discs for optic nerve pathology. Protocols, materials, outcomes, and results will be disseminated to other communities in order to expand detection of glaucoma, other eye diseases, and visual impairment, as well as to further refine these approaches in order to successfully scale the program up to a national level.

Comparison Between the amounts of Accommodation Activated by Printed Text vs. Text Displayed on a Computer Screen

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Purpose: Monocular Estimate Method (MEM) is an objective method to measure the amount of accommodation activated for a constant stimulation (Rouse et al., 1982; Locke et al., 1989). In previous research the comparison between the amounts of accommodation activated by printed text vs. text displayed on a computer screen were contradictory (Chu et al., 2011; Collier & Rosenfield, 2011). In this study we compare between the amounts of accommodation used to read a printed text vs. a computer screen.

Methods: Healthy subjects were recruited from the Department of Optometry. Refraction, distance and near VA (Snellen and Jaeger minimum 6/9 and J1 respectively), CT (no strabismus) and accommodation (Push up, minimum 5.00 D) were tested on all participants. Subjects read a text (50 cm distance) from a paper and from a computer screen while examiners performed MEM. Each test was done three times (by different examiners who were masked to each other's results), and the average and standard deviation were calculated. Correlation and Bland and Altman (1986) analysis were executed to assess agreement.

Results: 31 subjects (age 18-30, 24 females, mean age 23.5±2.23 years old) participated in the study. High correlation was found between the two tests (R=0.73). While the mean difference between tests was small (0.08D), the standard deviation was large (±0.46D).

Conclusions: There is clinical significance accommodation difference when reading from a paper or from a computer. This should take in consideration when prescribing spectacles especially for subjects with CVS (Computer Vision Syndrome).

Association of Myopia with Cognitive Function among One Million Israeli Adolescents

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Purpose: Myopia is considered the leading cause of visual impairment worldwide. While there is evidence that myopia is associated with higher intelligence quotients (IQ) among children, such evidence for adolescents is scarce. We aimed to evaluate the association of myopia with cognitive function among adolescents, as well as with verbal and non-verbal intelligence subsets. We hypothesized that verbal intelligence will have stronger association with myopia, in line with the near-work hypothesis.

Methods: Nationwide, population-based, cross-sectional study. Study population included Israeli candidates for military service between 1993 through 2012. As a routine, prior to their recruitment, candidates underwent visual acuity examination and cognitive function assessment. Myopia was defined as Spherical Equivalent $\leq$ -0.5 D in at least one eye. Cognitive assessment yielded a cognitive function score (CFS), classified to nine-point scale. Cognitive assessment battery is composed of two verbal intelligence subsets (Similarities; Verbal Instructions) and two non-verbal intelligence subsets (Arithmetic; Spatial). Subsets were classified to high and low by median. Associations were analyzed using logistic regression models adjusted for confounders. Results are presented as odds ratio (OR) with 95% confidence interval (CI).

Results: Prevalence of myopia was 32.2% among 1,022,425 adolescents (55.7% males), aged 17.2±0.3 years. A strong and consistent association was found between CFS and myopia, across all severity levels. Association accentuated after adjustment for age, gender, years of education, ethnicity, socioeconomic status, body mass index and height. Highest CFS increased the odds of having myopia (OR: 1.85; 95% CI: 1.81 to 1.89; P<0.001), while lowest CFS reduced the odds (OR: 0.59; CI: 0.57 to 0.61; P<0.001), as both were compared to intermediate CFS. All subsets of cognitive function assessment were significantly associated with myopia (P<0.001): Verbal instructions (OR: 1.63; 95% CI: 1.61 to 1.65), Similarities (OR: 1.55; 95% CI: 1.53 to 1.56), Arithmetic (OR: 1.45; 95% CI: 1.43 to 1.46), Spatial (OR: 1.38; 95% CI: 1.37 to 1.39).

Conclusions: We found cogent evidence that cognitive function is strongly and consistently associated with myopia among adolescents, across all severity levels. Stronger association was found for verbal intelligence, and this may support the near-work hypothesis, as high verbal abilities are acquired by reading.

Head-Mounted Projection System for Visual Stimulation and Cortical Recordings as a Novel Method for Studying Natural and Artificial Vision in Behaving Animals

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Purpose: Accurately assessing natural and artificial visual function performance in awake and behaving animals is of great importance for studying various retinal diseases and treatments. Here we present the development of a novel customized head-mounted projection system integrated with electrodes for recording visual evoked potentials (VEP) in response to natural and artificial stimulus for assessing visual functions in awake and behaving animals.

Methods: We devised and customized a Digital Mirror Device (DMD) based head-mounted system, to project high quality images at visible and near IR light onto the rat retina and performed computer simulations to characterize and optimize the optical properties of the system. The design included a periscope like system to relay the DMD projected image onto the rat retina, and fitted onto the rat skull using a customized head plate and adaptor.

VEPs were recorded using electrodes implanted into the visual cortex and embedded into the mounting head plate. VEPs induced by flashes with varying pulse durations (ranging from 0.25msec to 8msec), varying frequency (ranging from 1Hz to 32Hz) and varying contrast levels projected by the head mounted projector were investigated in both anesthetized and awake animals.

Results: The system enabled the projection of images with MTF values higher than 0.85, with optimal image quality obtained at a 1mm pupil diameter, with a retinal image diameter of 3mm corresponding to 45 degrees visual field in the rat. Robust VEP signals were recorded in response to images projected at various contrast and light intensity. The VEP amplitude decreased as a function of temporal frequency reaching the noise limit for frequencies higher than 32Hz and increased as a function of stimuli duration, reaching a plateau at pulses longer than 10ms. Similarly, a decrease in VEP amplitude for decreasing contrast was also observed, reaching the noise level at 6% contrast.

Conclusions: Our results demonstrate the feasibility of investigating visual function performance in rats using a novel head-mounted projection system. This system may prove to be a vital tool in studying natural and artificial vision in awake and behaving animals, and for the evaluation of various treatments or other interventions, such as training for the studying of visual cortex plasticity**.**

Perceptual Grouping of Moving items in the Barn Owl (*Tyto alba*) - Behavioral and Neural Study

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Purpose: Study perceptual grouping in barn owls.

Methods: We combined behavioral and electrophysiological approaches to explore motion based grouping in barn owls. Owls were shown displays of multiple dots on the screen with one dot moving oddly to the right while the remaining dots either moved opposite, upwards, downwards or a mixed of opposite upwards and downwards directions. Two owls were trained to fixate a red oval in the screen center to initiate a trial. A trial consisted of one of the above described moving dot displays. The owls spontaneously scanned the display while a head mounted camera ("Owl-Cam", 30 frames per second, ~60º view angle) was used to track their point of gaze. Search time and number of head fixations until the owls fixate on the oddly moving dot were measured. In a complementary set of experiments owls were sedated and immobilized with their gaze fix at the center of a large screen. Single and multi-unit neural activity was recorded from the superficial and intermediate/deep layers of the optic tectum (OT) while the owl viewed the same displays as in the behavioral experiments.

Results: We show that a target moving differently from a homogenously moving background was perceived more salient compared to a target moving differently from a non-uniform moving background. We further show neural correlates of this effect. In the intermediate/deep layers and not in the retinal recipient superficial layers of the Optic Tectum, neurons were more sensitive to the homogeneity of the background motion than they were to the motion-direction contrast between the receptive field and the surround.

Conclusions: This study demonstrates that in barn owls, likewise humans, the regularity of the background motion modulates the perceived saliency of objects. Our findings suggest that basic visual search mechanisms may be more universal across species than presently thought and point to a brain locus were the necessary computations may take place.

Binocular Summation and the Correlation Between Spatial and Temporal Visual Functions in Normal and Amblyopic Subjects

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Purpose: Studies have shown that both temporal and spatial visual performances decrease in amblyopia, but there is lack of information regarding the correlation between these visual functions in such patients. Similarly, there is lack of information regarding binocular summation in visual temporal functions. In this study, we investigated both the correlation between temporal and spatial visual function and binocular summation in normal and amblyopic subjects

Methods: We investigated the temporal visual function performance by measuring the Critical Flicker Frequency (CFF) using a customized setup, based on a software controlled led. To measure the spatial visual function we used monitor projected stimuli generated by a customized computer software. We studied the contrast sensitivity (CS) at different spatial frequencies, presentation times and backward masking (BM) technique using Gabor patches as the stimuli. The experiments were performed using the staircase method in a 3/1 paradigm.

Results: The various CFF tests were performed on 18 healthy subjects (age 25.71± 3.38 years old, mean ±STD) and 10 amblyopic subjects (age 24.15± 4.4 years old, mean ±STD). The various CS tests were performed on 9 out of the healthy and 6 out of the amblyopic subjects. A significant temporal binocular summation (~12%) was observed in normal subjects under mesopic luminance conditions. Binocular CS summation was observed in normal subjects with larger effect found for low spatial frequencies, longer stimuli presentation and long BM. Similar summation characteristics were found in amblyopesexcluding temporal summation. In both normal and amblyopic subjects there is significant correlation between spatial and temporal performance. The highest correlations were observed between CFF and CS of 6 cycle per degree, in normal subjects ($r=0.63$, $p<0.005$) and amblyopes ($r=0.75$, $p<0.001$).

Conclusions: The superiority of binocular vision has distinct and different characteristics for spatial and temporal functions. Correlation between these two visual functions are dependent on stimuli characteristics and are different in amblyopes as compared to normal subjects. This study furthers our understanding of temporal and spatial visual functions in amblyopic subjects.

Chromatic Multifocal Pupillometer for Objective Diagnosis of Neurodegeneration in the Eye and the Brain

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Purpose: To evaluate the use of chromatic multifocal pupillometry for objective diagnosis of neurodegeneration in the eye and brain.

Methods: Pupillary responses (PR) to red and blue light presented at 76 locations of a 30-degree visual field (VF) were tested in 10 glaucoma, 7 BEST macular dystrophy, 5 optic neuritis (ON) patients and 25 aged-matched controls. Pupillometry results were correlated with Humphrey 24-2 VF (HFA-VF) and optical coherence tomography (OCT) results. In the brain study, pupillometry results of 20 cognitively normal subjects (ages 60-74) were associated with cognitive testing (Montreal Cognitive Assessment, MoCA).

Results: Significantly diminished PR with delayed recovery were demonstrated in glaucomatous VF defects. ON patients demonstrated significantly reduced PR latency in response to blue light in areas with HFA-VF defects that improved following steroid treatment. BEST patients demonstrated significantly diminished PR and shorter PR latency in response to red stimuli that correlated with disease severity and OCT retinal thickness. Subjects with MoCA<26 showed significantly reduced PR to blue light throughout the VF and a milder reduction in PR in response to red light mostly in the nasal area.

Conclusions: Chromatic multifocal pupillometry may enable objective mapping of distinct defects in different locations of the VF associated with neurodegeneration and detect subtle changes in PR following recovery. Analysis of PR to different wavelength stimuli, using different PR parameters, may enable differential diagnosis of brain and eye neurodegeneration and inflammation, objective monitoring of disease progression and evaluation of treatment efficacy.

A Method for Rapid Objective Strabismus Angle Measurement

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Purpose: We are evaluating the accuracy and repeatability of a novel strabismus angle measurement method using an automatic objective system based on eye tracking, in comparison to the prism cover test (PCT) results. The angle of strabismus is conventionally measured by the PCT is subjective, time consuming, very difficult to perform on babies, toddlers and young children and relies heavily on the examiner's skill and experience. The novel method being tested may constitute a replacement to the PCT.

Methods: The concept being tested is similar to the PCT principle using a system comprising of a 3D display and glasses. Instead of shifting the line-of sight of the deviating eye by using prisms while gazing at a single target, the system displays alternately two moving dichoptic targets on a screen until the line-of-sight of each eye coincide with its corresponding target. An eye tracker is used to detect cessation of eye movements when both eyes fixate at their targets. No eye tracker calibration is required to perform the test. The strabismic prism diopter deviation is automatically calculated from the distance between the two dichoptic targets on the display and the distance of the eyes from the display. Tests were conducted under normal room lighting at 60 cm. Test group included 10 strabismic subjects, 25.9±11.2 years of age, who are evaluated in comparison with their PCT results.

Results: Test results of the strabismic group measured were 22.9±12.2 (SD) for the eye tracking method and comparable to the cover test results of 23.7±7.8 (SD) ($P>0.65$, paired t test). Test duration of the novel method was 23±11.6 (SD) seconds.

Conclusions: These preliminary results of this work in progress indicate the possible validity of the concept of measuring strabismus angles by a system based on a 3D screen and eye tracking module.

Use of Sonic Hedgehog Pathway Gene expression to predict Response to Vismodegib in Advanced BCC of Eyelid

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Purpose: Basal cell carcinoma (BCC) is the most common eyelid tumor. Uncontrolled activation of the Sonic Hedgehog (SHH) pathway accounts for its development. The mainstay of eyelid BCCs treatment is surgical removal. However, advanced BCC, defined by size, contraindication for standard treatment (due to location, number of tumors, patients' comorbidities, etc.) or metastasis is unresectable and may be treated by Vismodegib, an inhibitor of the SHH. Our aim was to predict the response of advanced BCC to Vismodegib based on expression levels of multiple genes in the Sonic Hedgehog (SHH) pathway.

Methods: Tissue samples of 48 BCCs were collected, 24 resectable BCCs and 12 advanced BCCs before and after treatment by Vismodegib. Nanostring method was used to analyze mRNA expression levels of 40 genes from the SHH pathway, and correlation to the clinical and histological data and outcome were examined.

Results: A statistically significant difference in the GLI1 mRNA levels was found post-treatment between the advanced BCCs that responded to Vismodegib and the non-responders ($P<0.05$), however not in the pre-treatment levels. Overexpression and underexpression of various genes of the SHH in BCC were not correlated to location or resectability of the tumor.

Conclusions: Mapping the SHH pathway is a possible step towards personalized medicine for eyelid advanced BCC patients, as it may predict response and recurrence after treatment with the only biologic agent available to date, Vismodegib. Identifying the alternative pathways in the resistant tumors may help customize additional treatments.

Acknowledgments

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Ntravitreal Chemotherapy for Treating Vitreoretinal Lymphoma – 20 Years Experience

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Purpose: To report our 20 years' experience in treating vitreoretinal lymphoma by intravitreal methotrexate injections

Methods: A retrospective analysis of all the patients with vitreoretinal lymphoma that were treated in the ocular oncology service of Hadassah Hebrew Universality Medical Center since March 1997. All the patients were treated by intravitreal injections of 400mg of methotrexate in 0.05-0.1 ml according to protocol of up to 25 injections.

Results: During the 20 years we treated 108 eyes of 62 patients (39 females; 23 males). The age range 21-92 years (mean 61.5 years). In 46 patients (74.2%) both eyes were involved, and in 16 the disease was monocular (RE-7; LE-9) 58 patients had B-cell lymphoma and 4 T-cell lymphoma. In 47 patients (75.8%) the ocular disease accompanied primary CNS lymphoma. In 22 the ocular disease preceded the CNS lymphoma and in 25 the CNS lymphoma preceded the ocular disease. All patients responded fully to treatment after 2-16 injections and in only one eye was there a recurrence after completion of the treatment (was treated successfully by a full second course of methotrexate). The side effects were mostly superficial (conjunctival hyphemia and keratopathy) and temporary and were reduced when using the methotrexate injections to 0.05ml.

Conclusions: Intravitreal chemotherapy using methotrexate is a very effective way of treating vitreoretinal lymphoma with 100% success rate and rare recurrences, with only superficial and temporary side effects.

Leaky Choroidal Nevi: A Clinical, Imaging and Therapeutic Analysis

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Purpose: To evaluate the clinical and imaging features as well as treatment offered to patients with Leaky Choroidal Nevi and their outcome.

Methods: The charts of patients with a choroidal nevus crossing the temporal arcades inwards and showing leakage on OCT were reviewed. We analyzed the clinical features, findings on ancillary tests (OCT, Color Fundus Picture, Fluorescein Angiography and Eye Ultrasound) and treatment methods used.

Results: Throughout the review of almost 12 years, 17 patients with the above diagnosis presented loss of at least one logMAR line in 57.14% of the cases; improvement in 28.57%, and stability in 14.29%. By Posterior Segment US, an increase of both mean tumor thickness and largest base was of 0.8mm. SRF was the most common finding on OCT. All lesions that required treatment received intravitreal Bevacizumab, with a mean number of injections of 5.41. 25% of these patients presented VA improvement. Although PDT was reserved as a 2-4 line of treatment, 3 out of 4 patients treated with this modality had an anatomical improvement and 1 out of 4 with a functional improvement. Intravitreal Ranibizumab, Focal LASER and TTT were also used.

Conclusions: Leaky Choroidal Nevi is a term proposed for borderline, suspicious lesions with deleterious effects on visual acuity. A short trial of Bevacizumab can be warranted initially and consolidated by PDT if needed. Close follow-up is suggested due to its morbidity and the risk of conversion to Choroidal Melanoma.

The mechanism of the toxicity of Intravitreal carboplatin injection in a rabbit model

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Purpose: Carboplatin is a platinum based antineoplastic widely used chemotherapy agent in the treatment of retinoblastoma via periocular, intravenous and intra-arterial delivery method. The purpose of this study was to lock into the mechanism of the cell toxicity of Intravitreal carboplatin injection in a rabbit model

Methods: Ten New Zealand male rabbits (1800-2000 gram) were injected with a single carboplatin intravitreal injection each, in decreasing dosage (8-3 µg) / 0.1 ml in one eye. The second eye was used as control .

The animals were evaluated clinically by Intraocular pressure (IOP) measurement, slit lamp examination and indirect ophthalmoscopic fundus examination, immediately post Injection, on day one day 7, day 14, day 30 and before euthanasia (day 45).

In addition to the clinical ophthalmic examinations, toxicity was evaluated using baseline and repeated (days 14, 30, 45) Electroretinogram (ERG), Optical Coherence Tomography (OCT) and Ultrasound (US) examinations .

After euthanasia the eyes were fixed and submitted for histopathological evaluation . To determine if the mechanism was cell toxicity or cell death we conducted retinal cell count in the outer nerve layer and inner nerve layer. All the animals were holed, anesthetized and euthanized with accordance to the ARVO protocols.

Results: IOP, anterior segment, fundus examinations OCT and US were normal in all eyes at all the examination points in the study and the control eyes. No significant ERG changes were noted and similar cell count was found in the study and control group in the dosage of 3- 4 µg/0.1 ml. ERG was decreased and decrease cell count as found in the study compared to the control group in the dosage of 5- 8 µg/0.1 ml yet no anatomical ocular changes were observed.

Conclusions: Intravitreal carboplatin injection appears to be safe in the dosage of 3- 4 µg/0.1 ml in a rabbit model. Dosage of 5-8 µg/0.1 ml decreases the ERG reading and decrease the average cell count but resulted in no anatomical ocular changes. Sequel Future studies are needed to examine the efficacy of 3- 4 µg/0.1 ml Intravitreal carboplatin injections.

Genome Wide Association Analysis for Sub Retinal Drusenoid Deposits

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Purpose: Sub retinal drusenoid deposits (SRDD) are associated with age related macular degeneration (AMD). Limited data is available with respect to the genetic factors which are associated with this phenotype. We aimed to gain additional insight into the genetics of SRDD in AMD.

Methods: 155 AMD patients, which were recruited at a single tertiary referral center, and that underwent genotyping using an exome-chip technique as part of the International AMD Genomic Consortium (IAMDGC) project, participated in this study. ~250K variants were genotyped and imputed to ~12 million variants by the IAMDGC. All 155 patients had available spectral domain optical coherence tomography (SD-OCT) and Infrared Reflectance (IR) images. Images were evaluated for the presence of SRDD by a masked observer. After quality control and exclusion of variants with a minor allele frequency less than 0.05, 8,892,303 variants were analyzed via the bioinformatics software PLINK and epacts, including informative principle components, gender and age as covariates analysis. Logistic regression was performed in an unbiased approach, as well as a biased approach via regression and single variant testing, investigating 17,450 variants in the 34 loci known to be associated with AMD.

Results: 68 of the 155 patients had SRDD, seen in both OCT and IR in at least one eye. Variants were compared between AMD patients with or without SRDD via an unbiased analysis. Top hitting variants in this analysis approached a significance level of $P \leq 0.00003$; none of these significant variants was known to be associated with a risk locus for AMD. Via a biased approach on 34 known AMD loci, 11/34 loci had $P<0.05$ associated with SRDD in AMD compared with AMD without SRDD. For example, via logistic regression, HTRA1 showed an association with SRDD (P=0.001, OR=0.31, 95% CI[0.14-0.64]). Single variant analysis using Fisher's exact testing confirmed these results in HTRA1 (P=0.001, OR=0.34).

Conclusions: The presence of SRDD in AMD patients may be associated with novel genetic risk variants and/or with variants that were previously associated with the risk for having AMD. It remains to be seen if these loci are associated with SRDD in other populations, and if they are related to the pathogenesis of this phenotype.

The Association of Demographic Factors with Visual Acuity of Neovascular Age-Related Degeneration under anti-VEGF Therapy

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Purpose: Israel comprises diverse ethnical, cultural and socioeconomic populations. Limited data is available with respect to the association between demographic factors and visual acuity (VA) of anti-vascular endothelial growth factor (anti-VEGF) treated neovascular age-related macular degeneration (nvAMD) eyes.

Methods: Visual acuity results as well as repatriation date, health maintenance organization pertinence and socio-economic cluster of 328 anti-VEGF treated nvAMD patients were collected. Statistical analysis using IBM SPSS Statistics, 23rd version was performed to asses VA results of first and second eye (diagnosed with nvAMD) of each patient in order to compare results by repatriation date cutoff, health maintenance organization pertinence and socio-economic cluster classification.

Results: Initial and final VA of first eye was significantly better for patients who repatriated to Israel since 1990 and on, compared with patients who repatriated before that year or were born in Israel (0.68±0.09 vs 0.92±0.05, p=0.05; 0.72±0.1 vs 1.01±0.05, p=0.03, accordingly (LogMAR ± SEM)). However no significant differences in VA were demonstrated analyzing by health maintenance organization pertinence or socio-economic cluster classification.

Conclusions: In nvAMD patients, a tendency towards better initial and better final VA was demonstrated for first nvAMD diagnosed eye of patients who repatriated to Israel since 1990 and on; Such a difference was not demonstrated for the second eye. The reasons of these findings are not yet clear. It is possible that different cultural attitudes influence the timing and speed of medical care seeking and that treatment initiation at an earlier stage enables better response and better final VA results.

Whole-Genome Association Study of Age-Related Macular Degeneration in the Israeli Population

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Purpose: The elderly Israeli population is composed of a few major ethnic groups (Ashkenazi Jewish, Sephardic Jewish, and Arab populations). Each population bares their own susceptibility to genetic disorders. We wished to analyze Israeli patients with age-related macular degeneration (AMD) from variable ethnic origins to discover possible risk factors for AMD on a genome wide level.

Methods: DNA was collected from AMD patients (n=403) and controls (n=256) from variable ethnic backgrounds in a single tertiary center. Demographics, clinical, and imaging parameters were retrospectively collected. Genotyping was performed via the International AMD Genomics Consortium (IAMDGC) exome chip platform, and bioinformatics was performed with PLINK and EPACTS. Data was imputed to around 12 million variants, but around 30% of variants were excluded after quality control (QC). A genome wide association study (GWAS) was performed using informative principle components, age, and gender as covariates. Variants with minor allele frequencies<0.01 were excluded. Variants were clumped via P-value and linkage was taken into account. Variants of interest were looked at as compared with the IAMDGC results and genetics from the Ashkenazi Genome Consortium to exclude ethnic bias. Significant P-value threshold for analysis was set at $1x10^{-3}$

Results: A GWAS in the total Israeli population between AMD patients and controls indicated verification of significant variants previously identified by the IAMDGC in ARMS2/HTRA1($P<2x10^{-9}$), CFH($P<4x10^{-10}$), C3(P=0.0001), C20orf85(P=0.0004), SLC16A8(P=0.0007) and SYN3/TIMP3 (P=0.0009). A copy number variation in ARMS2/HTRA1 is possibly higher in Ashkenazi AMD patients (P=0.001, homozygote n=42/215 cases, n=6/113 controls). Comparison between the Ashkenazi and Arab (n=36 cases, 30 controls) populations shows the top ranking variant known to be associated with AMD in the Arab population is in the ARMS2/HTRA1(P=0.0003), while the top ranking variant in the Ashkenazi population is CFH gene(P=5x10-9).

Conclusions: We report the first GWAS on the Israeli population of AMD patients. Variants already associated with AMD in other populations were validated in the Israeli population, albeit with differential significance levels between subpopulations.

Phase I/IIa Clinical Trial of Human Embryonic Stem Cell (hESC)-Derived Retinal Pigmented Epithelium (RPE, OpRegen®) Transplantation in Advanced Dry Form Age-Related Macular Degeneration (AMD): Interim Results

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Purpose: Transplantation studies using autologous RPE cells in AMD patients suggest that introducing healthy RPE cells may be of benefit. Over the last decade we developed the technology to derive RPE cells in-vitro from hESCs using a directed differentiation, xeno-free protocol. Safety and tolerability of this cell product, OpRegen, is now being evaluated in a dose-escalating Phase I/IIa clinical study in patients with advanced dry AMD accompanied by geographic atrophy. Here we report accumulated safety and imaging data from the 1st and 2nd cohorts of patients, who received a subretinal transplant of 50k or 200k OpRegen cells in suspension, with up to 1 year follow up.

Methods: Transplantation was performed by subretinal injection following conventional 23G vitrectomy under local anesthesia. Systemic immunosuppression is administered from 1 week prior to transplantation until 1 year after. Systemic and ocular safety is closely monitored. Retinal function and structure are assessed using various techniques including BCVA, and color, OCT and fundus autofluorescence (FAF) imaging.

Results: At date of writing, dosing of cohort 1 of 3 patients (ages 74-80 years) who received 50k cells has been completed with a follow-up of 1 year, 9 and 6 months, and 2 out of 3 patients from cohort 2 (ages 65 and 82) were dosed with 200k cells. Surgery was uneventful, with subretinal fluid absorbing within <48 hours. OCT imaging showed healing of the retinal penetration site by 2 weeks post-op. Treatment has been well tolerated systemically and with regard to ocular findings. Imaging changes associated with OpRegen include subretinal pigmentation in area of transplant in 4 out of 5 patients, often accompanied by hypo- and hyper-fluorescent spots on FAF imaging and irregular reflectance above areas of atrophy and host RPE on OCT scans. These changes develop over the first 2-3 months and persist through the latest time point examined. Of note, epiretinal membranes that do not require surgical intervention were observed.

Conclusions: Subretinal transplantation of OpRegen in patients with advanced dry AMD appears well tolerated to date. Findings on imaging suggest presence of cells in the subretinal space. These results provide a framework for functional assessments in cohorts at higher doses.

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