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

PROGRAM & ABSTRACTS

38th Annual Meeting

Kfar Maccabiah

7th-8th March, 2018

תכנית ותקצירים

הכינוס השנתי ה-38

כפר המכבייה

7-8 במרץ, 2018

עריכת התוכנית: פרופ׳ אירית בכר, דר׳ יגאל רוטנשטרייך, פרופ׳ ניצה גולדנברג-כהן, דר׳ עידי מצר, פרופ׳ דרור שרון

הפקת הכינוס:

כלים שלובים
כנסים, ארגון והפקות בע"מ

עיצוב והבאה לדפוס: דבורה מרקס אוחנה ודרור שרון

ISRAELI SOCIETY FOR VISION AND EYE RESEARCH
The 38th Annual Meeting, March 7-8, 2018
Program at a glance

Wednesday, March 7, 2018

Thursday, March 8, 2018

יושבי-ראש של האגודה הישראלית לחקר העין והראייה

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חברי ועד האגודה הישראלית לחקר העין והראייה

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

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ARVO
CHAPTER AFFILIATE

הכנס ה-38

של האגודה הישראלית לחקר העין והראיה

מלון כפר המכביה, פרץ ברנשטיין 7, רמת גן

7-8 במרץ 2018

בחסות:

BAYER

עיניים
המרכז הרפואי ד"ר לוינגר
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ומניעת עיוורון בישראל (ע"ר)

מרצים המקבלים השנה פרס על עבודות שהוצגו בכנס השנה שעברה (הכנס ה-37, 15-16 במרץ 2017)

Award Recipients for the Best Papers Presented at the Previous Annual Meeting (the 37th Meeting, March 15th-16th 2017)

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, באדיבות משפחת מנדלס לזכרם של מיכה שוקן ז״ל ושמעון מנדלס ז״ל, ובאדיבות עמותת "לראות".

1. Samer Khateb, Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

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

2. Aya Barzelay, Division of Ophthalmology, Tel Aviv medical center, Tel Aviv University

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

3. Chen Matsevich, Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

Characterization of Retinal Function and Structure in FAM161A Knockout Mice

4. Yael Kinarty, Department of Ophthalmology, Hadassah-Hebrew University Medical Center and Department of Medical Neurobiology, Institute for Medical Research Israel-Canada, The Hebrew University, Jerusalem

CEP78 Knockout Using CRISPR-Cas9 in Zebrafish

5. Elad Moisseiev, Tel Aviv Medical Center, Tel Aviv

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

6. Reem Taha, Technion-Israel Institute of Technology, Haifa

The Role of Nitric Oxide (NO) in Neuronal Adaptation in the Turtle Retina

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

LIROT was established in 2006 with the unique goal to fight blindness through preventive medicine and medical research.

In 2017 we organized conferences on innovation in genetics of blinding eye diseases in the family to support patients and the Israeli research consortium of degenerative retinal diseases.

Lirot summarized 5 years of the eye mobile project by checking more than 13.000 elderly in need and saving the vision of 21% of the diagnosed patients.

Lirot activities were supported by a new group of dedicated volunteers ready to help develop the association.

Lirot Board: Ohad Lahav: chairman, Prof. Ido Perlman: Chair of Scientific Committee

Board members: Prof Ari Barzilay, Prof. Dov Weinberger, Prof. Anat Loewenstein, Prof. Hanah Garzozi, Prof.Yacov Peer, Prof. Ehud Asia, Prof. Dror Sharon, Prof. Yair Morad, Prof. Avi Solomon, Prof. Hani Verbin, Prof. Melamed, Dr. Ronit Lewinger, Dr. Yafit Stark, Mrs. Iris Spiegel, Mr. Mark Amos, Dr. Nir Erdinest, Mr. Asher Grinbaum, Prof. Arie Solomon.

Lirot Staff: Nadine Hollander, CEO; Zedkyau Baruh, Eye Mobile director

We look for more young doctors and researchers to volunteer in our preventive medicine projects please contact Nadine@eyes.org.il

www.eyes.org.il www.lirot-rp.org www.lirot.org

הרצאות אורח בכנס ה- 38

Keynote Speakers at ISVER 2018

Wednesday, March 7 th 2018

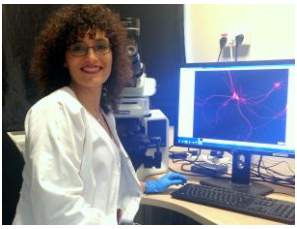
Prof. Nissim Benvenisty

Herbert Cohn Chair in Cancer Research and Director of The Azrieli Center for Stem Cells and Genetic Research at the Hebrew University

Title: Modeling genetic disorders including retinoblastoma using human pluripotent stem cells

Thursday, March 8 th 2018

Prof. Michal Be'eri



The Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, Israel.
The Icahn School of Medicine at Mount Sinai, Department of Psychiatry, New York, NY, USA

Title: The role of type 2 diabetes in cognition and brain damage

Wednesday, March 7th 2018

Coffee and Exhibition 8:00 – 8:55

Opening remarks 8:55 – 9:00
Dror Sharon

AMD 9:00 – 10:00

Moderators: Itay Chowers and Ori Segal

1 9:00 AC
High Content Screening of Macrophages from Patients with Age-related Macular Degeneration p. 33
Batya Rinsky, Shira Hagbi-Levi, Sarah Hayoun, Michelle Grunin, Itay Chowers
Dept. of Ophthalmology, Hadassah-Hebrew University Medical Center

2 9:07 AC
Accuracy and Precision of Intravitreal Injections of Anti-VEGF Agents in Real Life: What is Actually in the Syringe? p. 34
Itamar Loewenstein (1), Michaella Goldstein (1), Joseph Moisseiev (2), Elad Moisseiev (1)
(1) Department of Ophthalmology, Tel Aviv Medical Center, Tel Aviv, (2) Department of Ophthalmology, Sheba Medical Center, Ramat Gan

3 9:14 AC
Socio-Economic Status and Visual Outcome in nvAMD p. 35
Nadav Levinger (1), Gala Beykin (1), Michelle Grunin (1), Diego Almeida (1), Jaime Levy (1), Hagai Levine (2), Edward Averbukh (1), Itay Chowers (1)
(1) Department of Ophthalmology, Hadassah- Hebrew University Hospital, Jerusalem, (2) Braun School of Public Health and Community Medicine, Hadassah- Hebrew University Hospital, Jerusalem

4 9:21 AC
Is there any change in the thickness of the outer macula after multiple intravitreal injections? p. 36
Ofira Zloto (1,2), Iris Moroz (1,2), Oded sagiv (1,2), Joseph Moisseiev (1,2), Mordechai Rosner (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

5 9:28 AC

Evaluation of anti-oxidative treatments on the modulation of macrophages' functions and retinal degeneration p. 37

Sarah Hayoun, Batya Rinsky, Shira Hagbi-Levi, Michelle Grunin, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, and the Hebrew University – Hadassah School of Medicine

6 9:35

Full Thickness Macular Hole in AMD, Atrophic Scar: How can we Differentiate when there is a Doubt? p. 38

Achia Nemet (1), Shani Pillar (1), Elad Moisseiev (2), Hillel Greifner (3), Ori Segal (1)
(1) Department of Ophthalmology, Meir Medical Center, Kfar Saba, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, (2) Dept. of Ophthalmology, Tel Aviv Medical Center, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, (3) Dept. of Ophthalmology, Shaare Zedek Medical Center, Jerusalem

7 9:42

Activated Protein C stabilizes retinal barrier and inhibits laser induced choroidal neovascularization p. 39

Yael Nisgav (1), Iris Deitch (2), Mor Dahbach (1,3), Dov Weinberger (1,2,3) Tami Livnat (1,3,4)
(1) Laboratory of eye research, Felsenstein's Medical Research Center, Petah-Tikva, (2) Ophthalmology Dept., Rabin Medical Center, Petah-Tikva, (3) Sackler faculty of medicine, Tel Aviv University, Tel-Aviv, (4) The Israeli national hemophilia center, Sheba Medical Center, Ramat-Gan

9:49 **Discussion**

Refraction

10:00 – 10:45

Moderators: Zeev Zalevsky and Eithan Livny

8 10:00 AC

Nano-drops for correcting refractive errors p. 40

David Smadja (1,2), Moshe Lellouche (1), Mark Krauthammer (3), Yifat Harel (1), Adi Abulafia (2), David Zadok (2), Zeev Zalevsky (1)
(1) Bar-Ilan University, Institute of Nanotechnology and Advanced Materials, Ramat Gan; (2) Shaare Zedek Medical Center, Ophthalmology Department, Jerusalem, (3) Ophthalmology Department, Tel Aviv Sourasky Medical Center

9 p. 41

10:07

AC

SMART Intraocular Lens, a new concept of remotely activated presbyopic correction

David Smadja (1,2), Arkady Rudnitsky (1), Ronald Krueger (3), Zeev Zalevsky (1)

(1) Bar-Ilan University, Institute of Nanotechnology and Advanced Materials, Ramat Gan, (2) Shaare Zedek Medical Center, Ophthalmology Department, Jerusalem, (3) Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio, US

10 p. 42

10:14

AC

Complications and compliance in over-the-counter versus fitted contact lens wearers

Malaki Mattar (1), Eyal Gal (1), Barry Weisman (2,3), Rim Tarbia (1), Hadeel Agabrea (1), Ayat Abu Ahmad (1), Yara Jabaly (1), Einat Shneor (1), Liat Gantz (1)

(1) Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem, (2) Southern California College of Optometry at Marshall B Ketchum University, CA, USA (3) Stein Eye Institute, D Geffen School of Medicine at UCLA, CA, USA

11 p. 43

10:21

Does the traditional method for refraction produce optimal subjective visual acuity?

Lilach Aharon* (1,2), Michal Lahav Rice* (1,3) Ravid Doron (1)

(1) Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem, (2) Ophthalmology department Meir Medical Center, Kfar saba, (3) Ophthalmology department Rabin Medical Center. Petah tikva; *Equal contribution

12 p. 44

10:28

The effects of swaying (shokeling) on accommodative function during learning and praying among yeshiva students

Shalva Miller, Rachel Eichler, Rachel Silver, Einat Shneor, Ravid Doron

Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem

10:35 **Discussion**

Glaucoma

10:45 – 11:30

Moderators: Hani Levkovitch-Verbin and Arieh Markovitz

13 10:45 **Can we avoid underdiagnosis of pseudoexfoliation syndrome in pseudophakic patients?** p. 45

Amir Sternfeld (1), Moshe Luski (1,2), Ruti Sela (1,2), Alon Zahavi (1,2), Noa Geffen (1,2), Avihu Pereg, Elinor Megiddo (1), Irena Serov Volach (1), Tal Saban (1) Dan Gaton (1,2)
(1) Department of Ophthalmology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

14 10:52 **Reduction of intraocular pressure by digoxin derivatives that selectively inhibit Na,K-ATPase of the NPE** p. 46

Arie Marcovich (1,2), Adriana Katz (1), Daniel Tal (1), Yaniv Barkana (3), Steven Karlish (1)
(1) Biomolecular Sciences, Weizmann Institute of Science, Rehovot, (2) Department of Ophthalmology, Kaplan Medical Center, Rehovot, (3) Private practice, Shoham

15 10:59 AC **MIMS procedure: concept and experimental models** p. 47

Assaf Gershoni (1), Yoseph Glovinsky (2,3), Michael Rotenberg (4), Noa Geffen (1,3)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) Goldschleger Eye Institute, Sheba Medical Center, Ramat Gan, (3) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (4) Oxford Eye Hospital, Oxford University Hospitals, NHS Trust

16 11:06 AC **Objective perimetry in Glaucoma Patients Using Chromatic multifocal pupillometry** p. 48

Maya Gurevich (1,2), Alon Skaat (1,2), Daniel BenNer (1,2), Estela Derazne (2), Ifat Sher (1), Ygal Rotenstreich (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

17 11:13 AC **Non-Pigmented ciliary epithelium Exosomes surface proteins are crucial for Wnt signaling delivery** p. 49

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

11:20 **Discussion**

Coffee and exhibition 11:30 – 12:00

Guest lecture 1- Prof. Nissim Benvenisty 12:00 – 13:00

Herbert Cohn Chair in Cancer Research and Director of The Azrieli Center for Stem Cells and Genetic Research at the Hebrew University
Modeling genetic disorders including retinoblastroma using human pluripotent stem cells

Lunch break 13:00 – 14:00

Mini-Course: Genetics for Clinicians 14:00 – 14:30
Rayman Center

14:00 **Principals of genetic screening in patients with Inherited Retinal Diseases**
Tamar Ben-Yosef

14:15 **Phototransduction: The Biochemical Cycle of Vision- Enzymes and Genes**
Boris Rosin

Mini-Course: Imaging for Researchers 14:00 – 14:30
Rayman East

14:00 **OCT for the diagnosis of retinal diseases**
Dafna Goldenberg

14:10 **OCT-A for the diagnosis of retinal diseases**
Dov Weinberger

14:20 **Anterior Segment OCT (AS-OCT)**
Eitan Livny

Retina- clinical

14:35 – 16:00
Rayman Center

Moderators: Michal Kramer and Jaime Levy

18 14:35 **Nd:YAG Capsulotomy is associated with sustained IOP elevation in patients treated with anti-VEGF injections** p. 50

Amir Sternfeld (1,2), Rita Ehrlich (1,2), Dov Weinberger (1,2), Assaf Dotan (1,2)
(1) Department of Ophthalmology, Rabin Medical Center – Beilinson Hospital, Petach Tikva (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

19 14:42 AC **Determination of light stimulus parameters for assessment of rod-, cone- and melanopsin-mediated pupil response in different retinal locations** p. 51

Amit Hamburg (1,2), Yisroel Tucker (1,3), Ifat Sher (1), Ygal Rotenstreich (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) St George's, University of London, Nicosia, Cyprus

20 14:49 **Comparison of scleral buckle surgery with and without gas tamponade for the treatment of rhegmatogenous retinal detachment** p. 52

Assaf Dotan (1,2), Amir Sternfeld (1), Natalie Hadar Cohen (1), Rita Ehrlich (1), Matthew T.S. Tennant (2)
(1) Department of Ophthalmology, Rabin Medical Center, Beilinson Campus, Petach Tikva, (2) Department of Ophthalmology, Royal Alexandra Hospital, University of Alberta, Edmonton, Canada

21 14:56 **A Novel Method for Automated Visual Field Testing on Eyes with Severe Central Vision** p. 53

Binyamin Stern, Yaara Forer, Idit Gabay, Josh Kruger
Department of Ophthalmology, Hadassah Medical Center

22 15:03 AC

Uveitis induced by biologic agents used in cancer therapy

p. 54

Iris Deitch (1), Eyal Raskin (2), Zohar Habot-Wilner (3,4), Ronit Friling (4,5) and Michal Kramer (1,4)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) Barzilai University Medical center, Ashkelon, (3) Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv, (4) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (5) Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petah Tikva

23 15:10

Novel fluorescein angiography-based computer-aided algorithm for assessment of retinal vessel permeability in cases of proliferative diabetic retinopathy

p. 55

Jaime Levy (1), Jim Kukurin (2), Alon Friedman (2)
(1) Department of Ophthalmology, Hadassah University Medical Center, Faculty of Medicine, Hebrew University, Jerusalem, (2) Departments of Medical Neuroscience and Paediatrics, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

24 15:17 AC

A used spectral domain OCT machine without eye tracking is still a reliable tool: Real-life data

p. 56

Rachel Shemesh (1,2), Yinon Shapira (3), Ori Segal (1,2)
(1) Meir medical center, (2) Sackler school of medicine, (3) Rambam medical center

25 15:24

CMV specific T lymphocyte Infusion: A Novel Treatment for Resistant CMV Retinitis

p. 57

Tal Saban (1), Liat Shargian (2), Maya Eiger-Moscovich (1,3), Moshe Yeshurun (2,3), Michal Kramer (1,3)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) Institution of Hematology, Rabin Medical Center, Petach Tikva, (3) Sackler School of Medicine, Tel Aviv

26 15:31

Identification of visual field defects in Macular and Retinal Degeneration patients using Chromatic pupilloperimetry

p. 58

Ygal Rotenstreich (1,2), Maya Gurevich (1,2), Daniel BenNer (1,2), Amit Hamburg (1,2) Estela Estela Derazne (2), Ifat Sher (1)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

27 **Spectral-domain features in cases of preeclampsia and lack of relationship with systemic parameters.** p. 59

15:38 Zvi Gur (1), Tomer Batash (2), Ortal Buchbut (1), Jaime Levy (2)

AC (1) Department of Ophthalmology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva.,(2) Department of Ophthalmology, Hadassah University Medical Center, Faculty of Medicine, Hebrew University, Jerusalem

15:45 **Discussion**

Pediatrics and Oncology

14:35 – 16:00
Rayman East

Moderators: Chaim Stolovich and Jacob Pe'er

29 **Relations between convergence and stereoacuity in pediatric population** p. 60

14:35 Daphna Mezad-Koursh (1), Ari Leshno (2), Chaim Stolovich (1)

(1) Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, (2) Goldschleger Eye Institute, Sheba Medical Center, Tel-Aviv University, Tel-Hashomer

30 **Eye-tracking-based automated system for an objective rapid eye deviation measurement in children and adults** p. 61

14:42 Oren Yehezkel (1), Abraham Spierer (2), Dan Oz (1), Ran Yam (1), Michael Belkin (3), Tamara Wygnanski – Jaffe (2)

(1) Novasight Ltd, Airport city, (2) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (3) Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer

31 **Late Solitary Extraocular Locoregional Recurrence from Previously Resected Iris Melanoma** p. 62

14:49 Ido Didi Fabian (1,2), Caroline Thaung (2,3), Karen Sisley (4), Hardeep S Mudhar (5), Mandeep S Sagoo (2,3)

(1) Ocular Oncology Service, Goldschleger Eye Institute, Sheba Medical Center, Tel-Aviv University, Tel Aviv, (2) Ocular Oncology Service, Moorfields Eye Hospital, London, (3) UCL Institute of Ophthalmology, London, (4) Academic Unit of Ophthalmology & Orthoptics, Department of Oncology & Metabolism, The Medical School, The University of Sheffield, Sheffield, (5) National Specialist Ophthalmic Pathology Service, Department of Histopathology, Royal Hallamshire Hospital, Sheffield, UK

32 14:56 AC **Frequency of atypical vascularization during IAC for retinoblastoma** p. 63

Nadav Levinger (1), Jacob Pe'er (1), Jose Cohen (2), Shahar Frenkel (1)
(1) Department of Ophthalmology, Hadassah-Hebrew University Hospital, Jerusalem, (2) Department of Neurosurgery, Hadassah-Hebrew University Hospital, Jerusalem

33 15:03 AC **Serum exosome analysis as a predictive biomarker for metastatic uveal melanoma** p. 64

Shahar Luski (1), Shahar Frenkel (1), Pratibha Gaur (1), Jacob Pe'er (1), Saray Tabak (2), Elie Beit-Yannai (2)
(1) Department of Ophthalmology, Hadassah-Hebrew University Hospital, Jerusalem, (2) Department of Clinical Pharmacology & School of Pharmacy, Ben-Gurion University, Beer-Sheva

34 15:10 **Classification of Medulloblastoma Subgroups Based on Gene Expression Data** p. 65

Sivan Gershanov (1,5), Tamar Nehushtan (1), Helen Toledano (2,3), Albert Pinhasov (1), Nitza Goldenberg-Cohen (4,5,6), Mali Salmon-Divon (1)
(1) Department of Molecular Biology, Ariel University, (2) Department of Pediatric Oncology, Schneider Children's Medical Center of Israel, Petach Tikva, (3) Sackler Faculty of Medicine, Tel Aviv University, (4) Department of Ophthalmology, Bnai Zion Medical Center, Haifa, (5) The Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Petach Tikva, (6) The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa

28 15:17 **The effect of subsidized glasses and vision testing by the Israeli health funds on prevalence of refractive errors** p. 66

Aliza Geller, Rivka Lubin, Efrat Wolff- Ringer, Einat Shneor, Ravid Doron, Hadas Ben-Eli
Hadassah Academic College, Jerusalem

15:24 **Discussion**

Coffee and exhibition 16:00 – 16:30

Neuro-ophthalmology

16:30 – 17:10

Moderators: Ygal Rotenstreich and Libe Gradstein

35 16:30 AC

Azithromycin as a possible neuroprotectitive drug following optic nerve crush induction in mice

p. 67

Ofira Zloto (1,2), Moran Fridman (2,3), Shirel Weiss (2,3), Nitza Goldenberg-Cohen (3,4,5)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Petach Tikva, (4) Department of Ophthalmology, Bnai Zion Medical Center, Haifa, (5) The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa

36 16:37 AC

Association of structural retinal markers with brain structure and cognitive function in asymptomatic individuals at high risk for Alzheimer disease

p. 68

Inbal Sharvit-Ginon (1,2), Ifat Sher (3,4), Michal Schnaider Beeri (1,5), Aron Weller (2,6) Ramit Ravona-Springer (1,4,7), Ygal Rotenstreich (3,4)
(1) The Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, (2) Department of Psychology, Bar-Ilan University, Ramat-Gan, (3) Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, (4) Sackler Faculty of Medicine, Tel Aviv University, (5) The Icahn School of Medicine at Mount Sinai, New York, USA, (6) Gonda Brain Research Center, Bar Ilan University, Ramat-Gan, (7) Memory Clinic, Sheba Medical Center, Tel Hashomer

37 16:44

Motor Vehicle Accidents-associated Ocular Injuries - Visual and Social Outcomes

p. 69

Judith Brody, Irena Serov, Keren Mano, Inbal Avisar
Department of Ophthalmology, Rabin Medical Center, Petah Tikva

38 16:51 AC

Optic Neuritis monitoring using objective and subjective visual field testing

p. 70

Yisroel Tucker (1,2), Ifat Sher (2), Amit Hamburg (2), Daniel Ben Ner (2,3) Anat Achiron (3,4), Ygal Rotenstreich (2,3)
(1) St. Georges University of London Medical school, Nicosia, Cyprus, (2) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (3) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (4) Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer

39 16:58 AC

Novel *OPA1* mutation is associated with optic neuropathy and schizo-affective disorder

p. 71

Ohad Wormser* (1), Libe Gradstein* (2), Bibi Kanengisser-Pines (3), and Ohad S. Birk (1,3)
(1) The Morris Kahn Laboratory of Human Genetics at the National Institute of Biotechnology in the Negev, Ben-Gurion University, (2) Department of Ophthalmology, Soroka Medical Center and Clalit Health Services, Faculty of Health Sciences, Ben-Gurion University, (3) Genetics Institute, Soroka Medical Center, Faculty of Health Sciences, Ben-Gurion University, Beer Sheva, *Equal contribution

17:05 **Discussion**

Thursday, March 8th 2018

Coffee and Exhibition 8:00 – 8:50

Animal models 8:50 – 9:30

Moderators: Ido Perlman and Yoram Gutfreund

40 8:50 AC **Homozygous CEP250 knockout leads to a relatively late-onset retinal degeneration** p. 72

Alaa` Abu-diab (1), Chen Matsevich (1), Marije de jong (2), Alexey Obolensky (1), Ayat Khalaileh (1), Menachem Gross (2), Eyal Banin (1), Samer Khateb (1), Dror Sharon (1)
(1) Dept. of Ophthalmology and (2) Dept. of Otolaryngology, Hadassah-Hebrew University Medical Center, Jerusalem

41 8:57 **Blocking TNF-α receptors or intravitreal injection of TNF-α can lead to retinal ganglion cells preservation** p. 73

Moran Friedman (1,2), Shirel Weiss (1,2), Nitza Goldenberg-Cohen (3,4)
(1) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (2) The Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Petach Tikva, (3) Department of Ophthalmology, Bnai Zion Medical Center, Haifa, (4) Technion, Israel Institute of Technology, Haifa

42 9:04 AC **Retinal Degeneration and Impaired Phagocytosis of Photoreceptor Outer Segment Discs in *Prcd*-Knockout Mice** p. 74

Gilad Allon (1,2), Irit Mann (1), Ido Perlman (1), Tamar Ben-Yosef (1)
(1) Rappaport Faculty of Medicine, Technion- Israel Institute of Technology, Haifa, (2) Department of Ophthalmology, Rambam Health Care Campus, Haifa

43 9:11 AC **Attentional capture in barn owls (*Tyto alba*)** p. 75

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

44 9:18 **Subretinal and Intravitreal Delivery of the Photoreceptor-Specific AAV2-7m8-hGRK1-GFP Viral Vector in Mice** p. 76

Chen Matsevich (1), Avigail Beryozkin (2), Alexey Obolensky (1), Melissa Desrosiers (3), Ayala Ejzenberg (1), Deniz Dalkara (3), 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, (3) Institut de la Vision, Paris, France

9:25 **Discussion**

Therapy

9:30 – 10:30

Moderators: Eyal Banin and Michael Belkin

45 9:30 **Ataluren-mediated read-through of a nonsense mutation in the FAM161A gene which causes retinitis pigmentosa** p. 77

AC Avigail Beryozkin (1), Ananya Samanta (2), Samer Khateb (1), Eyal Banin (1), Dror Sharon (1), Uwe Wolfrum (2), Kerstin Nagel-Wolfrum (2)
(1) Ophthalmology Department, Hadassah-Hebrew University Medical Center, Jerusalem, (2) Inst. of Molecular Physiology, Johannes-Gutenberg University of Mainz, Germany

46 9:37 **Orbital fat derived mesenchymal stem cells rescue RPE from necrosis and differentiate towards RPE** p. 78

Aya Barzelay, Shira Wheisthak, Oded Ohana, Ran Ben Cnaan, Igal Leibovitch, Anat Loewenstein, Adiel Barak
Division of Ophthalmology, laboratory of Ophthalmology Tel Aviv medical center

47 9:44 AC
Dexamethasone Implant for Diabetic Macular Edema in Naïve Compared o Refractory Eyes. The International Retina Group Real-Life 24 Month Multicenter Study - The IRGRel-DEX Study p. 79
Dinah Zur (1), Matias Iglicki (2), Catharina Busch (3), Anat Loewenstein (1) for the International Retina Group
(1) Division of Ophthalmology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, (2) Private Retina Office, University of Buenos Aires, Argentina, (3) Department of Ophthalmology, University of Leipzig, Germany

48 9:51 AC
Microglia activation in RPE65/rd12 mouse model of retinitis pigmentosa p. 80
Ettel Bubis (1,2), Ifat sher (1), Ygal Rotenstreich (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

49 9:58 AC
Recombinant Adeno-Associated Virus [rAAV-7m8] Transfects Photoreceptor Cells Following Intravitreal Injection in Sheep p. 81
Maya Ross (1), Eyal Banin (2), Deniz Dalkara (3), Melissa Desrosiers (3), Alexey Obolensky (2), Raaya Ezra-Elia (1), Hen Honig (4), Esther Yamin (2), Alexander Rosov (4), Edward Averbukh (2), Elisha Gootwine (4), 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) Institute de la Vision, Paris, France, (4) ARO, The Volcani Center, Rishon LeZion

50 10:05 AC
Electrophysiological characterization of Human Embryonic Stem cells-derived photoreceptor precursors p. 82
Revital Schick (1), Nairouz Farah (1), Amos Markos (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

10:12 **Discussion**

Coffee and Exhibition 10:30 -11:15

Awards and ISVER update 11:15 - 12:00

Guest lecture- Prof. Michal Be'eri 12:00 – 13:00

Director, Biorobotics and Biomechanics Lab (BRML); Faculty of Mechanical Engineering; Technion Israel Institute of Technology
The role of type 2 diabetes in cognition and brain damage

Lunch 13:00 – 14:00

Genetics 14:00 – 15:30

Moderators: Eran Pras and Tamar Ben Yosef Rayman Center

52 14:00 AC

A missense variant in *CACNA1F* causes variable phenotype in female carriers and hemizygous males of three unrelated Jewish families of Russian origin

p. 83

Adva Kimchi (1,2), Vardiella Meiner (1), Orly Elpeleg (1), Michal Macarov (1,2), Anat Blumenfeld (2), Isabelle Audo (3), Christina Zeitz (3), Hadas Mechoulam (2), Eyal Banin (2), Dror Sharon (2), Claudia Yahalom (2)
(1) Department of Genetics and Metabolic Diseases, Hadassah-Hebrew University Medical Center, Jerusalem, (2) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (3) Institut de la Vision, Sorbonne Universités, UPMC, Paris, France

53 14:07

A frameshift mutation in RDH12 causes autosomal dominant retinitis pigmentosa in families of Tunisian Jewish origin

p. 84

Boris Rosin (1,2), Prasanthi Namburi (1), Muhammad Imran Khan (3), Frans P.M. Cremers (3), Eyal Banin (1,2), Dror Sharon (1)
(1) Department of Ophthalmology, Hadassah Hebrew University Medical Center, Jerusalem, (2) The Center for Retinal and Macular Degenerations, Hadassah Hebrew University Medical Center, Jerusalem, (3) Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

54 14:14

SLC38A8 Mutations in Israeli Families with Infantile Nystagmus Syndrome

p. 85

Chen Weiner (1), Nadav Shoshany (1), Ayala Kol (1), Noam Shomron (2), Eran Pras (1,2)
(1) Matlow's Ophthalmogenetic Laboratory, Assaf Harofe Medical Center, Zerifin, (2) Functional Genomics Laboratory Tel Aviv University

55 14:21 AC

Clinical and genetic characterization of Pseudoxanthoma Elasticum patients

p. 86

Iyar Sheps (1), Chen Weiner (2), Nadav Shoshany (1), Eran Pras (1)
(1) Ophthalmology Department, Assaf Harofe Medical Center, Zeriffin, affiliated to Tel Aviv University (2) Matlow's Ophthalmogenetic laboratory, Assaf Harofe Medical Center, Zeriffin

56 14:28

Pattern Dystrophies Associated with Mutations in the Peripherin/RDS Gene

p. 87

Margarita Safir (1), Reuven Pokroy (1), Chen Winer (2), Ayala Kol (2), Nadav Shoshany (1), Eran Pras (1)
(1) The department of Ophthalmology, Assaf Harofeh Medical Center, Zerifin, (2) The Matlow's Ophthalmogenetic laboratory

57 14:35 AC

Worldwide Carrier Frequency Analysis of Mutations Causing Autosomal Recessive Inherited Retinal Diseases

p. 88

Mor Hanany, Segev Meyer, Dror Sharon
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

58 14:42 AC

A heterozygous deletion of a noncoding part of the *PRPF31* gene causes retinitis pigmentosa in Ashkenazi Jews

p. 89

Prasanthi Namburi (1), Francesco Paolo Ruberto (2), Sara Balzano (2), Adva Kimchi (1), Tamar Ben-Yosef (3), Eyal Banin (1), Dror Sharon (1), Carlo Rivolta (2)
(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (2) Department of Computational Biology, University of Lausanne, Lausanne, Switzerland, (3) The Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa

59 14:49

A Homozygous Founder Missense Variant in Arylsulfatase G Abolishes its Enzymatic Activity Causing Atypical Usher Syndrome in Yemenite Jews

p. 90

Samer Khateb (1), Björn Kowalewski (2), Nicola Bedoni (3), Markus Damme (4), Netta Pollack (1), Ann Saada (5), Alexey Obolensky (1), Tamar Ben-Yosef (6), Menachem Gross (7), Thomas Dierks (2), Eyal Banin (1), Carlo Rivolta (3), Dror Sharon (1)

(1) Dept. of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (2) Dept. of Chemistry, Biochemistry I, Bielefeld University, Germany, (3) Dept. of Computational Biology, Unit of Medical Genetics, University of Lausanne, Switzerland, (4) Dept. of Biochemistry, University of Kiel, Germany, (5) Monique and Jacques Roboh Department of Genetic Research and the Department of Genetic and Metabolic Diseases, Hadassah-Hebrew University Medical Center, Jerusalem, (6) Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, (7) Dept. of Otolaryngology - Head and Neck Surgery, Hadassah-Hebrew University Medical Center, Jerusalem

60 14:56

Longitudinal Clinical Follow-up and Genetic Analysis of a French Cohort of Rod-Cone Dystrophy Associated with Mutations in *PDE6A* and *PDE6B* Genes

p. 91

Samer Khateb (1,2), Marco Nassisi (1), Kinga Bujakowska (1), Said El Shamieh (1), Cécile Mejecase (1), Christel Condroyer (1), Aline Antonio (1,2), Marine Foussard (1), Vanessa Demontant (1), Saddek Mohand-Saïd (1,2), Jose-Alain Sahel (1,2), Christina Zeitz (1) and Isabelle Audo (1,2)

(1) Sorbonne Universités, UPMC Univ Paris 06, INSERM, CNRS, Institut de la Vision, Paris, France (2) CHNO des Quinze-Vingts, DHU Sight Restore, INSERM-DHOS CIC1423, Paris, France

61 15:03 AC

Genetic diagnosis of Stickler syndrome caused by deep intronic mutation in COL2A1 in 10 family members

p. 92

Shirel Rossenwasser Weiss (1,2), Naama Orenstein (3), Nitza Goldenberg-Cohen (1,2,5)

(1) The Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Tel Aviv University, (2) Sackler School of Medicine, Tel Aviv University, (3) Pediatric Genetics, Schneider Children Medical Center of Israel, Petah Tikwa, (4) Rappaport Faculty of Medicine, Technion, Haifa, (5) Ophthalmology Department, Bnai Zion Medical Center, Haifa

62 15:10 AC

A Novel Intronic Founder Mutation of *PDE6B* is the Major Cause for Autosomal Recessive Retinitis Pigmentosa among Jews from the Caucasus p. 93

Yasmin Tatour (1), Shamaly Shamaly (2), Alona Yaakobi (3), Tom Rabinowitz (4), Eedy Mezer (1,5), Beatrice Tiosano (1,3), Ephrat Bril (6), Itay Chowers (6), Eyal Banin (6), Noam Shomron (4), Dror Sharon (6), Tamar Ben-Yosef (1)
(1) Rappaport Faculty of Medicine, Technion, Haifa, (2) Bnai Zion Medical Center, Haifa, (3) Department of Ophthalmology, Hillel Yaffe Medical Center, Hadera, (4) Faculty of Medicine, Tel Aviv University, Tel Aviv, (5) Department of Ophthalmology, Rambam Health Care Campus, Haifa, (6) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

15:17 **Discussion**

Cornea

14:00 – 15:30
Rayman East

Moderators: Irit Bahar and Ariel Gore

63 14:00

Safe collagen cross-linking of thin corneas: light attenuation (RF/UVA) versus limited photosensitizer penetration (WST-D/NIR) protecting the endothelium in corneas below 400µm p. 94

Arie Marcovich (1,2), Jurriaan Brekelmans (3), Alexandra Goz (1,2), Alexander Brandis (4), Effi Berko (1), Mor Dickman (3), Rudy Nuijts (3), Avigdor Scherz (2)
(1) Department of Ophthalmology, Kaplan Medical Center, Rehovot, (2) Department of Plant and Environmental Sciences, Weizmann Institute of Science, Rehovot, (3) University Eye Clinic Maastricht, Maastricht University Medical Center, Maastricht, the Netherlands, (4) Department of Biological Services, Weizmann Institute of Science, Rehovot

64 14:07

Superior efficacy of ziv-aflibercept over bevacizumab in reducing neovascularization following ocular chemical insult in the rabbit model p. 95

Ariel Gore, Tamar Kadar, Mayyan Cohen, Hila Gutman, Liat Cohen, Relli Gez, Shlomit Dachir, Vered Horwitz
Israel Institute for Biological Research, Ness-Ziona

65 14:14 AC

FS-LASIK Vs. Trans-PRK for the correction of high grade astigmatism (≥2.0D cylinder) p. 96

Assaf Gershoni, Igor Vainer, Eitan Livny, Irit Bahar
Assuta Optic Laser Center, Tel Aviv

66 14:21

Total detachment of DMEK grafts: results of repair of DMEK grafts freely floating in the anterior chamber. A case series p. 97

Avital Adler (1), Irit Bahar (1,2), Yoav Nahum (1,2), Uri Elbaz (1,2), Eitan Livny (1,2)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

67 14:28 AC

Amniotic membrane preparation and conservation made easy p. 98

Iris Deitch (1), Moran Friedman (2,3), Uri Elbaz (1,3), Irit Bahar (1,3), Yoav Nahum (1,3)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) The Krieger Eye Research laboratory, Felsenstein Medical Research Center, Petach Tikva, (3) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

68 15:35

Contrast sensitivity and crowding effect in patients with Keratoconus p. 99

Ravid Doron (1), Liron Levi (1), Yulia Pernikov (1), Riki Greenberger (1), Einat Shneor (1)
(1) Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem

69 14:42

A comparison between multifocal, extended range of vision and monofocal intraocular lenses p. 100

Luba Rodov (1), Olga Reitblat (2), Adi Levy (2), Ehud Assia, (2.3), Guy Kleinmann (1,3)
(1) Kaplan medical center, Rehovot, (2) Ein Tal eye center, Tel Aviv, (3) Meir medical center

70 14:49

Corneal committed cells restore the stem cell pool and tissue boundary following injury p. 101

Waseem Nasser (1), Aya Amitai-Lange (1), Rana Hanna (2), Beatrice Tiosano (2), Ruby Shalom-Feuerstein (1)
(1) Technion Israel Institute of Technology, (2) Hillel Yafe Medical Center

71 14:56 **Cytokines and chemokines present different expression pattern throughout the clinical course of sulfur mustard induced ocular injury.** p. 102

Vered Horwitz, Shlomit Dachir, Maayan Cohen, Hila Gutman, Liat Cohen, Hillel Buch, Gez Rellie, Tamar Kadar, Ariel Gore
Israel Institute for Biological Research, Ness Ziona

72 15:03 **DMEK versus DSAEK learning curves- first 100 cases** p. 103

Avital Adler (1,2) Eitan Livny (1,2) Yoav Nahum (1,2) Uri Elbaz (1,2) Orr Kaiserman (3), Irit Bahar (1,2)
(1) Ophthalmology department, Rabin Medical Center, Petach Tiqva, (2) Sackler Faculty of medicine, Tel-Aviv University, Tel-Aviv, (3) Barzilai Medical Center, Ashkelon

15:10 **Discussion**

Coffee and Exhibition 15:30 – 16:00

Retina- preclinical 16:00 – 17:10

Moderators: Tami Livnat and Dov Weinberger

73 16:00 **Photovoltaic Restoration of Sight in Rodent Models of Retinal Degeneration** p. 104

Daniel Palanker (1), Henri Lorach (1), Elton Ho (1), Georges Goetz (1), Xin Lei (1), Ted Kamins (1), Tiffany Huang (1), Keith Mathieson (2), Alexander Sher (3)
(1) Stanford University, Stanford, CA, USA, (2) University of Strathclyde, Glasgow, UK. (3) University of California, Santa Cruz, CA, USA

74 16:07 **Survival and integration of the retina/RPE allograft in rat models of retinal degeneration** p. 105

Daniel Palanker (1), Henri Lorach (1), Seungbum Kang (2), Alix Trouillet (1), Roopa Dalal (1)
(1) Stanford University, Stanford, CA, USA. (2) Catholic University of Korea, Seoul, Republic of Korea

75 **Effect of Histone Deacetylase Inhibitor (AN-7) on Vascular Permeability in the Retina** p. 106

16:42 AC

Elinor Megiddo-Barnir (1), Mor Dahbash (2,3), Yael Nisgav (2), Dov Weinberger (1,2,3), Ada Rephaeli (3,4), Tami Livnat (2,3,5)
(1) Department of Ophthalmology, Rabin Medical Center, Petah Tikva, (2) Laboratory of Eye Research, Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva, (3) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (4) Laboratory of Experimental Pharmacology and Oncology, Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva, (5) National Hemophilia Center, Sheba Medical Center, Tel Hashomer

76 **Detection of genes associated with proliferative diabetic retinopathy using nanostring technique** p. 107

16:14 AC

Jawad Abudbai (1), Shirel Rossenwasser Weiss (2,3), Oren Tomkins (1), Adel Shalata (3), Nitza Goldenberg-Cohen (1,2,5)
(1) Ophthalmology Department, Bnai Zion Medical Center, Haifa, (2) The Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Tel Aviv University, (3) Sackler School of Medicine, Tel Aviv University, (4) Genetics, Bnai Zion Medical Center, Haifa, (5) Rappaport Faculty of Medicine, Technion, Haifa

77 **Inhibitory Effect of Butyroyloxymethyl-diethyl phosphate (AN-7) on Choroidal Neovascularization in a Mouse Model** p. 108

16:21 AC

Mor Dahbash (1,2), Yael Nisgav (1), Nataly Tarasenko (2,3), Dov Weinberger (1,2,4), Ada Rephaeli (2,3) and Tami Livnat (1,2,5)
(1) Laboratory of Eye Research, Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Laboratory of Experimental Pharmacology and Oncology, Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva, (4) Department of Ophthalmology, Rabin Medical Center, Petah Tikva, (5) National Hemophilia Center, Sheba Medical Center, Tel Hashomer

78 **Intravitreal Trimethoprim and Sulfamethoxazole toxicity to the retina of albino rabbits** p. 109

16:28 AC

Orit Mazza (1,3)*, Zohar Habot-Wilner (2)*, Jonathan Shahar (2), Irit Mann (3), Anat Loewenstein (2), Ido Perlman (3)
(1) Department of Neurology, Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (2) Division of Ophthalmology, Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology and the Rappaport Institute, Haifa; *Equal contribution

79 16:35 AC **Up-regulation of thrombin activity in the posterior segment of STZ induced mice model of diabetic retinopathy** p. 110

Zehavit Goldberg (1,2), Efrat Shavit Stein (2,3), Yotam Taldan (2,3), Ifat Sher (1), Joab Chapman (2,3), Ygal Rotenstreich (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Department of Neurology and The J. Sagol Neuroscience Center, Sheba Medical Center, Tel HaShomer

51 16:49 **Hybrid Retina: A Novel Concept for Sight Restoration** p. 111

Yossi Mandel (1), Amos Markus (1), Gal Shpun (1), Revital Shick (1), Yoav Chemla (1), Itai Henn (1) and Nairouz Farah (1)
(1) Faculty of Life Sciences, School of Optometry and Visual Science and Institute for Nanotechnology and Advanced Materials (BINA), Bar-Ilan University, Ramat-Gan

16:56 **Discussion**

Concluding remarks 17:10 – 17:15

Dror Sharon

Abstracts

תקצירים

High Content Screening of Macrophages from Patients with Age-related Macular Degeneration

Batya Rinsky, Shira Hagbi-Levi, Sarah Hayoun, Michelle Grunin, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center

Purpose: Monocytes/macrophages have been implicated in the pathogenesis of age-related macular degeneration (AMD). We have previously shown that macrophages from patients with neovascular AMD (nvAMD) can be modulated by supplements. We have also demonstrated that TNFα is an important mediator of the proangiogenic effect of macrophages. These results raise the idea that macrophages can be used as therapeutic targets for nvAMD. In order to detect potential therapeutic compounds, we performed high content screening.

Methods: Monocytes were isolated from nvAMD patients (n=2). Cells were matured to macrophages, and then were re-plated at the Weizmann Institute of Science in concentrations of 2000 cells per well. The macrophages were polarized to an M1 phenotype using LPS+IFN-γ. A screen of 4065 compounds were added to the macrophages at a concentration of 5μM and incubated 24 hours. This screen included both natural supplements and approved drugs. Readout was defined as lower expression of TNFα measured via ELISA on macrophages' culture supernatant after exposure to the compounds. Validation of findings was performed using a detection assay to negate a possible connection between any of the compounds directly to TNFα. In addition, a cell viability test was performed in order to negate compounds that caused cell death.

Results: In the high content screening assay, we discovered 81 compounds that decreased expression of TNFα from M1 macrophages (threshold cut off 25% decrease in expression). In the detection assay, we found two compounds that bound directly to TNFα, and in the cell viability testing, we found 72 compounds that caused macrophage cell death. Through this method, we discovered 7 different compounds that decrease TNFα expression from macrophages isolated from nvAMD patients without causing cell death. These compounds inhibit several pathways which were previously associated with neovascularization or inflammation.

Conclusions: Through this high content screen of macrophages from nvAMD patients we discovered potential novel therapeutic compounds for the disease. Further research is required to assess the effect of these compounds using ex vivo and in vivo models for nvAMD.

Accuracy and Precision of Intravitreal Injections of Anti-VEGF Agents in Real Life: What is Actually in the Syringe?

Itamar Loewenstein (1), Michaella Goldstein (1), Joseph Moisseiev (2), Elad Moisseiev (1)
(1) Department of Ophthalmology, Tel Aviv Medical Center, Tel Aviv (2) Department of Ophthalmology, Sheba Medical Center, Ramat Gan

Purpose: To evaluate the accuracy and precision of anti-VEGF volume delivery by intravitreal injections in the clinical setup.

Methods: Volume output was measured in 669 intravitreal injections administered to patients, calculated from the difference in syringe weight before and after expelling the drug. Weight was measured using an electronic analytical balance, with a resolution of 0.1 mg. Volume output was then calculated using the specific density of each drug. Three groups were included: institutional pre-filled 1.0 mL syringe with bevacizumab (group 1, n=432), commercially available pre-filled small-volume syringe with low-dead-space plunger design with ranibizumab (group 2, n=125), and aflibercept drawn by the injecting physician and injected with a 1.0 mL syringe (group 3, n=112). The three groups represent different combinations of anti-VEGF agents, drawing techniques and syringes. Accuracy was analyzed by mean absolute percentage error (MAPE), and precision by coefficient of variation (CV).

Results: Volume outputs in all three groups were significantly different from the target of 50 µL (0.05 mL) ($p<0.0001$ for all). MAPE values were 12.25%±5.92% in group 1, 13.60%±8.75% in group 2, and 24.69%±14.84% in group 3. No difference was found between groups 1 and 2, but both were significantly more accurate than group 3 ($p<0.0001$ for both). CV values were 0.086 in group 1, 0.096 in group 2 and 0.136 in group 3. Volume outputs larger than the target of 50 µL were measured in 83.7% of the injections, and notably more in group 3 (96.4%) than in groups 1 and 2. A deviation of more than 10% of the intended volume delivered by the intravitreal injection was measured in 41.1% of cases.

Conclusions: This is the first study to evaluate the volume of intravitreal anti-VEGF agents delivery in the clinical setup, and it highlights their sub-optimal accuracy and precision. Use of a pre-filled (groups 1 and 2) syringe was associated with improved accuracy, and low-dead-space plunger design (as in group 2) may improve precision.

Socio-Economic Status and Visual Outcome in nvAMD

Nadav Levinger (1), Gala Beykin (1), Michelle Grunin (1), Diego Almeida (1), Jaime Levy (1), Hagai Levine (2), Edward Averbukh (1), Itay Chowers (1)
(1) Department of Ophthalmology, Hadassah- Hebrew University Hospital, Jerusalem
(2) Braun School of Public Health and Community Medicine, Hadassah- Hebrew University Hospital, Jerusalem

Purpose: Due to the high prevalence of AMD, it is of utmost importance to recognize factors that contribute to a lower visual outcome. Socioeconomic status, which is an important determinant of health, is such a potential factor. We aim to assess if socioeconomic status is associated with visual outcome in neovascular AMD (nvAMD) in the Israeli population.

Methods: Retrospective single center cohort study, with demographic and clinical data extracted from patient charts. Patients' residential address recorded in the electronic charts was used to determine socio-economic status (SES) based on the 2008 Israeli census. Statistical analysis was performed to define the relationship between the economic cluster and clinical parameters.

Results: 664 nvAMD patients treated at Hadassah medical center were identified. A weak correlation was found between the baseline visual acuity (VA) of the first eye and SES (R=-0.13, p=0.049). There was no association between baseline VA of the first eye with nvAMD and SES, when grouping the patients into four SES groups (p= 0.185). Nevertheless, there is a trend for better baseline VA in higher SES. No correlation was found between the SES and the VA at presentation of the second eye (R=-0.05, p=0.95). SES was not associated with the number of anti-VEGF injections to the first (p=0.943) or second eye (p=0.704). After one-year of follow-up, an insignificant correlation was identified between the SES and the VA of the first eye (R=-0.138, p=0.067), but not the second eye (R=0.007, p=0.067). No association was found between the SES and the VA of the first or second eye after 1 year of therapy (p=0.421, p=0.900 respectively).

Conclusion: The lack of association between socio-economic status and visual outcome in nvAMD followed up in Jerusalem, suggests that there are no social disparities in ophthalmologic care.

Is there any change in the thickness of the outer macula after multiple intravitreal injections?

Ofira Zloto (1,2), Iris Moroz (1,2), Oded sagiv (1,2), Joseph Moisseiev (1,2), Mordechai.Rosner (1,2)
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Purpose: To evaluate if there is a change in the thickness of the outer macula, that is not involved by disease, in patients who received multiple intravitreal injections.

Methods: Four areas of the outer macular retina were defined according to the ETDRS map: superior perifovea, inferior perifovea, temporal perifovea and nasal perifovea. All participants had a disease that was not extended to the perifovea. The thickness of the perifovea areas as measured by Optical Coherence Tomography (OCT) at the end of follow up was compared for each patient, to the measurements at the beginning of the follow up. The thickness of these retinal areas was also determined in two groups of patients (matched for age and gender): those that received less than 30 injections, and those that received 30 injections or more.

Results: 28 patients that received 30 intravitreal injections or more, and 28 patients that received less than 30 injections were included in the study. No change in thickness of the superior, inferior and nasal perifovea areas were found after 30 injections or more ($p= 0.258, 0.789, 0.853$, respectively, matched pairs). However, the temporal perifovea demonstrated significant thinning after 30 injections or more ($p=0.02$, matched pairs). When comparing the patients that received 30 intravitreal injections or more, to those who received less than 30 intravitreal injections, no significant differences in the superior and nasal areas were found ($p=0.595, 0.782$, respectively, t-test) in contrast to a significant thinning in the inferior and temporal retina ($p<0.001$, $p<0,001$, respectively, t-test).

Conclusions: The current study demonstrated a significant thinning in the temporal and inferior perifovea areas after 30 injections or more. Larger studies with documentation of the area of injection should be performed in order to suggest the causes of this finding.

Evaluation of anti-oxidative treatments on the modulation of macrophages' functions and retinal degeneration

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Purpose: Oxidative stress was implicated in the pathogenesis of age-related macular degeneration (AMD). In addition, studies have highlighted the involvement of macrophages in the progression of both atrophic (aAMD) and neovascular (nvAMD) AMD, and they could potentially serve as subjects of new therapeutic approaches. Here, we aim to investigate the effect of anti-oxidative treatments on macrophages from AMD patients and on photoreceptor survival.

Methods: Four anti-oxidative treatments were evaluated (G1, G2, G3, and G4). The compounds were added to the culture medium of M1 (LPS+INFɣ) and M2A (IL13+IL4) macrophages from AMD patients (n=7). Mouse choroidal tissue (n=7) was grown with different supernatants from treated M1/M2A macrophages, along with untreated macrophages' supernatant as a control, to evaluate the effect of treatments on macrophage's angiogenic properties via choroidal sprouting assay (CSA). Mouse retinal explants (n=7) were incubated with the groups of treated and untreated macrophages for 18 hours, and evaluated for photoreceptor apoptosis using TUNEL staining. Finally, 6-8 weeks old balb/c mice (n=8) were exposed to 8000 lux bright light for 3 hours, and were then administered all four anti-oxidative treatments, via gavage, during the week that preceded the light injury and 7 days afterward. Oxidative stress levels were assessed using HNE staining. Visual function and thickness of the outer nuclear layer were evaluated using electroretinography (ERG) and histological analysis.

Results: With regards to the ability of the anti-oxidative treatments to modulate macrophages' functions, only the group supplemented with G3 reduced M2A macrophages' angiogenesis in the CSA (n=7,0.46-fold, p=0.0027) and its neurotoxic effect in the retinal explant assay (n=7, 0.47-fold, p=0.04). In the light damage model, groups supplemented with G2, G3 and G4 strongly decreased the level of oxidative injury (n=8, 0.57- fold, p=0.0001, 0.54-fold, p= 0.002 and 0.54-fold, p=0.002, respectively). However, none of the treatments was associated with reduced photoreceptor cell loss per histology and ERG.

Conclusions: Administration of anti-oxidant treatment containing lycopene and carnosic acid was able to modulate M2a macrophages at the functional level. In addition, we found that anti-oxidative treatments considerably reduced the oxidative stress level in light-damaged retina. Additional research is required to assess if therapies may curb photoreceptor death or neovascularization in AMD.

Full Thickness Macular Hole in AMD, Atrophic Scar: How can we Differentiate when there is a Doubt?

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Purpose: Full thickness macular defects (FTMD) in Age-related macular degeneration (AMD) may be an expression of the atrophic nature of the disease, in essence atrophic holes (AH). However, due to the rising AMD prevalence, its concomitance with full thickness Macular Holes (MH) has become more common as well. Since AH currently has no well-established treatment, whereas MH are potentially treatable by surgical measures, an accurate diagnosis is essential.

This study aims to utilize spectral domain optical coherence tomography (OCT) for investigating morphologic abnormalities of FTMD's in order to differentiate AH from MH.

Methods: Clinical charts and OCT images of all patients, diagnosed with FTMD with underlying AMD between January 2011 and May 2017, were reviewed. OCT images were analyzed and findings recorded by a retina specialist.

Results: 23 eyes with FTMD were classified according to the holes' margin morphology. FTMD with round borders were assigned to the MH group (13 eyes), and those bordered by gradually thinning retina were defined as AHs (10 eyes). MHs were significantly associated with the presence of a pigment epithelial detachment (PED) ($p=0.04$). AH featured a window defect wider than the FTMD ($p=0.01$). The presence of a free operculum or of intra-retinal fluid on OCT trended toward an association with MH ($p=0.07$ and $p=0.08$ respectively). MH inner diameter was larger than that of AH (mean 686µm vs. 433µm, $p=0.03$), whereas outer diameter was smaller in the MH group (748µm vs. 1247µm, $p=0.02$), making the inner/outer ratio far larger in the AH group (3.2 vs. 1.3, $p<0.01$).

Conclusions: An observation of FTMD in AMD patients may present with diagnostic and therapeutic dilemmas. Discerning MH from AH in these patients is possible by using characteristic OCT features as criteria.

Activated Protein C stabilizes retinal barrier and inhibits laser induced choroidal neovascularization

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Purpose: We studied the ability of activated protein C (APC) to stabilize the blood retinal barriers (BRB) and to reduce choroidal neovascularization (CNV).

Methods: In vitro model: human retinal endothelial and retinal pigment epithelial (RPE) cells were cultured to achieve stabilized barrier cell structure. APC-induced cell permeability was evaluated based on spectrophotometric monitoring of the transport across the cell layer of labeled dextran. Cellular localization of the tight junction protein Zonula Occludens 1 (ZO-1) was studied using immunofluorescence staining and confocal 3D imaging. In vivo model: CNV was induced by laser photocoagulation on C57BL/6J mice. Immediately following injury mice were injected intravitreally with 0.1-5µg/eye APC. On day 5 following CNV induction, FITC-dextran was injected to the mice hearts, eyes were enucleated and retinal and choroidal flatmounts were prepared. CNV area, volume and vascular penetration were evaluated using 3D confocal imaging of perfused FITC-dextran. Quantification of FITC-dextran was performed by Imaris analysis.

Results: In vitro: APC induced translocation of ZO-1 to the cell membrane in RPE as well as retinal endothelial cells. Reduction in permeability and stabilization of retinal barrier was detected in RPE cells. In vivo: APC treatment significantly reduced CNV volume and blood vessels penetration to the retina, in a dose-dependent manner. Histologic examination showed no evidence of retinal toxicity in eyes that were injected with APC.

Conclusions: Intravitreal injection of APC stabilized BRB and reduce CNV growth. The current results offers an innovative approach that may lead to the development of novel therapeutic strategies targeting CNV.

Nano-drops for correcting refractive errors

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Purpose: To investigate the ability of eye-drops filled with synthetic nanoparticles with particular optical properties to correct various range of refractive errors

Methods: Experimental study analyzing the refractive changes of 10 pig eyes after instillation of various concentrations of eye-drops filled with synthetic nanoparticles. Refraction was measured with a handheld automated refractometer before and every 15mn after instillation of the eye-drops for two hours. The magnitude of the refractive change, the corneal refractive index, and the corneal shape modification have been recorded as well as an electronic microscopic examination in order to identify and analyze the distribution of the nanoparticles inside the cornea.

Results: A mean spherical equivalent correction of 2,24 +/- 0.07D has been achieved for myopic refractive error testing, whereas a correction of 2,74+/- 0.4D has been achieved for the hyperopic refractive error. No statistically significant changes (p = 0,6 and 0,5, respectively for myopic and hyperopic testing) have been observed in the corneal central keratometry. Encapsulated hypereflective nanoparticles of 0.68nm diameter on average were observed throughout the first 60 microns of the corneal thickness.

Conclusions: Eye-drops filled with synthetic nanoparticles have shown promising potential for a revolutionary non-invasive alternative for the correction of refractive errors.

SMART Intraocular Lens, a new concept of remotely activated presbyopic correction

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Purpose: To demonstrate the ability of an optical remotely activatable technology, that may fit to glasses and intraocular lens, to achieve multifocality and zooming capability.

Methods: We designed an optical setup simulating an externally influenced reflective lens. We used a multiple element lens with coating surfaces, on and in the lens, that have tunable reflectivity as they are made from a semiconducting nano-material whose reflectivity can be modified by an external control illumination at a wavelength that is selectively absorbed by the semiconducting coating layer.

Results: Using this optical setup in laboratory, we were able to achieved tunable multifocality by selectively bringing into focus the reading chart at 30cm (reading distance) or at 80cm (intermediary-computer distance). Zoom capacity was successfully achieved by magnifying the reading chart placed at distance of 3m by a factor 3.

Conclusions: These promising preliminary results might bring a revolutionary solution to overcome presbyopia symptoms as well as age-macular degeneration visual impairments, with the help of an image magnification externally activated. A new setup to fit a pairs of glasses is currently under development.

Complications and compliance in over-the-counter versus fitted contact lens wearers

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Purpose: In the State of Israel, contact lenses (CLs) may be legally purchased over the counter (OTC). However, incorrect fitting and usage of CLs may lead to ocular discomfort and to corneal infections. This study compared soft CL users who purchased contact lenses OTC (OTC_CL) to users who were fit and followed up in optometry practices (F_CL).

Methods: Healthy soft CL wearers were recruited from patients in the college clinics, two optometry practices and through ads. The study was approved by the institutional review board and subjects signed a consent form prior to their participation. Examiners filled out an online form with Likert-type scale including health history, contact lens usage information, current corneal, lid and sclera condition (based on slit lamp examination), tear film quality, contact lens fit, and Snellen monocular and binocular distance visual acuity. Outcomes from OTC_CL and F_CL were compared using one-way ANOVA and Chi Squared tests with a significance level of 0.05.

Results: There were 43 participants in the F_CL group (mean age 25.33± 4.12, range: 18-35, 35 female), and 41 in the OTC_CL group (mean age: 28.49±6.70, range: 18-43, 31 female) with no significant difference between age and sex. Ocular complications were significantly lower in the F_CL group ($F_{(df=1,82)}$ = 13.07, $p<0.001$). Namely, meibomian gland disorder ($p=0.02$), corneal neovascularization ($p=0.007$), corneal staining ($p=0.03$), and giant papillary conjunctivitis ($p=0.00$). Lens fit was significantly better ($F_{(df=1,82)}=5.02$, $p<0.05$) in the F_CL group with significant differences between lens overall diameter ($p=0.03$) and optical power ($p=0.03$). There was no overall effect of handling and compliance, but there was a significant difference between hand washing prior to lens handling ($p =0.01$).

Conclusions: Findings demonstrate that OTC_CL wearers suffer from more complications, wear lenses that are not well fit, and are less compliant with hand washing. Results of a larger cohort of this study should be brought to health regulation bodies to reexamine the current structure of contact lens sales in Israel.

Does the traditional method for refraction produce optimal subjective visual acuity?

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Purpose: The standard subjective refraction method is defined as maximum plus (or least minus) for maximum visual acuity (MPMVA). This method is mainly based on accommodation control and less on the subjective visual quality as perceived by patient feedback. Depth of focus can be defined as a perceptual tolerance that enables to see an object in the same brightness, contrast and shape in a range of refractive error. Therefore, it is reasonable to assume that maximum visual acuity can be identified within a range of refractive corrections. Studies have shown that under-correction is a risk factor for myopia progression. Moreover, over-correction ("over minusing") is often used for prevention of myopia progression. The aim of this study was to compare a novel method for subjective refraction based on maximum visual acuity with the traditional MPMVA method in terms of the final prescription and quality of the vision.

Methods: Healthy subjects underwent visual subjective refraction testing according to the standard method, MPMVA and according to the maximum visual quality improvement method. The quality of vision obtained at the end of the refractive tests (in each of the methods separately) was assessed using FACT chart contrast sensitivity, and visual acuity.

Results: 30 healthy subjects (21 females, mean age: 25.69±4.77, Range: 19-38), participated in the study. Visual acuity was equal for both methods (0.007±0.059). Visual refraction range was +0.75 to -10.25D and +0.25 to -10.25D for the standard and the new methods respectively. Sphere and spherical equivalent correction were significantly higher in the new method ($p<0.0001$; $p<0.0001$). Contrast sensitivity was significantly higher in the new method for 3, 6, 12, 18 cpd ($p=0.026$; $p=0.002$; $p=0.001$; $p=0.0001$) respectively. No difference was found for 1.5 cpd ($p=0.73$).

Conclusions: The suggested method enables good (and equal) visual acuity compared to the standard methods. Moreover, it provides a better visual quality, i.e., better contrast sensitivity that enables better functioning in daily life. These results are probably due to changes in depth of focus. The effects of the novel method on other visual functions and the possible link to myopia progression should be further investigated.

The effects of swaying (shokeling) on accommodative function during learning and praying among yeshiva students

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Purpose: Accommodation is the ability of the lens to focus on objects at different distances to obtain a clear retinal image (Lockhart and Shi, 2010). Near work habits in the ultra-orthodox community include long hours of sustained near work, with small text size and increased accommodative effort, accompanied by rocking movement back and forth (Ben Simon et al., 2004). The aim of this study was to compare the effects of swaying on accommodative facility and amplitude of accommodation among yeshiva students.

Methods: Healthy subjects with a minimum of 6/9 for distance and J1+ for near and normal binocular vision participated in the study. The study was approved by the institutional review board and subjects signed a consent form prior to their participation. Participants were divided into those that sway during learning or praying and those that do not (by use of a questionnaire). Over refraction was performed using retinoscopy and subjective refraction. Cover test, Amplitude of Accommodation (Push Up), and Monocular Accommodative Facility (±2.00 flippers) were then performed. Results were analyzed using correlation and unpaired T tests.

Results: 40 male yeshiva students (21 swaying, 19 control) between the ages of 18-30 years (average age 24.4 ± 3.72) participated in the study. We found that the swaying group and the control group had similar MAF ($p=0.47$) and Amplitude of Accommodation ($p=0.14$) results. We found no correlation between accommodative ability and the number of years in yeshiva and hours spent studying/ praying daily. Surprisingly, we found a high percentage of accommodative dysfunctions (38%) in both groups. (25% had complaints such as headaches, discomfort, blurred vision, burning and tearing in the eyes during the hours of study.

Conclusions: Swaying does not affect accommodative ability. Yeshiva students are advised to undergo extra screening for accommodative dysfunctions. It is important to educate yeshiva students about the impact their study habits and environments have on their visual system and to learn techniques that can prevent a reduction in accommodative ability from occurring. Further research on the effects of accommodative anomalies and the effects of swaying on myopia progression can be conducted in the future.

Can we avoid underdiagnosis of pseudoexfoliation syndrome in pseudophakic patients?

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Purpose: To examine how to improve the sensitivity and specificity of pseudoexfoliation syndrome (PES) diagnosis in pseudophakic patients.

Methods: The study cohort included 33 consecutive patients admitted for cataract surgery at the ophthalmology department of a single tertiary medical center. A detailed slit lamp examination of the patients including gonioscopic assessment of the iridocorneal angle, before and after pupillary dilation, was performed by a glaucoma specialist prior to surgery. An assessment form was completed for each patient, documenting the presence or lack of clinical signs of PES. Patients were re-examined in a similar fashion on a 1-2 weeks follow-up post-op visit by a masked glaucoma specialist.

Results: Twenty three patients (23 eyes) were included in the statistical analysis. PES was diagnosed preoperatively by the first observer in 13 patients (56.5%). PES diagnosis was based on 3 clinical features; Sampaolesi line (100% of cases), anterior capsular deposits (76.9%) and pupillary border deposits (61.5%). Postoperative PES diagnosis was based on the same criteria. Postoperatively, 9 of the 13 preoperatively established PES patients were diagnosed with PES (69.2% sensitivity), and one preoperative non-PES patient was diagnosed with PES (90% specificity). The correlation between the pre and postoperative diagnoses was statistically significant ($X^2=11.37$, $p<0.01$). Pupillary border deposits (88.9% of cases) and Sampaolesi line (66.7% of cases) were the corner stones of postoperative PES diagnosis. However, anterior capsular deposits were evident only in the minority of postoperative examinations (33.3%).

Conclusions: Underdiagnosis of PES in pseudophakic patients is common, and may have significant implications on appropriate management. Careful attention to pupillary border anatomy and a meticulous gonioscopic assessment of the iridocorneal angle in the search of clues for PES are essential for accurate diagnosis. Preoperative documentation of PES is important and would help avoid this diagnostic pitfall.

Reduction of intraocular pressure by digoxin derivatives that selectively inhibit Na,K-ATPase of the NPE

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Purpose: We have synthesized digoxin derivatives with selectivity for the $\alpha 2\beta 3$ isoform of the Na/K ATPase that effectively reduce IOP in rabbits when applied topically. The purpose of the current study was (1) to compare these derivatives with available glaucoma drugs, (2) to produce a pro-drug in order to avoid potential toxic side-effects on the cornea and (3) to find a better vehicle for better efficacy of the drug.

Methods: A single drop of the study drug or one of 3 glaucoma medications was applied to one eye of New Zealand White healthy rabbits. IOP was measured in both eyes of awake animals using a pneumotonometer, before drop application and subsequently after 1, 2, 4, 6, 8, 10, 12 and 24 hours. Magnitude of IOP reduction was calculated relative to the untreated control eye.

Results: The $\alpha 2\beta 3$ selective digoxin derivative was found to reduce peak IOP by 23% comparable to the reduction of Timolol 0.5%(16%), Latanoprost 0.005%(20%), Dorzolamide 2% (20%). Combined application of the digoxin derivative with Latanoprost increased peak IOP reduction to 30%. There were no noticeable side effects on the ocular surface or corneal thickness 2. We produced a pro-drug which was found to be ineffective as an inhibitor of the major isoform of the Na,K-ATPase in the cornea $\alpha 1\beta 1$, but upon penetration into the eye reduced the IOP 3. We found a vehicle containing polysorbate to be more efficient than water.

Conclusions: A novel $\alpha 2\beta 3$-selective digoxin derivative is effective in reducing IOP in normotensive rabbits. Its efficacy and apparent safety is consistent with selective targeting of the Na/K ATPase isoform specific to the secretory ciliary epithelium.

MIMS procedure: concept and experimental models

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Purpose: To evaluate the safety and performance of a novel surgical system for a Minimally Invasive Micro Sclerostomy (MIMS) in experimental models.

Methods: MIMS (Sanoculis Ltd, Israel) is an ab-externo stent-less procedure used to reduce intraocular pressure (IOP). An activation system is used to operate a hand piece that includes a 600 µm needle containing an injectable 300 µm triangular blade that spins around its longitudinal axis. The needle is inserted into the subconjunctival space > 5mm away from the superior limbus and the blade is injected at the limbal area creating a 50-100 µm drainage channel at the sclero-corneal junction, connecting the anterior chamber to the sub-conjuctival space. The first generation of MIMS surgical system was tested in bilateral procedures in 6 pigs and unilateral in 10, following Mitomycin C injection. All adverse events, IOP measurements and bleb descriptions were recorded for up to 14 weeks. Histopathological analysis and AS-OCT imaging were performed as well.

Results: No device mal-functions were recorded. Scleral tunnels were repeatedly achieved in all models. No significant intra or post-operative complications were recorded in vivo. Mean IOP in the in vivo unilateral study was significantly decreased from 18.9±3.2 mmHg to 11.1± 4.9 on the first postoperative day ($P<0.001$) and gradually returned to normal after 14 weeks (18.2±1.9 mmHg) as compared to the un-operated eye which remained 18.9±4.1 mmHg on average at all time points. Similar IOP results were achieved in the bilateral in-vivo study (average pre-op IOP of 18.5± 4.2 mmHg was reduced to 13.25±3.8 on the first day followed by a gradual return to normal). Histological analysis of the interrogated tissue was generally not associated with significant tissue reaction, and without any significant collateral damage to the eye. Effective fluid percolation was achieved with a documented drainage channel which was observed in all eyes but one (95.4%).

Conclusions: Throughout the course of these experimental studies, the MIMS procedure exhibited a consistent and excellent safety and efficacy profile. In the near future, this innovative stent-less procedure could provide a novel solution for uncontrolled IOP in glaucoma patients.

Objective perimetry in Glaucoma Patients Using Chromatic multifocal pupillometry

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Purpose: To objectively assess visual field defects in glaucoma patients using chromatic multifocal pupilloperimetry.

Methods: Eleven glaucoma patients (5 females and 6 males, age: 73.9±9.7, mean± SD) and twelve healthy age-matched controls were enrolled (7 females and 7 males age: 66.6±4.2 mean). Pupil response to focal blue and red light stimuli (peak 485 and 624 nm, respectively) presented at 54 targets in a 24-2 visual field were recorded. The pupil response of patients was compared to the pupil response of controls and were correlated with patients' Humphrey 24-2 perimetry.

Results: Significantly lower percentage of pupil contraction (PPC) and maximal relaxation velocity (MRV) were recorded in glaucoma patients in response to blue light in visual field locations that were abnormal by Humphrey perimetry. A milder defect was recorded in response to red light stimuli. Glaucoma patients demonstrated significantly lower absolute deviation in PPC and maximal relaxation deceleration in response to blue light, and in MRV in response to red light compared with controls (all $p<0.01$).

Conclusions: This study demonstrates the potential feasibility of using pupillometer-based chromatic perimetry for objectively assessment of visual field defects in glaucoma patients. In glaucoma, the pupil response to blue light and pupil response parameters PPC and MRV were most affected, but the latency of the pupil response was normal. These findings suggest that analysis of different parameters of pupil response to chromatic light may differentiate between optic nerve and retinal pathologies.

Non-Pigmented ciliary epithelium Exosomes surface proteins are crucial for Wnt signaling delivery

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Purpose: Our purpose was to investigate the specific mode by which Non-Pigmented ciliary epithelium (NPCE) exosomes deliver their signals to the Trabecular meshwork (TM) cells. In order to elucidate the role of exosomes surface protein in Wnt signaling pathway attenuation in TM cells, we treated the NPCE exosomes with Proteinase-K.

Methods: Exosomes were isolated by PEG 8,000 method and concentrations were determined by Tunable Resistive Pulse Sensing (TRPS) method. NPCE derived exosomes were treated with proteinase K to achieve clearance of surface proteins on exosomes. Analysis by cryo-TEM was performed to ensure exosome membrane integrity. Next, western blot analysis was done to verify complete removal of CD81 protein known to be present in untreated NPCE exosomes. NPCE derived exosomes treated with proteinase K were incubated with TM cells for 8 hr, and proteins expression was determined using western blot analysis. Untreated NPCE exosomes were used as control in all the experiments.

Results: Cryo-TEM analysis of NPCE derived exosomes after Proteinase-K treatment demonstrates that the treatment didn't damage exosomes membrane. Tracking the expression of CD81 protein indicates that a complete removal of the protein marker for exosomes was achieved. The expression of Wnt signaling proteins in TM cells, which were incubated with untreated NPCE exosomes, was decreased compare to untreated TM cells. In addition, NPCE exosomes treated with Proteinase-K diminished this effect in TM cells.

Conclusions: Our findings show that Wnt proteins treated with NPCE exosomes and proteinase K were affected and their expression levels were increased compare to untreated exosomes. Hence, we believe that a specific uptake of NPCE exosomes by TM cells requires recognition of TM cells with exosomes surface proteins.

Nd:YAG Capsulotomy is associated with sustained IOP elevation in patients treated with anti-VEGF injections

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Purpose: To assess the effect of lens status on sustained IOP elevation in patients treated intravitreally with anti-VEGF agents.

Methods: Data were retrospectively collected for all patients treated with intravitreal injections of anti-VEGF medication at a tertiary medical center in July 2015. Findings were analyzed by lens status during 6 months' follow-up. The main outcome measure was a sustained increase in IOP (IOP ≥21 mmHg or change of ≥6 mmHg from baseline on >2 consecutive visits, or addition of a new IOP- lowering medication during follow-up).

Results: A total of 119 eyes of 100 patients met the study criteria: 40 phakic, 40 pseudophakic, and 39 pseudophakic after Nd:YAG capsulotomy. The rate of sustained IOP elevation was significantly higher in the post-capsulotomy group (23.1%) than in the phakic/pseudophakic groups (8.1%) (p=0.032), with no statistically significant differences among the 3 groups in mean number of injections, either total (p=0.82) or by type of anti-VEGF mediation (bevacizumab: p=0.19; ranibizumab: p=0.13), or mean follow-up time (p=0.70).

Conclusions: Nd:YAG capsulotomy appears to be a risk factor for sustained IOP elevation in patients receiving intravitreal anti-VEGF injections. This finding has important implications given the growing use of anti-VEGF treatment and the irreversible effects of elevated IOP.

Determination of light stimulus parameters for assessment of rod, cone and melanopsin mediated pupil response in different retinal locations

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Purpose: To determine the optimal light stimulation duration and intensity for mapping rod, cone and melanopsin-mediated Pupil Light Reflex (PLR) in different locations of the visual field (VF).

Methods: The PLR for small (0.43°) chromatic light stimuli was tested in the right eye of ten healthy subjects, age 24–45 years. Blue (485±20 nm) and red (625±15 nm) light stimuli, were presented at increasing light intensities (0.5 – 3.75 log cd/m2) and durations of 50-6000 milliseconds in four peripheral (24°) and four central (6°) VF locations using a computerized multifocal pupilloperimeter.

Results: The red light induced smaller PLRs compared to blue light of matching intensity in all VF locations. A substantial rod-mediated PLR was obtained by presenting blue light stimuli at 1.5 log cd/m^2 for 200 milliseconds in central and peripheral VF locations. To achieve a similar PLR for the red light, a 10- and 18- fold higher light intensity was required at central and peripheral VF locations, respectively, and a minimal duration of 500 milliseconds, suggesting that the PLRs under these conditions are mainly cone-mediated. A sustained melanopsin-mediated PLR was induced in central VF locations using blue stimuli at 3.8 log cd/m^2 for at least 6 seconds.

Conclusions: Chromatic multifocal pupillometry enables the assessment of rod-, cone- and melanosin- mediated PLR at different VF locations by using small light stimuli. The optimal light intensity and stimulus duration determined here for assessing the focal activation of the three photoreceptor systems will be used as a model for objective testing of VF defects in subjects with retinal and optic nerve degenerations.

Comparison of scleral buckle surgery with and without gas tamponade for the treatment of rhegmatogenous retinal detachment

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Purpose: To compare the outcomes and complications of scleral buckle surgery with and without gas tamponade for the treatment of rhegmatogenous retinal detachment.

Methods: Retrospective multicenter chart review of 213 eyes of 213 patients were collected. One hundred and twelve patients underwent SB surgery with gas tamponade between 2013-2015 in Royal Alexandra Hospital. One hundred and one patients underwent SB surgery without gas tamponade between 2005-2015 in Rabin Medical Center. Only patients followed for at least 12 months were included.

Results: The final average visual acuity in the SB without gas group was 0.3 logMAR versus 0.6 logMAR in the SB with gas group (P=0.056). The final rate of central anatomical success in the last examination (12 months) was 99% in the SB without gas group versus 97% in the SB with gas group (P=0.623) while 10.9% and 4.5% respectively had sill areas of retinal detachment in their final examination. On 1 week examination 7.9% in the SB without gas group and 3.6% in the SB with gas group needed laser photocoagulation treatment. On final twelve months examination 7.9% of the SB without gas group and 12.5% of the SB with gas group had postoperative complications (P=0.145).

Conclusions: There were no significant differences in the final rate of anatomical success and complications between the two groups. Both Scleral buckle with and without gas tamponade had high anatomical success rate in our study.

A Novel Method for Automated Visual Field Testing on Eyes with Severe Central Vision

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Purpose: Reliable visual field testing requires the tested eye to be fixated on a target. This poses a major obstacle for eyes with severe central vision loss. This study presents a method that can be used if the fellow eye has sufficient visual acuity to reliably fixate.

Methods: A green filter was placed over the fellow eye. A Fastpac algorithm was used with a red stimulus. The green filter prevented transmission of the red stimuli, but allowed visualization of the white fixation light. Subjects were tested by both the conventional and the novel method, performed in a randomized order. The primary outcome was the degree of eye motion on gaze tracking.

Results: Eight subjects were recruited with visual acuity of hand motion or light perception in one eye and at least 6/60 in the fellow eye. In all cases there was less eye motion. A paired t test had a two-tailed p value of less than 0.0001. The mean reduction in motion was 69% (standard deviation 17%).

Conclusions: The novel method described provided a dramatic improvement in reliability, and offers a feasible solution for visual field testing in patients with unilateral severe central vision loss.

Uveitis induced by biologic agents used in cancer therapy

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Purpose: To report cases of uveitis induced by biologic therapy given for the treatment of cancer.
Methods: A retrospective analysis of uveitis in cancer patients treated with Vemurafenib, Nivolumab or Osimertinib between 2011 and 2016. Medical records were reviewed for demographic data, clinical presentation, and disease course.

Results: Included were 5 patients (age range 14-81 years, all were females) treated with Vemurafenib (n=3), Nivolumab (n=1) or Osimertinib (n=1). Oncologic diagnosis included metastatic thyroid carcinoma, pleomorphic xanthoastrocytoma, metastatic melanoma, adenocarcinoma of the lung, and metastatic breast cancer. Ocular manifestations appeared 3-82 weeks after the biologic treatment initiation, and were bilateral in 3 patients and unilateral in 2 patients. The most common presentation was anterior uveitis (4 patients, 7 eyes). One patient was diagnosed with an intermediate uveitis (1 eye). All cases presented with a sudden onset (8 eyes). Mean duration of uveitis was 31 weeks (range 10 - 150 weeks). Treatment included topical steroids (4 patients), and a single intravitreal steroid injection in one eye of one patient.

Conclusions: Uveitis may rarely be induced by biologic therapy used in cancer therapy. Both oncologists and ophthalmologists should be aware of this potential side effect. After exclusion of infection, early detection and treatment can prevent permanent complications and save the patient's vision.

Novel fluorescein angiography-based computer-aided algorithm for assessment of retinal vessel permeability in cases of proliferative diabetic retinopathy

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Purpose: Fundus fluorescein angiography (FA) has been used for more than 50 years and remains the ‘‘gold standard’’ for the evaluation of the integrity of the retinal vasculature. However, the interpretation of FA is still based on subjective physician assessment. Conventional fundus photography used for standard FA only evaluates about 30% of the total retinal area. Technological advances now allow us to image more than 80% of the retina with a single 200° ultra widefield (Optos UWF).

Our purpose is to present a novel method for quantitative assessment of retinal vessel permeability using a UWF-FA-based computer algorithm in cases of proliferative diabetic retinopathy (PDR).

Methods: Retrospective analysis of 40 subjects with PDR who underwent UWF-FA. Image pre-processing included removal of non-retinal and noisy images and registration to achieve spatial and temporal pixel-based analysis. Permeability was assessed for each pixel by computing intensity kinetics normalized to arterial values. A linear curve was fitted and the slope value was assigned, color-coded and displayed.

Results: Permeability maps were successfully generated for all subjects with PDR. Clear differences were found between cases before and after laser panretinal photocoagulation in terms of vascular leakage and vascular anatomy.

Conclusions: The new algorithm allows quantification of retinal vessel permeability and provides objective, more sensitive and accurate evaluation than the present subjective clinical diagnosis. Future studies with a larger patients' cohort and different retinal pathologies are awaited to further validate this new approach and its role in diagnosis and treatment follow-up. Successful evaluation of vasculature permeability may be used for the early diagnosis of brain microvascular pathology and potentially predict associated neurological sequelae. Finally, the algorithm could be implemented for intraoperative evaluation of microvascular integrity in other organs or during animal experiments.

A used spectral domain OCT machine without eye tracking is still a reliable tool: Real-life data

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Purpose: To test reproducibility of retinal nerve fiber layer (RNFL) measurements retinal thickness, Inner plexiform layer (IPL) and Ganglion cell layer (GCL) in healthy eyes using OCT Maestro Topcon.

Methods: forty-two healthy eyes of 84 subjects were included in the study. Two consecutive examination that took place in one visit of each patient were evaluated. For each OCT examination protocol, two series of OCT scans were obtained. Both eyes of each subject were imaged. The eyes were imaged two times by an examiner to assess intraobserver repeatability. For every patient, one eye was randomly chosen for analysis. Test-retest analyses were conducted for one eye per subject. Image quality higher then 25 (in first test and retest) were included in the analyses. A dependent sample T-test was used to compare mean values of first test versus retest for each parameter for each of the tests (macula, optic disk, macula v). Reliability measures for each parameter for each of the tests were calculated and included intraclass correlation coefficients (ICCs) and coefficients of variation (COVs).

Results: Retinal thickness, RNFL, GCL and IPL measurements were highly reproducible and reliable .
Averages of first and the repeat Macula tests (dependent samples t-test) were not significantly different for all comparisons. Averages of first and the repeat Optic Disk test (dependent samples t-test) were not significantly different for all comparisons. Averages of first and the repeat tests Macula V (dependent samples t-test) were not significantly different for all comparisons .

Image quality was on average the same in first and repeat tests.
Conclusions: Retinal thickness, RNFL, GCL and IPL measurements obtained using used OCT Maestro Topcon show good repeatability for healthy eyes. It seems that even a used OCT Maestro device after thousand working hours can be considered a reliable tool for measuring retinal and optic nerve parameters in normal eyes.

CMV specific T lymphocyte Infusion: A Novel Treatment for Resistant CMV Retinitis

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Purpose: To report a novel therapy for resistant CMV retinitis using CMV specific T lymphocytes.

Methods: Case history: A 26-year-old male presented to our uveitis clinic with sings of retinitis in his left eye, which were clinically compatible with CMV infection, accompanied by CMV viremia.
Past medical history is remarkable for aplastic anemia treated with allogeneic stem cell transplantation. Post transplant follow up was complicated with several events, among them an EBV reactivation which led to chemo refractory monoclonal extra nodal post-transplant diffuse large B cell lymphoma. In an attempt to restore anti-viral immunity against EBV, he received partially human leukocyte antigen (HLA) matched third party in vitro expanded EBV specific cytotoxic T lymphocyte (CTLs) serial infusion and achieved sustained complete response.
Treatment for the retinitis included Gancyclovir followed by Foscarnet intravitreal injections, both of which successfull initially, but ultimately failing due to a new onset drug resistance mutation. The patient experienced progression of the retinitis, with threatening of the central macula
Similar to the solution found for refractory EBV lymphoma it was decided to stop systemic pharmacologic anti-viral treatment and treat the patients with partially matched fourth party in vitro expanded CMV specific CTLs. In concern for reactive inflammation in the form of immune recovery vitritis, intravitreal foscarnet injections were continued, and the time of treatment was chosen as the best possible control of infection. Treatment included 3 weekly infusions.

Results: Remarkable response was noted, with complete resolution of viremia within 3 days after the first lymphocyte infusion, and complete resolution of the retinitis within 6 days of the second infusion.
A further one year follow up demonstrates long term cure from both systemic and ocular CMV without any evidence of GVHD

Conclusions: Further studies are necessary to determine whether this treatment modality may be applicable to the population of patients whose CMV retinitis responds poorly to aggressive systemic and intravitreal antiviral therapy

Identification of visual field defects in Macular and Retinal Degeneration patients using Chromatic pupilloperimetry

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Purpose: To objectively assess visual field (VF) defects in patients with macular and retinal degeneration using chromatic multifocal pupilloperimetry.

Methods: In the retina study, 10 retinitis pigmentosa (RP) patients (2 females and 8 males, age: 41.3± 16.2, mean± SD) and thirty-five healthy age-matched controls enrolled (20 females, 15 males age 50.7± 15.5). In the macula study, 10 age-related macular degeneration (AMD) patients (3 females and 7 males age: 68.7± 8.8) and 23 age-matched controls were enrolled (12 females, 11 males age: 60.1± 9.7). Pupil responses (PR) to blue and red light stimuli (peak 485 and 624 nm, respectively) presented at 54 targets in a 24-2 VF were recorded. The PR of patients was compared to the PR of controls and were correlated with patients' Humphrey 24-2 perimetry. Regression analysis was performed to identify the VF test point in which the PR of patients was significantly lower than the PR of controls.

Results: The PR was significantly diminished in RP patients compared with controls in areas that were "non-seeing" by the Humphrey perimetry. The PR to both light colors was reduced, but more VF test points were affected in response to blue light than to red light in accordance with disease pathology that is characterized by a primary defect in the rod system. The absolute deviation in all PR latency parameters were significantly higher and more variable in RP patients than controls (all $p<0.0001$). AMD patients demonstrated significantly reduced contraction velocity and pupil re-dilation velocity in the center of the VF in response to red and blue light. Other PR parameters did not significantly differ between AMD patients and controls.

Conclusions: Lower PR velocity was recorded in the center of the visual field in macular degeneration patients, whereas in RP a more diffused patterned of reduced PR was observed and the response to blue stimuli was more affected than the response to red stimuli. The latency of PLR was aberrant in RP patients but similar to control subjects in AMD patients. Taken together, multifactorial analysis of pupil response to focal chromatic light enables differential diagnosis of central and peripheral pathologies and identification of VF defects.

Spectral-domain features in cases of preeclampsia and lack of relationship with systemic parameters.

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Purpose: Visual symptoms are common in patients with preeclampsia, and are caused by various underlying pathological changes in the retina. The severity of maternal retinopathy may reflect the state of the placental vasculature and correlates with the severity of preeclampsia and fetal mortality. For this reason, the worsening of ophthalmic symptoms may indicate termination of pregnancy. We herein report 9 cases of preeclampsia with visual symptoms demonstrated by spectral domain optical coherence tomography (SD-OCT) and examined the possible relationship with systemic features.

Methods: We retrospectively reviewed nine patients with preeclampsia who complained of blurred vision. In all cases, ophthalmoscopic examination was performed including best corrected visual acuity, slit-lamp biomicroscopy and SD-OCT. Features on OCT evaluated included central foveal thickness, subretinal/intraretinal fluid, ellipsoid zone integrity, ondulation or irregularity peripapillary sensory detachment, Elschnig spots, and hyper-reflective retinal dots. Systemic parameters were also evaluated including age, gestational age, blood pressure, urine creatinine, serum hemoglobin, presence of headache, blurred vision, abdominal pain, pulmonary edema, and presenting visual acuity.

Results: SD-OCT examination showed a serous neurosensory detachment of the macula in all cases. No relationship between any of the SD-OCT and systemic features was found.

Conclusions: In our patients with preeclampsia, SD-OCT provided a useful method for the precise assessment of retinal changes. In our case series, no relationship between SD-OCT and systemic parameters was found. Further research may help to clarify the pathophysiological retinal changes seen in preeclampsia.

Relations between convergence and stereoacuity in pediatric population

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Purpose: To investigate the relationship between convergence amplitude and stereoacuity measurements in a large cohot of pediatric population

Methods: Retrospective chart review of patients aged 6-16.

Patients with amblyopia, manifest strabismus, visual acuity at the documented examination lower than 20/30 in either eye were excluded. Stereoacuity was measured by randot test and near positive convergence amplitude was measured using base out prism bar. A single examiner performed all tests.

Stereoacuity was defined as normal (≤40msec), subnormal (50-400msec) poor (>400 msec). Convergence amplitude was defined as none (fusion break point (BP)=0) very poor (fusion BP)<20PD base out (BO)), poor (fusion BP<30PD BP BO or recovery point (RP) <20PD BO), normal (BP ≥30PD BO and RP ≥20PD BO) and excelent (fusion does not break at 40PD BO). The association between convergence and stereoacuity was evaluated using regression analysis. Demographic and clinical parameters were also taken into account. Cross-tabulation was used to determine the distribution of stereoacuity among the convergence groups.

Results: A total of 2,348 subjects (1,123 males and 1,225 females) met the criteria and were included in the final analysis. Decreased convergence was found significantly associated with reduced stereoacuity (Pearson Correlation = -0.125, $P < 0.001$). Statistical significance was maintained after correcting for age, sex and refraction. In accordance, the rate of normal stereoacuity increased significantly among groups with better convergence amplitude (26.7%, 56.4%, 66.2%, 67.3% and 71.1% respectively, $P < 0.001$). A similar trend was observed after exclusion of subjects with myopia, hyperopia, or anisometropia. Only a small subgroup of patients with reduced convergence had follow up; improvement in both convergence and in stereoacuity was observed in several cases.

Conclusions: Convergence is considered a motor skill that can be improved by practice while stereoaucity is considered a binocular sensoric function which reflects binocular sensory visual function. Our findings prove those functions might be related. Further investigation regarding the roll of convergence improvement exercise on stereoacuity should be performed.

Eye-tracking-based automated system for an objective rapid eye deviation measurement in children and adults

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Purpose: Manifest and latent eye deviation are conventionally measured by the Unilateral Prism Cover Test (UPCT) and Alternate Prism Cover Test (APCT), respectively. Both tests are subjective, time consuming, difficult to perform in babies, toddlers and young children, and heavily rely on the examiner's skill and experience. The novel method being tested may constitute a replacement to both the UPCT and APCT. We have recently demonstrated the high accuracy and repeatability of a newly developed eye-tracking-based strabismus measurement system (Eyeswift), comprising a 3D display and glasses as tested on adults. Here we present newly developed active full-occlusion glasses, designed to automatically perform both types of cover test, thus enabling rapid, objective ocular deviation measurements in both children and adults. Moreover, this system enables continuous simultaneous measurements in both occluded and non-occluded eyes, allowing complete and exact deviation characterization.

Methods: Four children with strabismus were tested on the automated system and the traditional UCPT (average age 7.9±2.4 years, mean±std). During the test, a moving target is presented to the non-occluded eye until a fixation is achieved. Next, the occlusion is switched to the other eye. This way, instead of adjusting the line-of-sight of the deviating eye by using prisms while gazing at a single target, an eye tracker is used to detect cessation of eye movements when both eyes fixate at their corresponding targets. No eye tracker calibration is required to perform the test. The deviation direction and magnitude are automatically calculated from the distance between the two final target positions and the viewing distance. Tests were conducted under normal room lighting, at 60 cm.

Results: The results showed a deviation of 10.98±2.7 (mean±se) for the eye tracking method, which is highly correlated to the UCPT measurement of 11.6±2.5 (mean±se; R=0.93).

Conclusions: These preliminary results indicate the potential clinical utility of a novel strabismus angle measurement method using an automatic, objective, rapid and accurate system based on eye tracking.

Late Solitary Extraocular Locoregional Recurrence from Previously Resected Iris Melanoma

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Purpose: To report on cases of late extraocular relapse of previously resected iris melanoma, without concurrent intraocular recurrence.

Methods: A retrospective chart review of 4 patients diagnosed with late subconjunctival relapse of previously resected iris melanoma.

Results: Three females and one male underwent iris tumour resection and presented to our service with suspicious conjunctival lesions at a median of 22 years later (mean: 21). None showed intraocular relapse. Treatment of the conjunctival tumours included excisional biopsy (n=4) followed by cryotherapy (n=3) and/or brachytherapy (n=3). In all cases, histopathology confirmed malignant melanoma, with no intraepithelial component or associated melanosis. Genetic sequencing (n=3) showed wildtype *BRAF* and *NRAS* in all. *GNA11* mutation was found in 1 case. On array CGH (n=3), gain of 6p was found in 2 cases and gain of 8 in 2. Overall, findings were strongly suggestive of a diagnosis of late extraocular relapse from previously resected iris melanoma. In a median of 2.5 years (mean: 7.7) from the subconjunctival relapse, no further episodes of intra/extraocular recurrence were recorded, and all patients were free from distant metastasis.

Conclusions: Patients undergoing iris melanoma resection are at risk of developing late solitary extraocular relapse even over 30 years after surgery. In the absence of an intraocular component, diagnosis may be challenging, as tumours mimic a primary conjunctival lesion. Management by excisional biopsy followed by adjuvant therapy was successful, and histopathology and genetic analysis supported a diagnosis of extraocular uveal tumour spread rather than a primary conjunctival tumour.

Frequency of atypical vascularization during IAC for retinoblastoma

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Purpose: Intra-arterial chemotherapy (IAC) in the treatment of retinoblastoma is administered at the osteum of the ophthalmic artery to deliver a high dose of chemotherapy to the eye. In some cases, injection of dye through the intra-arterial catheter does not demonstrate the classic choroidal flush and the drug needs to be administered through branches of the external carotid artery. The purpose of this study was to evaluate the arterial anatomy around the eye of children with retinoblastoma in a referral center in Israel.

Methods: A cohort of children with retinoblastoma was treated with IAC as a primary or secondary treatment. The angiograms were reviewed and the main vessel supplying the eye was noted.

Results: 14 children were treated with a mean of 2.35 treatments per child. In 20 times the Ophthalmic artery was open, and in 12 an alternative route was required for drug administration. In one case we could not complete the procedure. In four cases when the IAC was repeated the ophthalmic artery was occluded and an alternative route was required. In one of these two cases, a third treatment showed some opening of the ophthalmic artery which allowed treatment through what previously appeared to be a closed artery.

Conclusions: Our findings in the Israeli population match those of the MSK group that in many cases IAC needs to be delivered through collateral vessels and not from the internal carotid into the ophthalmic artery.

Serum exosome analysis as a predictive biomarker for metastatic uveal melanoma

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Purpose: Exosomes secreted from tumors have been suggested as a mean by which tumors prepare their target organs to accept metastases. The purpose of this study was to evaluate the possibility to extract exosomes from frozen archival sera of uveal melanoma patients and to use an exosomal analysis from the first visit as a predictive marker for the metastatic disease.

Methods: Sera of uveal melanoma patients were collected at the initial visit when uveal melanoma was diagnosed and on every follow-up visit. Samples were separated and kept frozen in (-70) degrees Celsius. Exosomes were extracted from archival sera of the diagnostic visit by a series of ultracentrifugations. The vesicular nature and size of the purified exosomes were confirmed by electron microscopy (EM). Exosomal size, counts, and concentrations were quantified using a Tunable Resistive Pulse Sensing (TRPS) method.

Results: Twelve samples from patients who developed metastases and twelve who were metastasis-free for over 5 years were analyzed. The exosomes mean size (± SD) was greater in sera from patients who developed metastases (126 ± 23 microns vs. 110 ± 15 microns, respectively, p=0.047). The mean mode size (± SD) was similar between the tested groups (114 ± 15 vs. 105 ± 15 microns, respectively, p=0.13). The mean (± SD) counts were 1.54 E+10 ± 1.76 E+10 particles/mL for the patients who have not developed metastases and 5.81 E+11 ± 1.90 E+12 particles/mL for the patients who developed metastases, with medians of 9.1 E+9 particles/mL and 10 E+9 particles/mL, respectively (p=0.31). There was no correlation between the exosomal count and the time the sera were frozen.

Conclusions: This preliminary study proved that exosomes can be extracted from archival samples. In sera from the first visit of uveal melanoma patients who developed metastases, there were larger exosomes, but the mode size and counts were similar. The preliminary findings of this study require further analysis in a larger group before this analysis is used as a prognostic test.

Classification of Medulloblastoma Subgroups Based on Gene Expression Data

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Purpose: Medulloblastoma (MB), is the most common malignant brain tumor of childhood, diagnosed secondary to symptoms of high ICP pressure and papilledema. MB is divided into four tumor subgroups: WNT, SHH, Group 3 and Group 4, representing distinct molecular entities. The aim of the study is to identify biomarkers for clear and fast MB subgroup classification. These biomarkers can be in the future accessible in clinical use for accurate diagnosis of patients' tumor subtype that will accelerate the design of patient's specific targeted therapies and optimize clinical decision.

Methods: With this aim, machine-learning based classification was performed on public mRNA expression profiling data generated using microarray technology.

Results: Applying k-nearest neighbor (KNN) modelling identified 5 potential biomarkers (GSG1, IMPG2, RUNX1T1, RNU6-608P, RN7SL492P), of them three are protein-coding genes, and two are non-coding RNAs (ncRNAs). These results lead to average sensitivity of 0.98 while preserving high specificity of 0.99. When focusing on Group 3 and Group 4, our analysis detected three potential biomarkers of which two are ncRNAs (ENSG00000199263, RN7SKP230, GSG1) differentiating between these two groups. Adding these three genes to the set of known 12 MB genes, and re-run the KNN analysis, increases the accuracy in 2%, reducing the false positive rate in 0.7% and 9.8% in Group 3 and Group 4 respectively.

Conclusions: This approach detected the non-coding RNA as a promising class of genetic factors worth being deeply investigated as markers for MB diagnosis, development, prognosis, and clinical decision-making.

The effect of subsidized glasses and vision testing by the Israeli health funds on prevalence of refractive errors

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Purpose: To compare the incidence of refractive errors and age at first eye examination of children, before and after the implementation of program to subsidized glasses, in order to test the influence of health funds.

Methods: This study includes data regarding 2,060 subjects, boys and girls aged 5-12 years old, who were examined in the eyeglass chain "Einit" prior (1,030 subjects, 12/2007-12/2010) and after (1,030 subjects, 12/2013-12/2016) the subsidy program was implemented. For each subject the amount of sphere, cylinder, visual acuity, and anisometropia were recorded. Subjects were divided according to myopia and hyperopia severity: low myopia <3.00D, moderate 3.00-6.00D and high >6.00D. Statistical analysis was performed for each parameter before and after the funding program using T-Test and ANOVA. Chi-squared and correlations were examined for categorical variables while adjusting for gender and age by stratification.

Results: Means of age and low myopia before the program were higher than the post-program period (8.78 ± 1.86 vs 8.39 ± 1.85 years, $p < 0.001$; -2.39 ± 4.07D vs. -2.12 ± 1.34D, $p < 0.001$, respectively). The mean visual acuity in the amblyopic group was worse prior to program entry (0.56 ± 0.17 vs. 0.62 ± 0.12; $p < 0.02$). There was a significant difference in the amount of myopia between different sex groups and age before and after the program ($p < 0.01$). There was a larger number of subjects in the low and moderate myopia groups after the subsidy program ($p < 0.01$). However, there was no difference in the number of subjects in the high myopia group between the periods ($p = 0.68$). In addition, there was no statistically significant difference between the averages of hyperopia, astigmatism and anisometropia before and after the funded program ($p = 0.41$, $p = 0.19$, $p = 0.43$, respectively), and no association was found between anisometropia and amblyopia ($r = -0.46$ before and $r = 0.05$ after).

Conclusions: The subsidy program by the Israeli health funds assists in lowering the age of examination and therefore helps in the early detection of myopia and other visual impairments that facilitate the development of amblyopia.

Azithromycin as a possible neuroprotectitive drug following optic nerve crush induction in mice

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Purpose: Azithromycin (AZ) is a macrolide antibiotic approved worldwide to treat a variety of community-acquired infections. Recently, it was reported that AZ reduced oxidative stress in lung ischemia and protected mice following ischemic stroke. Optic nerve crush (ONC) is a common model simulating optic neuropathy and is used in this study to evaluate the neuroprotective effect of AZ.

Methods: Twenty four C57Bl/6 male mice were randomly allocated to the study, all underwent ONC induction, 12 with a single intraperitoneal (IP) injection of AZ and 12 served as control. Histological analysis of retinal thickness, RGCs count and axonal loss, was conducted on 21 days from the ONC (n=6 each group) as well as immunohistochemistry staining. Analysis of gene expression in the retinas and optic nerves (6 each group) was performed on day 1.

Results: on day 21, in the ONC only, retinal thickness in the injured RE was 159 µm (±6) and 210 µm (±6) in the healthy LE, while the group of ONC and AZ showed RE thickness of 196 µm (±11) in the injured eye .

RGCs loss of 46% was detected post ONC without AZ and less, 32% with a single AZ injection. Molecular analysis is under investigation .
Conclusions: AZ has a neuroprotective effect following ONC when injected immediately post damage induction, as shown histologically. Giving AZ, a common and safe drug, immediately after trauma, may facilitate preservation of RGCs.

Association of structural retinal markers with brain structure and cognitive function in asymptomatic individuals at high risk for Alzheimer disease

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Purpose: To characterize early structural retinal changes in asymptomatic offspring of Alzheimer disease (AD) patients.

Methods: 118 subjects were enrolled, 77 offspring of AD patients (FH+) and 41 age-matched controls (FH-). Ophthalmic assessments included complete ophthalmic examination and multicolor spectral domain optic coherence tomography (SD-OCT) imaging. Cognitive assessment included executive function and episodic memory tests. MRI brain imaging was performed on 87 of the subjects (FH+=64; FH-=23) on a 3T MRI (GE-HDxt, version 16VO2).

Results: In FH+ subjects, better performance in episodic memory was associated in both eyes with larger thickness of the macular retinal nerve fiber layer (mRNFL) (left eye, OS: r=0.348; p=.010; right eye, OD: r= 0.297; p=0.028) and macular ganglion cell layer (mGCL, OS: r=0.397; p=0.003, OD: r=0.301; p=0.026) as well as with larger thickness of the macular inner plexiform layer (mIPL) in the left eye (r=0.430; p=0.001). In FH- subjects, better working memory was associated in both eyes with greater total mRNFL (OS: r=0.401; p=0.028; OD: r=0.478; p=0.008) and mGCL (OS: r=0.360; p=0.051; OD: r=0.400; p=0.029 in the RE). In FH+ subjects, larger right hippocampal volume was associated with greater thickness of the mGCL (r=0.313; p=.030) in the right eye. A similar trend was observed for the association of right hippocampal volume with mRPE thickness (r=0.272; p=.062).

Conclusions: Our preliminary results show that beyond family history status, the thickness of inner retinal layers and supporting RPE in the macula are associated with cognitive functioning, as well as with hippocampal volume. Of major importance are the associations observed in the asymptomatic subjects, between macular thickness and performance in memory, the primary cognitive domain first affected by AD pathology. AD family history status differentially affected the relationships of the retina with brain markers. Taken together the thickness of macular layers may present a novel biomarker for very early detection of AD.

Motor Vehicle Accidents-associated Ocular Injuries - Visual and Social Outcomes

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Purpose: This study describes the visual and social outcomes of motor vehicle accidents (MVA)-associated ocular injuries.

Methods: Data were collected retrospectively from medical records of patients that sustained MVA-associated ocular injuries between the years 2000 to 2010, and were referred to the ophthalmology department at Rabin Medical Center. We documented the demographics, mechanism of injury and ophthalmological findings. A telephone questionnaire was conducted to incorporate additional details regarding the accident as well as the visual and functional outcomes.

Results: Over the 10 year period, 274 MVA-victims inflicted by ocular injury were identified. The study population included 141 males (62%); the mean age was 43 (range 16-85). Seventy-one percent did not use any means of precautions. Seventy-nine of patients (34%) sustained an orbital fracture. Forty individuals (15%) completed the questionnaire and the mean age was 31 years (range 17-67); in 60% of cases airbags or seatbelts were employed. Ocular injuries consisted of bone fractures (67.5%), subconjunctival hemorrhage (40%), eyelid involvement (27.5%) corneal injury (12.5%), retinal injury (7.5%) and globe perforation (2.5%). Most orbital fractures involved the lateral wall (40%) followed by roof (30%), floor (27.5%), medial wall (15%) and optic canal (5%) involvement.
The majority of patients returned to work (25 individuals, 62.5%) and resumed driving (28, 70%) within a year. These rates were not associated with the use of precautions, type of accident or fracture occurrence.
Only a minority of patients had visual decline resulting in reading and watching television difficulties (5% each) and blindness (2.5%). Ocular involvement was perceived as a minor injury by the majority of patients (70%).
No association was found between severe injuries and the use of precautions, type of accident or the occurrence of fractures. Similarly, no association was observed between visual changes and the use of precautions, type of accident or the occurrence of fractures.

Conclusions: We have shown that the majority of patients achieved good visual and functional recovery following MVA- associated ocular injuries. To the best of our knowledge, this is the first study to report the consequences and associated quality of life characteristics following MVA- associated ocular injuries.

Optic Neuritis monitoring using objective and subjective visual field testing

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Purpose: To objectively asses visual field defects in optic neuritis patients by measuring pupillary response using a multifocal chromatic pupilloperimeter.

Methods: Four optic neuritis patients (three females and one male, mean age 31.75 ± 5.85) and 6 age-matched healthy controls (six females for the left eye, mean age 34.83 ± 3.76; Four males and two females for the right eye, mean age 30.5 ± 3.45). A chromatic, multifocal, monocular pupilloperimeter was used to record pupillary responses to red and blue light stimuli (peak 485 nm and 625 nm, respectively) presented in a 24-2 visual field. The percentage of change of pupil size (PPC) and maximal relaxation velocity (MRV) were correlated with the patients' results of best corrected visual acuity (BCVA), Humphrey's 24-2 perimetry, Spectral Domain Optical Coherence Tomography (SD-OCT) and compared individually to the mean pupillary response of the controls.

Results: When compared to the mean response of the controls, optic neuritis patients showed a reduction in MRV and in PPC in their affected eye mainly in response to red light stimuli. The pupilloperimetry results correlated with the Humphrey perimetry results but showed a more extensive pattern of damage in locations that were not detected in the Humphrey perimetry.

Conclusions: Chromatic pupillomperimetry may objectively detect damaged areas in the visual field of optic neuritis patients. The pupilloperimeter can detect subtle changes in pupil response to light stimuli and may potentially be used to determine the severity and extent of damage caused by the optic neuritis. Further analysis of different pupil response parameters along with different wavelength of light stimuli may give us the opportunity to differentially diagnose optic neuritis and objectively monitor the disease progression and response to treatment.

Novel *OPA1* mutation is associated with optic neuropathy and schizo-affective disorder

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Purpose: To delineate the clinical presentation and identify the molecular basis of apparently autosomal dominant optic atrophy associated with psychiatric disorders in a Jewish Ashkenazi family.

Methods: Affected individuals underwent thorough ophthalmological examination. Blood samples were collected, and genomic DNAs were extracted. Molecular analysis included whole-exome sequencing (WES) analysis of the proband, and 750k SNP array of all family members. Haplotype reconstruction was done using data from SNP arrays. WES variants which passed a filtering cascade were screened in our in-house 40 Ashkenazi controls, and gnomAD database of relevant 9848 alleles of Ashkenazi Jews. Restriction fragment length polymorphism was later used to test the identified disease-associated variants in 100 ethnically matched controls.

Results: A Jewish Ashkenazi family presented with apparently autosomal dominant heredity of optic atrophy combined with psychiatric disorders, mostly schizophrenia. Since the disease phenotype is age-dependent, only 9 older family members with a confirmed diagnosis were included in the study. A novel *OPA1* mutation (c.1063 C>G, p.H337D) was identified in one of the two relevant loci segregating as expected for dominant heredity. The mutation was not found in open access databases (dbSNP147, HGMD™, ExAC and gnomAD, HapMap, and 1000 genomes) or in our in-house database of whole exome sequences of over 40 Ashkenazi controls, as well as in gnomAD database of 9848 alleles of Ashkenazi Jews. The *OPA1* H337D mutation is within the GTAPase domain, next to the location of most of the other *OPA1* disease-causing variants described to date. This position is highly conserved throughout evolution. SIFT and Polyphen2 predict this mutation to be ‘Damaging’ and ‘Probably Damaging’, respectively, and the combined CADD score is very high (31.000).

Conclusions: While the majority of patients with dominant optic atrophy present with isolated optic nerve involvement, some develop additional neurological abnormalities; however, schizophrenia has not been described in this regard. We suggest that the novel *OPA1* p.H337D mutation not only causes optic atrophy, but is also associated with psycho-affective disorders.

Homozygous CEP250 knockout leads to a relatively late-onset retinal degeneration

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Purpose: We reported previously that a nonsense mutation in the centrosome-associated protein *CEP250* (C-Nap1) gene causes an atypical form of Usher syndrome (USH) in patients of Iranian Jewish origin. To better characterize CEP250, we generated and studied a knockout (KO) mouse model for Cep250.

Methods: Heterozygous mice for a conditional non-activated construct were generated by an outsource company; 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, 12, 18 and 20 months) and retinal structure by histological analysis. Gene expression analysis has been applied on the KO and control mice. Differences in hearing threshold between KO and WT mice were detected using auditory brainstem recording (ABR) at the age of 20 months.

Results: In the previous meeting, we reported a follow-up of the KO mice until the age of 12 months with minimal findings. We raised thus far 37 homozygous animals up to the age of 20 months. While ERG testing at the age of 6 months did not revealed any clear evidence for retinal degeneration, testing at ages 12 and 20 months showed a 42% and 71% decrease respectively in the a- and b-wave amplitudes comparing to WT. Light-adapted ERG of KO mice at 12 months showed only a 11% decrease compared to the WT, on the other hand at 20 months it showed a larger decrease of 82%. ABR test illustrated that the hearing threshold significantly increased for the KO mice at the age of 20 months.

Conclusions: Many of the known mouse models for Usher syndrome were identified due to their characteristic circling and head-tossing behavior that results from vestibular dysfunction. Despite that, these mice do not possess severe mutant phenotypes in their retinas. To the best of our knowledge, this is the first animal model for usher syndrome that shows both retinal degradation and hearing loss, although at a relatively late onset.

Blocking TNF-α receptors or intravitreal injection of TNF-α can lead to retinal ganglion cells preservation

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Purpose: Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine produced by macrophages and T-cells. It plays an important role both in inflammation and apoptosis. In the eye, TNF-α appears to enhance apoptosis following trauma or inflammation. As predicted, TNFR1/2 knockout mice showed resistance to optic nerve crush (ONC) damage. Herein, we report a paradoxical neuroprotection effect of a single intravitreal (IVT) injection of TNF-α following ONC induction.

Methods: Histological analysis of 30 wild type (WT) mice was performed, with/without IVT TNF-α injection following ONC at 3, 7 and 21 days after the crush (n=5 each). Retinal thickness and the number of retinal ganglion cells (RGCs) were measured. ONC was performed to the right eye only; the left eye served as a control. Also, immunofluorescent staining with CD45 and glial fibrillary acidic protein was used to demonstrate inflammatory reaction and gliosis.

Results: Histologically, RGCs were preserved in the retinae of the TNF-α injected group as compared to the control ONC-induced mice. After 21 days, RGCs count revealed 8.2±1.9% reduction in the WT group compared to the healthy eye, whereas the TNF-α injected group preserved all cells. However, retinal thickness showed greater loss in the TNF-α injected groups of 8.8±3.8% compared to 3.3±3% thinning in the WT group. Immunofluorescent staining revealed impressive reactive gliosis in both groups. Whereas the TNF-α injected group showed higher inflammatory response in both eyes.

Conclusions: Previously, we showed that TNFR1/2 KO mice were resistant to ONC damage, with higher molecular expression levels of TNF-α. We assumed that the lack of receptors blocked its proapoptotic effect. In the present study, against expectations, IVT injection of TNF-α induced better preservation. A possible model of action is associated with increased inflammatory response, promoting the repair mechanism through resident macrophages in the retina, causing a paradoxical neuroprotective effect. As TNF-α inhibitors are used as neuroprotective drugs, the benefits and risks of using TNF-α or TNF-α blockers is not yet completely understood and needs to be further explored.

Retinal Degeneration and Impaired Phagocytosis of Photoreceptor Outer Segment Discs in *Prcd*-Knockout Mice

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Purpose: To generate and characterize a mouse model for *PRCD*-deficiency in humans.

Methods: Targeted deletion of *Prcd* in mice was obtained by homologous recombination in embryonic stem cells. Characterization of retinal structure and function was obtained by light microscopy of fixed retinal sections, and by electroretinography (ERG). Immunohistochemistry was performed to measure the phagocytosis of photoreceptor outer segment (OS) discs by the retinal pigment epithelium (RPE).

Results: In 20-weeks-old *Prcd*-knockout mice, both scotopic and photopic ERG responses were significantly reduced compared to wild-type controls. At this age, the outer nuclear layer was significantly thinner in knockout mice, indicating photoreceptor degeneration. In 5-weeks old *Prcd*-knockouts phagocytosis of OS discs by the RPE was severely impaired.

Conclusions: *Prcd*-knockout mice serve as a good model for retinitis pigmentosa caused by *PRCD* mutations in humans. Impaired phagocytosis of photoreceptor OS discs in *Prcd*-knockout mice implies that PRCD is involved in this process. This study has important implications for understanding the function of PRCD in the retina, as well as for future development of treatment modalities for *PRCD*-deficiency in humans.

Attentional capture in barn owls (*Tyto alba*)

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Purpose: Study top-down and bottom-up attention in barn owls.

Methods: We tested barn owls in a visual search task which examines interactions between top-down and bottom-up attention. We trained two barn owls to search for a vertical Gabor patch (the target) presented on an LCD computer screen. To track their point of gaze a lightweight wireless video camera ("Owl-Cam", 30 frames per second, ~60º view angle) was mounted on the owls' head. Owls initiated a trial by fixating a red oval at the center of the screen. Then the fixation point disappeared and the target appeared, randomly positioned, either right or left from the center of the screen. Search time and number of head saccades to reach the target were measured and compared in four stimulus conditions: 1) the target + five distractors 2) the target + 9 distractors, 3) the target + five distractors + a red circle surrounding one of the distractors, 4) the target + five distractors + a brief sound at the initiation of the stimulus.

Results: It was found that the search time and saccades to target deteriorated when the number of distractor was increased (condition 2) and when an additional irrelevant salient cue, auditory or visual, was added to the scene (conditions 3 and 4).

Conclusions: This study demonstrates that in barn owls top-down mechanisms interacts with bottom-up mechanisms to shape behavior in ways similar to humans. The findings suggest similar attentional mechanisms in taxa which have been evolutionary separated over 300 million years.

Subretinal and Intravitreal Delivery of the Photoreceptor-Specific AAV2-7m8-hGRK1-GFP Viral Vector in Mice

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Purpose: In preparation for testing gene augmentation therapy in a *FAM161A* mouse model of RP and later-on in humans, our purpose here was to evaluate the transduction efficacy and safety of the viral vector AAV2-7m8-hGRK1-GFP following subretinal versus intravitreal injection in mice.

Methods: 2µl of an AAV2-7m8 viral vector containing 2.8 x 10E10 viral particles carrying the reporter GFP gene under control of the photoreceptor-specific promoter human rhodopsin kinase (hGRK1) were unilaterally delivered subretinally or intravitreally into the eyes of naïve (n=19) mice that are the background for the *FAM161A* model. The fellow eye received a similar injection of BSS and served as control. At 1,2,3,4.5,6 and 7 months following injection, GFP expression was monitored *in-vivo* using the Micron III system equipped with the proper filters. Retinal structure was studied by histological analysis (H&E staining) following enucleation at 7 months post-injection. Efficacy and specificity of transduction in photoreceptors was confirmed by anti-GFP immunohistochemistry (IHC).

Results: The pattern of GFP expression differed between the two administration routes: following subretinal delivery, GFP expression was relatively strong but limited sharply to the area that corresponds to the subretinal bleb that formed during the injection. Following intravitreal delivery of the vector, GFP expression was more disperse and mainly detected near the optic nerve, along the major retinal blood vessels and along the far retinal periphery. IHC showed a high level of GFP expression in the Outer Nuclear (photoreceptors) Layer (ONL). H&E staining showed that retinal structure was well-preserved in all eyes, confirming safety of both subretinal and intravitreal injections.

Conclusions: The AAV2-7m8-hGRK1-GFP vector may be safely delivered into the subretinal space or vitreous providing specific transfection of the photoreceptors in normal mice that serve as the background for the *FAM161A* model. In the very near future a similar vector carrying the normal *FAM161A* gene will be injected into the eyes of *FAM161A* mutant mice in an attempt to slow/halt progression of disease. Results of these experiments may serve as an important step towards future application of gene therapy in *FAM161A*-RP patients.

Ataluren-mediated read-through of a nonsense mutation in the FAM161A gene which causes retinitis pigmentosa

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Purpose: FAM161A mutations are currently the most common cause of autosomal recessive retinitis pigmentosa (ARRP) in the Israeli population. This gene is responsible for approximately 12% of all RP cases in Israeli Jewish patients, with only two mutations identified in this population. One of these mutations is nonsense (p.Arg523*) which results in a premature stop codon (PTC). Transitional read-through inducing drugs (TRIDs) suppress PTCs and thereby induce the re-expression of full-length proteins. Ataluren is one of the promising compounds for transitional read-through of nonsense mutations currently being used in clinical phase II trials for nonsense mutations in Aniridia. In this research, we investigate Ataluren as a potential treatment option for patients with the FAM161A nonsense mutation.

Methods: We generated fibroblast cell lines from 8 Israeli patients affected with ARRP due to the p.Arg523* nonsense mutation in FAM161A and age-matched healthy controls. FAM161A protein expression and localization was monitored in control, untreated and Ataluren-treated patient-derived fibroblasts by immunocytochemistry. Primary ciliogenesis and cilia length was analyzed in starved control fibroblasts, patient-derived and Ataluren treated patient-derived fibroblasts by immunofluorescence analysis.

Results: We observed FAM161A expression in ciliated fibroblasts from healthy individuals located along cytoplasmic microtubules and in the Golgi apparatus. In patient-derived cells, FAM161A expression was barely or not at all detectable after starvation. We detected defective ciliogenesis in patient-derived cells compared to healthy cells. However, Ataluren treatment of patient-derived cells restored FAM161A localization in all treated cells and furthermore restored ciliogenesis in 67% of FAM161A p.Arg523* patient treated cells.

Conclusions: FAM161A is expressed in fibroblast cells along microtubules and the Golgi apparatus. In patient-derived cells, FAM161A localization and ciliogenesis can be restored after Ataluren treatment. These results emphasize the feasibility of Ataluren as a therapeutic strategy tackling RP caused by the FAM161A nonsense mutation.

Orbital fat derived mesenchymal stem cells rescue RPE from necrosis and differentiate towards RPE

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Purpose: Orbital adipose tissue is of neural crest origin similar to most of the ocular and orbital components including the RPE. Here we isolated and characterized orbital fat derived mesenchymal stem cells (OMSCs), evaluated the protective effect of OMSCs on necrosis of RPE, as well as the potential of OMSCs to differentiate towards RPE.

Methods: Human OMSCs were harvested from orbital fat of patients undergoing blepheroplasty. OMSCs were cultured until reaching passage three. Phenotype of OMSCs was evaluated by immunostaining and FACS analysis for stem cells markers (CD105, CD90, CD73, CD45). Multipotency of OMSCs was evaluated by differentiation studies to osteocytes and adipocytes. Cytokine secretion of OMSCs was studied by protein array on collected culture medium. A co-culture of OMSCs and human RPE, or human RPE alone, was subjected to oxidative stress by exposure to 1.5mM hydrogen peroxide (H2O2). H2O2 induced RPE necrosis was measured by Annexin V/ propidium iodide staining and flow cytometry analysis. The differentiation potential of OMSCs towards RPE was evaluated using td-tomato marked RPE and GFP marked OMSCs seeded in a co-culture. GFP marked OMSCs were then isolated by FACS sorter and analyzed for early eyefield markers (OTX2, PAX6, SIX3) by qRT-PCR and immunostaining.

Results: OMSCs express mesenchymal stem cells markers (CD90 100%±3.7, CD105 97.8%±3.9, CD73 97.3%±12.2, CD45 1.5%±1) and able to differentiate to both osteocytes and adipocytes (Alizrin red 60%±15.4, Oil red 75%±20.3, respectively, %cells per high field). OMSCs secrete anti-inflammatory (IL-11 89±29.4, IGFBP-6 1737±463.8, IL-6 632.7±450; median signal intensity, $p<0.05$) and neurotrophic cytokines (HGF 61809±5002.2, BDNF 43.1±19.3; median signal intensity, $p <0.05$) in culture. Treatment of RPE with OMSCs prevented H2O2 induced necrosis (40% decrease±3.4, $p <0.05$). After 7 days in co-culture, OMSCs upregulated early eyefeild markers(Pax6 57.6±5.6, Otx2 929.7±76.2, Six3 338.2±33.0; folds of control).

Conclusions: OMSCs express classic markers of mesenchymal stem cells and are multipotent. OMSCs cytokine secretion profile is anti-inflammatory and neurotrophic. Conditioned medium of OMSCs prevents RPE necrosis. Finally, OMSCs have a differentiation potential towards RPE**.** These data suggest the potential of using OMSCs as a therapeutic tool in future studies for regenerating RPE.

Dexamethasone Implant for Diabetic Macular Edema in Naïve Compared o Refractory Eyes
The International Retina Group Real-Life 24 Month Multicenter Study - The IRGRel-DEX Study

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Purpose: To investigate efficacy and safety of repeated dexamethasone (DEX) implants over 24 months, in diabetic macular edema (DME) eyes that were treatment-naïve compared to eyes refractory to anti-VEGF treatment, in a real-life environment.
Methods: This multicenter international retrospective study assessed best corrected visual acuity (BCVA) and central subfield thickness (CST) of naïve and refractory eyes to anti-VEGF injections treated with DEX implants. Safety data (intraocular pressure rise and cataract surgery) were recorded.

Results: 130 eyes from 125 patients were included. Baseline BCVA and CST were similar for naïve and refractory eyes. Both groups improved significantly in vision after 24 months ($p < 0.001$). However, naïve eyes gained statistically significant more vision than refractory eyes (BCVA 0.36 ± 0.14 versus 0.47 ± 0.23 logMAR, $p=0.005$) and were more likely to gain ≥ 10 letters (OR 4.2, 95% CI 1.38 - 12.90, $p=0.01$). At 6, 12 and 24 months, CST was significantly decreased compared to baseline in both naïve and refractory eyes; however, CST was higher in refractory compared to naïve eyes (CST 279 ± 61 versus 313 ± 125, $p=0.06$).

Conclusions: Over a follow up of 24 months, vision improved in DME eyes following treatment with DEX implants, both in eyes that were treatment-naïve and eyes refractory to anti-VEGF treatment; however, improvement was greater in naïve eyes.

Microglia activation in RPE65/rd12 mouse model of retinitis pigmentosa

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Purpose: Characterization of microglial activation in RPE65/rd12 mouse model of retinitis pigmentosa due to retinoid cycle defect.

Methods: RPE65/rd12 mice and C57BL wild type control mice were evaluated for retinal function by electroretinogram (ERG) at postnatal days p21-p84. Retinal structure was assessed by spectral domain optical coherence tomography (SD-OCT) and histology analysis. For the identification of the presence of microglial cells in various retinal layers at different time points, cryosections and retinal flat mounts were stained with microglial marker Ionized calcium-binding adapter molecule 1 (Iba-1) and counterstained with DAPI.

Results: Significantly lower maximal ERG b-wave was recorded under dark adaptation in RPE65/rd12 at p35 compared with controls (mean±SE: 70.9 ± 48.7 μV vs. 322±46.8 μV). However under light adaptation a similar maximal ERG b-wave was recorded in RPE65/rd12 and control mice (103.9 ± 15.4 μV vs. 113.9 ± 22.5μV). SD-OCT demonstrated no significant difference in outer nuclear thickness between RPE65/rd12 and WT mice. By contrast, the photoreceptor outer segment layer in RPE65/rd12 mice was significantly thinner than in WT counterparts of the same age (95±11.3μm Vs 103.3±1.67μm). Immunohistochemical staining demonstrated activated microglia in the outer nuclear later as early as p21 and in the inner outer segment layer as early as p28 in RPE65/rd12 mice. In WT mice microglial cells were confined to the inner retina, in the ganglion cell layer.

Conclusions: Activated microglia infiltrate the outer retina as early as P21 in RPE65/rd12 mice. This infiltration precedes thinning of retinal photoreceptor outer nuclear layers and is associated with reduction in retinal function. Microglia targeting may potentially present a new strategy to slow down retinal degeneration in Retinitis Pigmentosa due to retinoid cycle defect.

Recombinant Adeno-Associated Virus [rAAV-7m8] Transfects Photoreceptor Cells Following Intravitreal Injection in Sheep

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Purpose: 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, advanced surgical techniques and specialized operating rooms, and limit the area of retina that is treated. Intravitreal delivery of the vector would overcome these disadvantages. To transfect the retina, a vector injected intravitreally must penetrate through the inner limiting membrane (ILM) and evade the immune response. In this study we evaluated whether engineered AAV-7m8 vectors, with better retinal penetration properties, can transfect cone photoreceptors following intravitreal injection in sheep.

Methods: Normal sheep were serologically tested and AAV seronegative sheep were chosen for surgery. AAV2- and AAV9-7m8 vectors, carrying GFP under the control of either a ubiquitous or a cone-specific promoter, were injected intravitreally in normal sheep. Some intravitreal injections were preceded by mechanical scratching of the ILM with the aim of increasing its permeability. Subretinal injection served as a positive control. GFP expression was evaluated *in-vivo* every four weeks by fundus photography with a fluorescein angiography lens. Sixteen weeks post-surgery sheep were sacrificed and GFP expression was evaluated by immunohistochemistry with an anti-GFP antibody. Safety and toxicity were evaluated by ophthalmic examination, electroretinographic recordings pre- and post-operatively and histology.

Results: *In-vivo* imaging of eyes injected subretinally revealed high GFP expression beginning four weeks post-treatment. Eyes injected intravitreally began showing moderate GFP expression 8-12 weeks post-treatment. Immunohistochemistry confirmed retinal GFP expression in subretinally and intravitreally injected eyes. Intravitreal Injection of vectors carrying GFP under the control of a ubiquitous promoter resulted in GFP expression mostly in the ganglion cell layer, while injection of vectors carrying GFP under the control of a cone-specific promoter resulted in reporter gene expression in cone photoreceptors. Mild postoperative attenuation of photopic ERG responses was observed in subretinally-injected eyes.

Conclusions: AAV-7m8 vectors injected intravitreally penetrate the ovine retina and result in photoreceptor transduction.

Electrophysiological characterization of Human Embryonic Stem cells-derived photoreceptor precursors

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Purpose: Cell replacement therapy, specifically transplantation of photoreceptor precursors (PRPs), offers an innovative and promising approach for vision restoration in patients suffering from outer retinal degenerative diseases, such as retinitis pigmentosa (RP) and age related macular degeneration. Notwithstanding their great importance, little is known about their electrophysiological characteristics. The aim of the current research is to fully characterize the electrophysiological activity of PRPs, and investigate their expression pattern of different voltage-gated ion channels.

Methods: Human embryonic stem cells (hESC line H9) were differentiated into PRPs, through two different differentiation protocols. In the first protocol the cells were differentiated with eIWR 1, SAG and CHIR 99021 for up to 90 days. In the second protocol, after 24 days the following factors were added: retinoic acid, triiodothyronine (T3), activin A (days 24-31) and taurine. Whole-cell recordings of 30- 60- and 90-days old PRPs were performed for electrophysiological characterization. In addition, qPCR analysis was performed on PRPs at these 3 time-points to characterize the expression pattern of the following voltage-gated ion channels: KCNV2, HCN1, SCN2A, CACNA1F, TMEM16B and the calcium pump PMCA. Finally, to characterize the electrically induced calcium currents we employed calcium imaging (rhod2) to visualize intracellular calcium dynamics in response to electrical activation.

Results: Voltage clamp recordings revealed that PRPs express both voltage-gated sodium channels and voltage-gated potassium channels, as evident from the acquired current traces. Interestingly, these voltage-gated ion currents are present in cells only after 60 days of differentiation. These results are further supported by qPCR analysis which revealed significant and continuous increase in expression of voltage-gated channels from day 24 to 60 and 90, simultaneously with increase in CRX expression. Furthermore, PRPs grown with the 2^{nd} factors protocol displayed increase in expression of all studied ion channels compared to the 1^{st} protocol. Calcium imaging demonstrated a marked increase and decrease (approximately 3%) in intracellular calcium following cathodic and anodic electrical pulses, respectively.

Conclusions: The full characterization of PRPs is an important step in devising cell therapy based vision restoration treatment strategies for patients suffering from degenerative diseases of the outer retina.

A missense variant in *CACNA1F* causes variable phenotype in female carriers and hemizygous males of three unrelated Jewish families of Russian origin

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Purpose: Mutations in *CACNA1F* have been reported to cause X-linked congenital stationary night blindness (CSNB), Aland Island eye disease and cone-rod dystrophy (CRD). Phenotypic expression in females was previously reported in some families. We report here genetic and clinical analysis of three unrelated Jewish families of Russian origin that were referred due to variable ophthalmic phenotypes including congenital nystagmus, CSNB, cone dystrophy (CD) and CRD.

Methods: Whole exome sequencing (WES) or Sanger sequencing were used to detect the disease-causing mutation in three index cases. Complete ophthalmologic examination was performed including visual acuity (VA), refraction, color vision testing, slit-lamp examination, fundoscopy and electroretinography (ERG).

Results: WES and Sanger sequencing revealed a previously described missense mutation c.2225T>G; p.F742C in *CACNA1F* (NM_001256789.2) as the cause of disease in all three families. WES data showed a shared haplotype suggesting p.F742C is a founder mutation. We identified four affected males, most showing moderate non-progressive visual impairment, and six carrier females with normal to moderate decreased vision. Congenital nystagmus was found in all affected males and in 4/6 female carriers. Nyctalopia and myopia was a common finding in both males and females. ERG responses had atypical features for CSNB, with mild to moderate decreased response in most patients (cones and rods). Two patients had mainly photopic function affected. Based on the initial presentation, patients received the clinical diagnosis of CD, CRD or CNSB.

Conclusions: Our data suggests that p.F742C in *CACNA1F* is a possible founder mutation in Jewish families originating in Russia. This mutation causes a variable phenotype that was expressed in most female carriers. The variable expressivity of symptoms in female carriers supports the mechanism of differential X-inactivation. Our results highlight the importance and relevance of WES in the clinical setting, allowing fast and accurate genetic diagnosis when the clinical phenotype is unclear and in pedigrees in which X-linked inheritance is not the initial assumed inheritance pattern.

A frameshift mutation in RDH12 causes autosomal dominant retinitis pigmentosa in families of Tunisian Jewish origin

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Purpose: To characterize the genetic cause of disease and the clinical phenotype in patients of Tunisian-Jewish origin with retinitis pigmentosa (RP) with a dominant pattern of disease inheritance.

Methods: We performed genetic analysis using molecular inversion probes (MIPs) analysis and Sanger sequencing. Ocular and retinal function and structure were assessed by a full clinical ophthalmological exam, full field electroretinography, elecotrooculography and color vision testing as well as optical coherence tomography (Heidelberg Engineering GmbH), and wide-field pseudocolor and autofluorescent imaging (OPTOS system).

Results: The pedigrees demonstrated an autosomal dominant inheritance pattern, involving approximately half of the family members in each generation. However, examination of the candidate genes for common autosomal dominant mutations causing RP did not yield a result. In order to obtain a genetic diagnosis, we performed MIPs analysis of 109 genes known to cause inherited retinal disease and identified a heterozygous frameshift mutation (c.759del, p.Phe254Leu*24) towards the end of the open reading frame of the *RDH12* gene (NM_152443.2), coding for retinol dehydrogenase 12. All affected family members exhibited clinical and electrophysiological findings typical of RP. Notably, the onset of symptoms was delayed and the severity reduced in comparison to autosomal recessive cases associated with variants in the *RDH12* gene. This milder phenotype was also evident in the ffERG responses, with some of the patients retaining sizable dark-adapted white flash and cone-flicker responses well into the 5th decade of life.

Conclusions: All but one reported *RDH12* mutations were previously demonstrated to cause autosomal recessive Leber's congenital amaurosis and early-onset RP. Here we describe the second *RDH12* mutation causing an autosomal dominant inheritance pattern in families with relatively mild RP. The mutation we identified affects the same *RDH12* region as the previously described dominant frameshift mutation. We hypothesize that due to the proximity to the stop codon, the nonsense-mediated mRNA-decay system does not recognize the defected mRNA; yielding production of an abnormal RDH12 protein that is toxic to the photoreceptor cell.

SLC38A8 Mutations in Israeli Families with Infantile Nystagmus Syndrome

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Purpose: To identify underlying mutations in three non-related Israeli families with Infantile Nystagmus Syndrome (INS), with or without foveal hypoplasia.

Methods: Three non-related INS families were recruited. Following clinical examination, Whole Exome Sequencing (WES) was performed on ten DNA samples from two Karaite families. Followed by bioinformatic analysis and variant validation using Sanger sequencing. For the 3rd family, Sanger sequencing was used to screen the entire gene.

Results: Among the six affected patients ascertained from three families, biallelic mutations were identified in five. In four Karait patients a previously reported (in Indian Jews) homozygous mutation (c.95T>G p.Ile32Ser) was identified, while for the fifth Karaite patient this mutation was identified heterozygously only. In the third family, of Indian Jews ethnicity, the proband also carried c.95T>G p.Ile32Ser heterozygously. Further screening of the entire *SLC38A8* coding region identified another novel mutation (c.490_491delCT p.L164Vfs*41) in the Indian Jewish patient but failed to identify a second mutation in the karait patient.

Conclusions: A novel mutation contributing to compound heterozygosity has been found in an infant of Indian Jewish ancestry. The finding of *SLC38A8* p.I32S, previously reported only In Indian Jews ("Bene Israel"), also in Karaite families suggests a possible common founder for both ethnicities. While all homozygous patients had fovea hypoplasia, our analysis revealed that the heterozygous patient had a normally appearing fovea. The presence of nystagmus in the heterozygous carrier warrants further investigation for another causative variant contributing to the unique clinical appearance.

Clinical and genetic characterization of Pseudoxanthoma Elasticum patients

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Purpose: To identify underlying mutations in five Pseudoxanthoma Elasticum (PXE) patients of different ethnicities with variable disease expression.

Methods: Five affected individuals (two sib-pairs and a single patient) were recruited. Medical history, clinical findings and OCT were recorded. Mutation analysis of *ABCC6* gene was followed by Sanger sequencing and whole-exome sequencing (WES) in cases unsolved by single gene sequencing.

Results: Various retinal findings ranging from peau d'orange, angioid streaks and CNV to severe retinal atrophy were documented. Skin papules were found in both sib-pairs, but were absent in the single patient, who demonstrated severe retinal changes. He was found to be a compound heterozygote to two *ABCC6* mutations – a previously described missense mutation (p.G1475E), and a novel, frame-shift causing, single nucleotide deletion (c.1413delG). Sib-pair 1 was found to carry a homozygous splice site mutation by WES. Sib-pair 2 molecular analysis is underway.

Conclusions: Our study stresses the significance of thorough history taking and clinical examination when evaluating patients suspected for PXE. It expands the repertoire of PXE mutations, presenting a novel single nucleotide deletion contributing to compound heterozygosity in a patient with an irregular phenotype. Finally, it highlights the role of genetic tools in present and future medical practice, empowering the physician to achieve diagnosis through molecular methods.

Pattern Dystrophies Associated with Mutations in the Peripherin/RDS Gene

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Purpose: To determine the underlying molecular basis of retinal pattern dystrophy identified in two Moroccan Jews families and one Christian Arab family, and to describe their phenotypes.

Methods: Affected patients and their family members underwent detailed ophthalmologic examination including funduscopy, autofluorescence imaging, and optical coherence tomography (OCT). Selected family members underwent fluorescein angiography (FA) and electrophysiological testing. Blood samples were obtained from the participants for DNA extraction and mutation screening of the peripherin/RDS gene.

Results: A truncating peripherin/RDS gene mutation (c.441delT) was identified in the Moroccan Jewish families, whereas a missense mutation (R142W) was found in the Christian Arab family. Funduscopic examination revealed a vitelliform butterfly-type macular dystrophy in the Moroccan families, and Stargardt-like macular changes in the Christian Arab family. Over time both mutations resulted in progressive macular atrophy and visual acuity deterioration. OCT revealed typical deposits at the level of the RPE, and in advanced stages- diffuse geographic atrophy. Electrophysiology may show abnormal EOG readings.

Conclusions: Among the 6 ascertained patients a phenotypic difference was suggested between those who carry a truncating mutation and those with a missense mutation of the peripherin/RDS gene.

Worldwide Carrier Frequency Analysis of Mutations Causing Autosomal Recessive Inherited Retinal Diseases

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Purpose: Inherited Retinal Diseases (IRDs) are a group of diseases that cause photoreceptor loss due to genetic mutations in the photoreceptors and RPE cells. There are currently over 250 genes that are known to cause IRDs. Carrier frequency of IRD mutations in different human populations is unknown, but two previous studies in the early 2000's roughly estimated it as 1 out of 5 to 6 individuals. We previously estimated that carrier frequency in the Israeli population is 1/3 expecting a total of 2.8 million carriers of IRD mutations in Israel. Our main purpose is to calculate the worldwide carrier frequency per population for different IRD mutations and genes based on data deposited in gnomAD.

Methods: We created an SQL database including information on sequence variants identified in 177 IRD-causing genes extracted from the gnomAD database that contains genetic information on more than 138,000 whole exomes and whole genomes from various populations around the world. Variants were filtered based on allele frequencies, number of alleles and homozygotes in gnomAD, information in mutations databases, and publications in order to identify pathogenic mutations.

Results: We identified 4,305 IRD pathogenic mutations and calculated the total carrier frequency in the different worldwide populations as ranging from 1/2.3 individuals in the African population to 1/5.2 individuals in the Finnish population. The mutation that shows the highest carrier frequency worldwide is ABCA4-p.G1961E (1/109 individuals), followed by ABCA4-p.Gly863Ala and GDF6-p.Ala249Glu. We identified 91 individuals in gnomAD who are homozygous for IRD-causing mutations and therefore are expected to be affected with the corresponding disease. Carrier frequency per gene shows a large variability with EYS, USH2A, and ABCA4 being the most common IRD genes.

Conclusions: Our analysis show that carrier frequency of IRD mutations worldwide is about 1:3. In other words, about 2.5 billion individuals are expected to carry at least one mutation that can cause an autosomal recessive IRD disease. These calculations can aid in the identification of the genetic cause of IRDs in newly-diagnosed patients in an efficient way. The carrier frequency is relatively high compared to other known diseases, and we estimate that this is due to the large number of genes that can cause IRDs when mutated.

A heterozygous deletion of a noncoding part of the *PRPF31* gene causes retinitis pigmentosa in Ashkenazi Jews

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Purpose: PRPF31 gene encodes the ubiquitous splicing factor PRPF31 that lies in a head-to-head arrangement with TFPT, with the two genes partially sharing exon 1. Mutations in PRPF31 have been reported to be associated with autosomal dominant retinitis pigmentosa (adRP) with haploinsufficiency. This study was aimed to identify the disease causing mutation in an autosomal dominant retinitis pigmentosa (adRP) family with reduced penetrance.

Methods: We studied a family of Ashkenazi descent, using sanger sequencing, whole exome sequencing (WES) and multiplex ligation-dependent probe amplification (MLPA) of the *PRPF31* gene. Five members of the family, comprising three affected, one unaffected carrier, and one unaffected spouse, were selected for the study.

Results: Three family members (two siblings and their paternal grandmother) showed typical signs of RP while the father showed no symptoms but mildly reduced scotopic electroretinography amplitudes. WES analysis of the four individuals did not reveal any potential pathogenic mutations, but linkage analysis was compatible with PRPF31 as the cause of disease. MLPA analysis of the *PRPF31* gene revealed a putative deletion in exon 1, which is noncoding in the two affected siblings. At the genomic level, the mutation was characterized by serial very-short-range PCRs, followed by a long-range PCR, and finally by a diagnostic PCR encompassing the deletion area and providing a binary output (presence/absence of amplification product). This allowed to characterize the mutation as a 3567bp deletion in 19q13.3, encompassing *PRPF31*'s core promoters, as well as its first exon. The deletion also affected exons #1 and 2 of *TFPT*, a gene transcribed in the opposite direction compared to *PRPF31*. At the RNA level, transcript analysis in lymphoblastoid cell-lines showed that patients expressed lower levels of *PRPF31* mRNA, compared to controls. The unaffected carrier of the deletion had intermediate levels of mRNA.

Conclusions: Our study shows that PRPF31-associated adRP can be caused by mutations in noncoding parts of the gene, leading in turn to reduced mRNA expression and to disease, via a haploinsufficient mechanism.

A Homozygous Founder Missense Variant in Arylsulfatase G Abolishes its Enzymatic Activity Causing Atypical Usher Syndrome in Yemenite Jews

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Purpose: We aimed to identify the cause of disease in Yemenite Jewish patients suffering from a unique form of atypical Usher syndrome (USH).

Methods: Whole exome and genome sequencing in five patients from three families of Yemenite Jewish origin, suffering from retinal degeneration and sensorineural hearing loss were performed. Functional analysis of the wild-type and mutant proteins was performed in human fibrosarcoma cells.

Results: We identified a homozygous founder missense variant, c.133G>T (p.D45Y) in arylsulfatase G (*ARSG*). All patients shared a unique retinal phenotype with ring-shaped atrophy along the arcades engirdling the fovea and exacerbating with age, resulting in ring scotoma. In addition, patients developed moderate to severe sensorineural hearing loss. Both vision and hearing loss were of late onset, appearing around the age of 40 years. The identified variant affected a fully conserved amino acid that is part of the catalytic site of the enzyme. Functional analysis of the wild-type and mutant proteins showed no basal activity of p.D45Y.

Conclusions: Homozygosity for ARSG-p.D45Y in humans leads to protein dysfunction causing an atypical combination of late onset Usher syndrome without leading to the generalized clinical manifestation of lysosomal storage diseases. To the best of our knowledge, this is the first report linking a mutation in this gene to a human phenotype.

Longitudinal Clinical Follow-up and Genetic Analysis of a French Cohort of Rod-Cone Dystrophy Associated with Mutations in *PDE6A* and *PDE6B* Genes

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Purpose: To establish the prevalence of mutations in *PDE6A* and *PDE6B* in a large cohort of rod-cone dystrophies (RCD) and compare the corresponding phenotype and structural changes for disease modeling.

Methods: Patients harbor mutations in *PDE6A* and *PDE6B* genes underwent retrospectively full clinical examination including personal and familial history, best-corrected visual acuity (BCVA), refraction, color vision, ocular examination, full-field electroretinography (ffERG), Goldmann visual fields (VF), color fundus photographs, spectral domain optical coherence tomography (SD-OCT), near infrared (NIRAF) and short-wavelength fundus autofluorescence (SWAF) imaging. Genetic analysis was performed using ASPER microarray, targeted next-generation sequencing (NGS) and Sanger sequencing. IBM SPSS Statistics v. 21.0 was used for data analysis.

Results: We identified 19 patients carrying pathogenic mutations in *PDE6A* and 35 in *PDE6B*, accounting for a prevalence of 1.6% and 2.4%, respectively. Among 49 identified genetic variants, 14 in *PDE6A* and 15 in *PDE6B* were novel. All the patients presented with a typical rod-cone dystrophy phenotype, BCVA and central VF deteriorating linearly in both groups of patients, with relative preservation in older ages. Structural pattern of change based on SD-OCT, SWAF and NIRAF measurements were similar between both groups and inversely associated with age. Mean annual rate of constriction ranged 3.3-5.95% horizontally and 1.85-3.87% vertically for the different imaging modalities. No genotypic differences were found among both groups.

Conclusions: To the best of our knowledge, this is the largest cohort of patients with *PDE6A* and *PDE6B* mutations reported to date accounting for 1.6% and 2.4%, respectively, of French RCD. A total of 29 novel variants are reported to expand the spectrum of mutations in these genes. Disease severity progression was comparable in both genetic groups with relative preservation of visual function at older ages. In addition, our comprehensive functional and structural findings constitute the basis of disease modeling which may be used for better prognosis prediction and candidates' selection for potential photoreceptor rescue therapies.

Genetic diagnosis of Stickler syndrome caused by deep intronic mutation in COL2A1 in 10 family members

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Purpose: Stickler syndrome (STL1) is a dominant inherited disorder with highly variable expressivity. Here we present a family including 10 affected family members, over 5 generations, with variable presentations that were not diagnosed.
The proband is a 4.5 YO boy with progressive high myopia (-12.5D SPH, BE) who came for strabismus operation. On exam he had esotropia. Best corrected visual acuity was 6/9 in each eye, mild cortical cataract on his left lens and otherwise normal anterior and posterior segment exam.
His mother also had strabismus operation for esotropia at childhood and showed very high myopia of-25D SPH BE. Genetic analysis was carried as the boy and his mother had mild but similar dysmorphism, as well as other family members (maternal grandfather and two brothers, two step uncles and their children and the patient's brother (3 YO).

Methods: Setting/Venue: pedigree drawing and Whole-exome sequencing (WES).

Results: WES of the proband, his parents (syndromatic mother and healthy father) and his symptomatic grandfather revealed a deep intronic mutation in COL2A1 gene, c.1527+135G>A leading to missplicing. Diagnosis led to Stickler syndrome.

Conclusions: Here we present a family with different presentations (myopia, strabismus, cleft palate and blindness) all compatible with stickler disease leading to diagnosis of autosomal dominant inheritance caused by intronic mutation. Stickler syndrome is phenotypically overlapping connective tissue disorder characterized by various presentations involving eyes, ears and cleft palate. The signs vary widely among affected individuals, and therefore not often diagnosed genetically.
The family members here had either high myopia with strabismus and cataract or "traumatic" retinal detachment and visual loss. Few had cleft palate. Deep intronic mutation in *COL2A1* gene have been found in only one previous study and would not be found on genetic screening, thus we recommend of full gene screening when mutation screening fail for *COL2A1*and the family members are clearly affected.

A Novel Intronic Founder Mutation of *PDE6B* is the Major Cause for Autosomal Recessive Retinitis Pigmentosa among Jews from the Caucasus

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Purpose: To identify the genetic basis for Retinitis Pigmentosa (RP) in a cohort of Jewish patients from the Caucasus.

Methods: Genetic analysis was performed by a combination of Whole Exome Sequencing (WES) and Sanger sequencing. Bioinformatic analysis of WES results was performed via a customized pipeline. Pathogenicity of the identified intronic variant was evaluated *in silico* using the webtool Human Splicing Finder.

Results: The cohort included 9 Jewish patients from 8 unrelated families, all originally from the Caucasus. All patients were diagnosed with RP, based on electroretinography and characteristic fundus findings. Only two of the families were consanguineous. WES analysis in one patient revealed a novel homozygous intronic variant, located at position -9 of *PDE6B* intron 15. This variant (c.1921-9C>G) is predicted to generate a novel acceptor splice site, 8 bases upstream of the original splice site of intron 15. The use of this splice site is expected to lead to an 8-bp insertion into *PDE6B* coding sequence, which, in turn, will generate a frameshift and premature termination of translation (p.T641Lfs*5). WES and Sanger sequencing identified the same variant homozygously in 5 additional patients from our cohort.

Conclusions: The c.1921-9C>G mutation of *PDE6B* is a founder mutation which underlies at least 62% of autosomal recessive RP among Jewish families from the Caucasus. This result is highly important for molecular diagnosis, carrier screening and genetic counseling in this population.

Safe collagen cross-linking of thin corneas: light attenuation (RF/UVA) versus limited photosensitizer penetration (WST-D/NIR) protecting the endothelium in corneas below 400µm

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Purpose: Different collagen cross-linking (CXL) modalities or protocols achieve different chromophore concentrations at the endothelium. This results in different photodynamic activity and thus risk on endothelial damage. This study set out to experimentally assess human corneal endothelial cell safety in different CXL modalities.

Methods: A Stromal RF and WST-D distribution was imaged by confocal fluorescence microscopy of ex vivo chromophore impregnated pig eyes (n=40). For both RF and WST-D CXL, a standard curve for endothelial toxicity was determined in vitro (HCEC-12, DSMZ, Germany) using combinations of different chromophore concentrations and light intensities.

Results: RF showed full stromal penetration in all corneas, whilst WST-D penetrated to variable depths, negatively related to the concentration of added Dextran. No WST-D was seen at the endothelium in any cornea.
The in vitro study showed cellular toxicity linearly related to RF concentration and UVA intensity. For WST-D, a threshold around a concentration of 0.01mg/mL was seen for all NIR intensities. NIR alone did not cause endothelial toxicity.

Conclusions: In RF/UVA CXL, full stromal RF impregnation is needed to meet safety requirements, which results in potentially toxic photodynamic activity at the endothelium. The safe nature of NIR light allows effective stiffening without full stromal WST-D impregnation, excluding the risk of any photodynamic toxicity at the endothelial level. Control of chromophore penetration depth may allow safe CXL by WST-D/NIR of corneas thinner than 400µm.

Superior efficacy of ziv-aflibercept over bevacizumab in reducing neovascularization following ocular chemical insult in the rabbit model

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Purpose: To compare the efficacy of ziv-aflibercept and bevacizumab in ameliorating corneal neovascularization (NV) following ocular chemical insult of sulfur mustard (SM) in the rabbit model.

Methods: Chemical SM burn was induced in the right eye of NZW rabbits by vapor exposure. Ziv-aflibercept (2mg) was applied once to neovascularized eyes by subconjunctival injection at 4 weeks post exposure while subconjunctival bevacizumab (5 mg) was administered twice a week, for 3 weeks. Non-treated exposed eyes served as a control. A clinical follow-up employing the slit-lamp microscope, was performed up to 12 weeks following exposure and digital photographs of the cornea were taken for measurement of blood vessels using the image analysis software. Eyes were taken for histological evaluation 2, 4 and 8 weeks following treatment for general morphology and for visualization of NV, using H&E and Masson Trichrome stainings, while conjunctival goblet cell density was determined by PAS staining.

Results: Corneal NV developed, starting as early as two weeks after exposure. A single subconjunctival treatment of ziv-aflibercept at 4 weeks post exposure, significantly reduced the extent of existing NV already one week following injection, an effect which lasted for at least 8 weeks following treatment, while NV in the non-treated exposed eyes continued to increase. The extensive reduction in corneal NV in the ziv-aflibercept treated group was confirmed by histological evaluation. Bevacizumab multiple treatment showed a benefit in NV reduction but to less extent compared to the ziv-aflibercept treatment. Finally, following the decrease in conjunctival goblet cells due to SM exposure, a single ziv-aflibercept treatment re-populated the conjunctiva with goblet cells.

Conclusions: Subconjunctival ziv-aflibercept single treatment presented a highly efficient long-term benefit in corneal NV reduction following ocular chemical exposure. These findings show the robust anti-angiogenic efficacy of ziv-aflibercept and demonstrate the advantage of this treatment over the other standard anti-angiogenic therapy, bevacizumab, in ameliorating corneal NV and protecting the ocular surface

FS-LASIK Vs. Trans-PRK for the correction of high grade astigmatism (≥2.0D cylinder)

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Purpose: To examine and compare the safety, efficacy predictability and clinical outcomes of Femtosecond laser assisted in situ keratomileusis (FS-LASIK) and Trans epithelial photorefractive keratectomy (Trans-PRK) procedures performed for the correction of high astigmatism (≥2.0D cylinder).

Methods: A Retrospective cohort study was performed. The study reviewed medical files of patients who underwent Trans-PRK surgery and FS-LASIK surgery for the correction of high astigmatism (≥2.0D) between the years 2013-2014. The FS-LASIK group comprised of 93 eyes, and 186 eyes were examined in the Trans-PRK group. The pre-operative Spherical equivalent (SE) for FS-LASIK was -3.65±2.05 and -4.99±2.46 for Trans-PRK ($p<0.001$), and the pre-operative cylinder was -2.76±0.79 and -2.72±0.84, respectively ($p=0.732$)

Results: There were no statistically significant differences between FS-LASIK and Trans-PRK in both post-operative SE (-0.1±0.7 and -0.11±0.7, respectively, $p=0.958$) and for post-operative residual cylinder (-0.79±0.54 and -0.82±0.63, respectively, $p=0.685$), as the results were almost identical. However, Trans-PRK was associated with worse outcomes compared to FS-LASIK in both the safety (0.89±0.21 and 1.03±0.17, respectively, $p<0.0001$) and efficacy (0.86±0.22 and 1.00±0.18, respectively, $p<0.0001$) indices. These results remained significant in multivariate analysis after correcting for age, gender, preoperative refractive error, and pachymetry. FS-LASIK was also superior to Trans-PRK in the percentage of eyes achieving an uncorrected vision of 20/40 or better (98.9% and 91.4%, respectively, $p=0.013$), though this did not remain significant after the above-mentioned multivariate analysis. Post-operative microstria was detected in 2 eyes (2.2%) of the FS-LASIK group, though both achieved an uncorrected vision of 20/25. In the Trans-PRK group, 10 eyes (5.4%) presented with haze which was associated with an uncorrected vision acuity of 20/25 or worse. Post-operative elevated intraocular pressure (IOP) was measured in 3 eyes (1.6%) in the Trans-PRK group, while all of the eyes in the FS-LASIK group exhibited normal post-operative IOP ($p=0.218$).

Conclusions: Although both procedures achieved a desirable post-operative SE, FS-LASIK showed vast superiority over Trans-PRK for the correction of high-grade astigmatism (≥2.0D cylinder).

Total detachment of DMEK grafts: results of repair of DMEK grafts freely floating in the anterior chamber. A case series

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Purpose: DMEK surgery is gaining popularity in cases of endothelial dysfunction, due to its unprecedented visual results, rapid visual rehabilitation and low rejection rate. One of the most common complications of the surgery is graft detachment. Not very often, total detachment of the graft from the host cornea occurs and results in a free floating graft in the anterior chamber. In such instances, the option are either to replace the graft or to re-attach the graft by re-staining it, re-unfolding it and re-lifting it to the host stroma . We hereby present 4 cases in which the grafts were preserved and re-attached rather than replaced. The purpose of this study is to present the technical means used to re-attach these grafts and the results of these cases.

Methods: 4 patients who underwent DMEK surgery due to Bullous keratopathy. In all cases, fully detached and free floating DMEK grafts were identified in the anterior chamber shortly after the surgery. In all cases we performed repositioning and re-attachment of these grafts.

Results: In all 4 cases the surgery provided well oriented, fully attached grafts. 1 month following surgery 3/4 cases showed clearing of the cornea resulting in significant improvement of vision. One year later, 3/4 cases showed graft failure of the fully re-attached grafts and one case showed a clear cornea with good vision but with very low endothelial cell count.

Conclusions: Technically, fully detached DMEK grafts following surgery can be re-attached. The short term visual results following re-attachment surgery may be satisfactory, however in the cases described the grafts failed quickly. Based on this experience, the authors advice in these cases to explant the totally detached graft and replace it all together.

Amniotic membrane preparation and conservation made easy

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Purpose: To report a simplified amniotic membrane (AM) preparation and cryopreservation method, and to examine epithelial cells viability 18 months after preservation.

Methods: A donor who underwent a planned cesarean section was screened for transmissible infections after an informed consent was obtained. The placenta was placed in a sterile container while clamping the umbilical cord to prevent blood clots accumulation. In the operating room, the AM was separated from the chorion and washed thoroughly using a washing medium, prepared from 478ml DMEM (Dulbecco's Modified Eagle Medium), 16.5ml L-glutamine (200mM), 5ml (Penicillin-Streptomycin-Amphotericin B Solution) and 0.5ml Gentamicin (50mg/ml).
The AM was spread on a nitrocellulose paper, epithelial side up, cut into 2x4cm rectangles, placed in a preservative medium-filled tube and immediately stored at -70oC. The preservative medium was prepared from 428ml DMEM, 16.5ml L-glutamine, 5ml PSA, 0.5ml Gentamicin and 50ml of DMSO (Dimethyl sulfoxide) added right before storage at -70oC.
Epithelial cells viability was assessed using a trypan-blue based viability assay, taken 18 months after tissue harvesting and preservation. Briefly, the sliced AM was soaked in 0.4% of trypan-blue for up to 5 minutes. Under an inverted light microscope, 3 areas of 50X50µm were examined, counting viable and dead cells.

Results: During the preservation period, the tissue was used in multiple cases for the treatment of acute alkali injuries and ocular surface reconstruction, yielding satisfactory clinical results. Viability assay showed a viability rate of over 90%, 18 months following preservation.

Conclusions: Our method for AM preparation and cryopreservation which is a simplified and updated version of previous reported techniques, resulted in a highly viable tissue and is greatly important for the treatment of ocular surface diseases.

Contrast sensitivity and crowding effect in patients with Keratoconus

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Purpose: Keratoconus (KC) is a corneal disease that may leads to severe visual impairments. Subjects with KC can often have normal VA but suffer from poor quality of vision such as light scatter. Several studies suggested that KC subjects present lower contrast sensitivity (CS) compared to healthy subjects but the magnitude of the reduction and the link to severity are varied in the literature. Moreover, Crowding effect (CE) has not been studied yet in relation to KC. The aim of this study was to examine how and if CS and CE change in KC patients with relation to the progression stages of the disease using psychophysics measurements and compare these functions to normal healthy control.

Methods: KC was diagnosed based on abnormal topography and tomography, and at least on one clinical signs. KC severity was defined according to the Amsler-Krumeich classification. Healthy controls subjects have been matched to KC by age, gender and refractive error. The study was approved by the institutional review board and subjects signed a consent form prior to their participation. VA, auto refraction and over refraction correction test were performed. CS and CE of KC and controls were tested using psychophysical tests, and were compared and correlate to the severity of the disease.

Results: 9 KC subjects (7 eyes in stage 1, 2 eyes in stage 2, mean age of 23±3.84 years) and 9 healthy subjects (mean age of 26±0.70 years) have participated in the study. Significant difference was shown for KC compared to controls for Cyl ($p=0.004$), for the thinnest site of the cornea ($p=0.014$) and for CS ($p=0.002$, $p=0.05$, $p=0.04$ for 6, 9 and 12 cpd respectively). No difference was found between KC and control eyes for CE. No correlation was found between KC severity and for thickness to CS and CE.

Conclusions: At the early stage of the disease, KC subjects, show significant lower CS in all frequencies compared to healthy subjects. Further investigation of visual parameters in different stages of the disease may provide a better understanding of the progression of the disease

A comparison between multifocal, extended range of vision and monofocal intraocular lenses

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Purpose: To assess visual outcomes and patient's satisfaction of multifocal and extended range of vision intraocular lenses (IOLs) in comparison to monofocal IOL implantation with and without monovision.

Methods: Consecutive patient's records who underwent bilateral IOL implantation following cataract extraction surgery and had 1 month postoperative manifest refraction, were reviewed. Spectacle independence, patient satisfaction, and photic subjective phenomena were analyzed using a questioner survey. Four groups of IOLs were selected: (1) extended range of vision IOL, (2) trifocal IOL, (3) monofocal IOL, and (4) monofocal IOL using the mono-vision method.

Results: The extended range of vision IOL group comprised 38 patients and the other groups 50 patients. The mean postoperative uncorrected distant, intermediate and near visual acuities (LogMAR) were: 0.07±0.10, 0.08±0.13 and 0.23±0.15 (extended range of vision IOL); 0.07±0.09, 0.08±0.11 and 0.06±0.08 (trifocal IOL); 0.17±0.14, N/A and N/A (monofocal IOL); and 0.08±0.12, N/A and 0.07±0.12 (monovision). 95%, 96%, 48% and 80% of patients respectively, reported to be distant spectacles independent . 87%, 96%, 4% and 80% did not require intermediate range visual aid. 55%, 86%, 36% and 52% were spectacles independent for near vision. 13%, 38%, 2% and 6% of the patients reported experiencing postoperative halos or glare. 72%, 76%, 56% and 72% were satisfied with their IOLs and would choose them again.

Conclusions: Trifocal IOLs are more effective at improving intermediate and near vision relative to extended range of vision and monofocal IOLs. However, patients with trifocal lenses reported more glare and haloes. Our data suggest that refractive outcomes outweigh the adverse effects of multifocal IOLs, resulting in a high overall satisfaction score. Motivation to achieve spectacle independence is likely to be the deciding factor

Corneal committed cells restore the stem cell pool and tissue boundary following injury

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Purpose: To identify limbal stem cells (LSC) and test the impact of surgical removal of stem cells (SCs) on corneal epithelial homeostasis

Methods: We used triple transgenic mouse model with K15-GFP transgene that labels the limbus with green fluorescent protein and R26R-Confetti;K14-CreERT2 that allow multi-color cell lineage tracing with 4 different fluorescent genes. Surgical removal of K15-GFP+ limbus was followed by monitoring potential SC recovery (K15-GFP) and cell origin (Confetti label) in real time under anesthesia.

Results: We discovered that K15-GFP transgene labels the murine corneal epithelial boundary and SC niche known as the limbus. K15-GFP^{+} basal epithelial cells expressed SC markers and were located at the margin site of corneal regeneration, as evident by lineage tracing. This models allows the sorting and characterization of K15-GFP+ LSCs. Remarkably, surgical deletion of the entire LSC pool was restored by Confetti+ corneal committed cells which underwent dedifferentiation into bona fide LSCs. Notably, the recovered corneas displayed normal marker expression and appropriate dynamic of LSC regeneration. Interestingly, however, damage to the limbal stromal niche abolished K15-GFP recovery and led to loss of corneal transparency.

Conclusions: Altogether, this study indicates that committed corneal cells have large plasticity to dedifferentiate, repopulate the SC pool and correctly reform tissue boundary. By contrast, loss of SC and boundary of the cornea lead to impaired tissue functionality and pathology. We provide direct evidence for pathological wound healing by conjunctival cells that was accompanied by neovascularization, loss of transparency and blindness

Cytokines and chemokines present different expression pattern throughout the clinical course of sulfur mustard induced ocular injury.

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Purpose: The sight threatening sulfur mustard (SM) induced ocular injury presents specific symptoms for each clinical stage. The acute injury is characterized by erosions and severe inflammation, while the irreversible long-term pathology is clinically expressed by chronic inflammation and neovascularization (NV). In this study we analyzed the expression pattern of various cytokines and chemokines at different clinical stages of the ocular injury aiming to reveal pathological processes that may direct us towards novel treatment options.

Methods: Rabbits eyes were exposed to SM vapor and a clinical follow-up was carried out up to 4 weeks. Corneal and limbal tissues were collected at 48h, 1w and 4w post exposure and IL-1α, IL-1β, IL-6, TNFα, macrophage chemotactic protein (MCP)-1 and IL-8 levels were measured by commercial ELISA kits.

Results: Typical SM-induced ocular injury was developed, presenting an acute injury that was partially resolved within a week in all of the exposed eyes, followed by an irreversible long term pathology in 50%-80% of the eyes.
At the peak of the acute injury, at 48 h, significantly higher levels of corneal IL-1α, IL-8, and TNFα and limbal IL-1α and MCP-1 were found. At 1w, corneal IL-1β, IL-6, IL-8 and TNFα and limbal IL-8 and MCP-1 levels were significantly higher compared to naïve. During the long term pathology, at 4w, elevated levels of corneal IL-1β, IL-6 and MCP-1 and limbal MCP-1 and IL-8 were found only in eyes presenting NV.

Conclusions: The levels of the studied factors changed throughout the dynamic course of the ocular injury. The prolonged increased levels of limbal MCP-1 and IL-8 may contribute to the continuous recruitment of inflammatory cells, characterizing the chronic long term pathology. The specific expression pattern of these cytokines and chemokines during the different clinical stages of the ocular injury may point out towards stage-specific therapeutic options.

DMEK versus DSAEK learning curves- first 100 cases

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Purpose: The aim of the study is to compare the performance, complications, and outcome of the first 100 DSAEK procedures versus DMEK performed at Rabin medical center, with emphasis on the learning curve.

Methods: A retrospective, comparative case series study
First 102 consecutive cases of DSAEK and first 104 DMEK performed between September 2008 and July 2017 at a major medical center
A comparison between the first and the last 50 cases was performed between the 2 groups. Primary outcome measures included: visual acuity, donor dislocation rate, primary failure rate, secondary failure rate and endothelial cell loss.

Results: Visual outcomes did not correlate with surgical experience in the two groups. Final VA was found better in DMEK group versus DSAEK group. There was no difference between the groups in the primary or secondary failure rate nor in dislocation rate.
Dislocation rate was 25% in the first 50 DMEK cases, and 24% in the last 50 cases. Dislocation rate was 20% in the first DSAEK cases, and 14% in the last 50 cases. Endothelial cell loss at the last follow up visit was significantly better in the DSAEK group versus DMEK.

Conclusions: Compared with DSAEK, DMEK provided better visual recovery but inferior endothelial cell counts. A steeper learning curve was found in the DMEK group, though similar safety when compared to DSEAK.

Photovoltaic Restoration of Sight in Rodent Models of Retinal Degeneration

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Purpose: Subretinal prostheses are designed to elicit visual responses in patients blinded by the loss of photoreceptors using electrical stimulation of the remaining inner retinal neurons. We evaluate the spatio-temporal characteristics of retinal response to subretinal stimulation and contrast sensitivity of prosthetic vision mediated by the photovoltaic arrays ex-vivo and in-vivo in rats with retinal degeneration.

Methods: Ex-vivo assessment of the retinal responses to complex visual stimuli delivered at naturalistic (20-30Hz) frequencies via photovoltaic subretinal implants were performed using Multi Electrode Arrays, and compared to normal visual responses. For in-vivo evaluation, 1 mm-diameter and 30um thin photovoltaic arrays were implanted subretinally in rats with retinal degeneration (RCS). Contrast sensitivity was assessed using their startling response to contrast steps, with pulse durations in the range of 1 to 12ms. Visual acuity was measured using VEP response to alternating gratings.

Results: Ex-vivo, subretinal photovoltaic stimulation of the degenerate retina elicited ON and OFF responses, with the antagonistic center-surround organization of receptive fields, similar in size to natural. At 12% contrast, firing patterns of prosthetic response exhibited similarly significant changes as with 2.3% contrast steps in healthy retinas illuminated by visible light. In-vivo, rats exhibited startling response to prosthetic stimulation with positive and negative contrast steps, and contrast sensitivity of 12%. Visual acuity with 70 and 55 um pixels matched the pitch of the photovoltaic arrays.

Conclusions: Subretinal photovoltaic arrays elicit fast and spatially localized responses to onset and offset of light at naturalistic frequencies. Ease of implantation of such modular and wireless arrays, combined with spatial resolution on the retina below 50um (20/200 acuity in human eye), opens the door to restoration of central vision in patients blinded by AMD.

Survival and integration of the retina/RPE allograft in rat models of retinal degeneration

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Purpose: To study the survival and integration of the retina/RPE allografts from healthy rats into rats with retinal degeneration.

Methods: Retina/RPE sheet explants (1mm in diameter) were harvested from wild type Long Evans and Sprague Dawley rats (P25-P70). Recipients were RCS (>P150) and S334ter-3 (>P60) rats after complete degeneration of photoreceptors. Optical coherence tomography (OCT) was used to monitor reattachment of the retina and the implant survival over time. Integration of the transplant with the host inner retina was assessed after explantation, using histology and immunohistochemistry.

Results: Upon successful surgery, we observed no rejection of the retina/RPE transplant in the subretinal space of degenerated retinas, with all the strains or ages of donors and recipients. Photoreceptors survived only when RPE was included in the transplanted sheet. Based on OCT, the structure of the transplant was preserved during the 5 months follow-up period. Ganglion cell layer completely disappeared, likely due to the cut axons, and the inner plexiform layer thinned-down to about 30% of its initial thickness. However, inner nuclear layer and photoreceptors remained preserved, including up to 6 layers of photoreceptor nuclei with their inner and outer segments. Immunostaining of the rod bipolar cells with PKC alpha, combined with bassoon presynaptic staining, revealed some evidence of the dendrites sprouting from the host bipolar cells and synaptogenesis with bipolar cells in the transplant.

Conclusions: We demonstrate the long-term survival of mature retina/RPE transplants in rats with retinal degeneration. Essential for this success was co-transplantation of RPE and minimal trauma during surgery. Surprisingly, the success did not depend on the donor age or strain, as was previously assumed. The morphological indications of reconnection to the host retina will have to be confirmed by electrophysiological recordings.

Effect of Histone Deacetylase Inhibitor (AN-7) on Vascular Permeability in the Retina

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Purpose: To determine whether the histone deacetylase inhibitor (HDACI) butyroyloxymethyl - diethyl phosphate (AN-7), can reduce permeability *in vitro* and vascular leakage *in vivo* in a mouse model.

Methods: *In vitro* model: Human retinal pigment epithelial cells (RPE; ARPE-19) were cultured to confluency on transwell inserts. At the day of the experiment, permeability was triggered by exposure of the cells to hypoxic conditions ($1\%O_2$, $5\%CO_2$) for 24 hours in the absence or presence of increasing concentrations of AN-7 (0-100µM). Cell permeability was evaluated based on spectrophotometric monitoring of the passage of FITC labeled dextran across the cell layer.
In-vivo model: Laser-induced choroidal neovascularization (CNV) model was used for the induction of retinal vascular leakage in mice. AN-7 was given by intraperitoneal injection (IP) in 2 doses (10mg/kg, 20 mg/kg AN-7) or per os (PO, 20 mg/kg). The optimal dose and route of administration of AN-7 was tested. Evaluation of leakage was performed using Fluorescein Angiography (FA) with Optos imaging system. FA images were taken sequentially on days 2-7 post laser induction. Laser spots appearance were interpreted by two blinded retinal specialists, and were classified to "leakage", hyperfluorescent lesion with blurred margins increasing in size; or "staining", hyperfluorescent lesion with distinct margins lacking a progressive increase in size or intensity.

Results: *In vitro* analysis indicated that AN-7 stabilized the RPE monolayer and reduced the permeability as indicated by the decrease in FITC-dextran leakage.
In vivo analyses showed that AN-7 reduced vascular leakage in both IP and PO administrations. AN-7 dose of 20 mg/kg was more effective in reducing vascular leakage than 10 mg/kg.

Conclusions: AN-7 given IP or PO may prevent vascular leakage in a mouse model. HDACI might have therapeutic activity in human ocular diseases that are complicated by neovascularization or excessive vascular permeability

Detection of genes associated with proliferative diabetic retinopathy using nanostring technique

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Purpose: Proliferative diabetic retinopathy (PDR) develops in patients with severe uncontrolled diabetes. It is difficult to predict who will develop retinal neovascularization. Measuring the RNA expression of various genes may identify the genetic pathways involved in retinas with a high risk of developing PDR. This data may lead to identifying targets to prevent PDR and blindness.
The aim of this study was to assess mRNA expression of genes involved in the immunology pathway in the serum of PDR patients, as compared with healthy subjects and non proliferative diabetic retinopathy (NPDR) patients using a nanostring technique.

Methods: The study was approved by the institutional ethics review board and all patients gave informed consent. The study group consisted of patients diagnosed with PDR (n=13), NPDR (n=14) or controls (n=10). Total RNA was extracted from whole blood samples using the MagNA Pure Compact (Roche, LTD) and MagNA Pure Compact RNA Isolation Kit (Roche, LTD). mRNA expression levels were quantified and analyzed using Nanostring technology (Agentek ltd, Israel) for 9 PDR, 8 NPDR and 7 controls.

Results: 578 genes including IL-17, TNF, NF-kappa B of 15 different pathways were analyzed. Signaling pathways of inflammation and cancer PI3K - Akt pathway were included.
Of the 66 genes (11.5%) found statistically different ($P < 0.05$) between the PDR group and the others (NPDR and control groups), the most prominent were TGFb1 and TGFb1R of the inflammatory pathway, IL23R, BAX, and CFB.

Conclusions: Many efforts are invested in identifying risk factors for the development of PDR. The mRNA study may facilitate the diagnosis of the pathways involved. Surprisingly not only angiogenic but rather inflammation and proliferation pathways are involved. This may enable development of targeted inhibition.

Inhibitory Effect of Butyroyloxymethyl-diethyl phosphate (AN-7) on Choroidal Neovascularization in a Mouse Model

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Purpose: To determine whether the histone deacetylase inhibitor, butyroyloxymethyl - diethyl phosphate (AN-7), has an inhibitory effect on choroidal neovascularization (CNV) in a mouse model.

Methods: CNV was induced on the right eye of C57bl mice by 3 laser photocoagulation applications. To test the optimal dose and route of administration of AN-7, mice were treated with AN-7 or saline as control, given by intraperitoneal injection (IP; 10 or 20 mg/kg AN-7) or per os (PO; 20 mg/kg AN-7), thrice a week. On day 7 following CNV induction, FITC-dextran was injected to the mice hearts, eyes were enucleated and choroidal flatmounts were prepared. Flatmounts images were taken using fluorescent microscope and quantification of FITC-dextran area representing CNV was performed by Image J analysis. For histological studies eyes were enucleated and cryopreserved on days 3 or 7 post-laser and were stained for CD31 (endothelial cells marker), VEGF, FGF2, acetylated histone-H3 and H&E. ANOVA was used for statistical analyses (p-value<0.05 was considered statistically significant).

Results: AN-7 treatment significantly reduced CNV area in a dose-dependent manner as compared to control (p-value<0.05). AN-7 inhibitory effect was noted in both IP and PO treatments.

Immunofluorescent staining of cryosections of the laser lesions site showed elevation in histone-H3 acetylation following AN-7 treatment. Reduction in VEGF and FGF2 staining levels, accompanied by a reduction in endothelial cells staining in AN-7 compared to saline treated eyes were also noted.
Conclusions: Systemic treatment with AN-7 has a significant inhibitory effect on CNV in mice. AN-7 effect is partially mediated by VEGF and FGF2. These results suggest that AN-7 should be further evaluated for therapeutic potential for the treatment of pathologic choroidal angiogenesis.

Intravitreal Trimethoprim and Sulfamethoxazole toxicity to the retina of albino rabbits

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Purpose: To evaluate retinal toxicity of intravitreal Trimethoprim-sulfamethoxazole.

Methods: Ten albino rabbits were included in the study. In each rabbit, 1600 µg/0.1 ml was injected into the vitreous of the right (experimental) eye and 0.1 ml saline was injected into the vitreous of the left (control) eye. Electroretinogram (ERG) and Visual Evoked Potential (VEP) were recorded before injection, 3-days, 1-, 2- and 4-weeks post injection. Clinical examination was conducted at all-time points. Retinal structure and expression of Glial Fibrillary Acidic Protein (GFAP) were performed on retinas, which were prepared for histology and immunocytochemistry at termination of the follow-up period.

Results: ERG responses of the experimental eye were similar to those recorded from the control eye in 9 rabbits. One rabbit had extremely reduced ERG recordings in the experimental eye. VEP responses were reduced in the experimental eye as compared to the control eye of all rabbits. No histological damage was seen, but immunocytochemical analysis showed increased expression of glial fibrillary acidic protein in Muller (glial) cells in all experimental eyes, but not in the control eyes. Clinical examination was normal in all eyes.

Conclusions: Intravitreal injection of 1600 µg Trimethoprim-sulfamethoxazole is potentially toxic to the retina of albino rabbits, and may damage the functional integrity of the visual pathways.

Up-regulation of thrombin activity in the posterior segment of STZ induced mice model of diabetic retinopathy

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Purpose: Activation of protease-activated receptor-1 (PAR-1) plays a role in neurological dysfunction in diabetes. Recent studies indicate that PAR-1 and its activating proteases thrombin and MMP-1 are expressed in the ocular microenvironment of patients with diabetic retinopathy. The aim of this study was to establish an STZ induced mice model of diabetic retinopathy and assess thrombin protease activity in the posterior segment.

Methods: Diabetes was induced by injection of 140 mg/kg STZ in ten C57Bl/6J mice. Fifteen mice were untreated and used as control. Retinal function was examined weekly by electroretinogram (ERG). Retinal structure and vasculature were assessed by multicolor fundus imaging, spectral domain optical coherence (SD-OCT) imaging and histology analysis. Five weeks and 4 months following STZ injection mice were sacrificed, eyes were enucleated and the posterior segment was separated from the cornea, the lens and the iris under a surgical microscope. Thrombin protease activity was determined by fluorescence activity assay.

Results: An STZ induced mouse model of diabetic retinopathy was established. Diabetic mice demonstrated significantly lower maximal a-wave ERG response compared with non-treated mice (90.7±8.2 μV vs. 43.3±7.1 μV, p=0.02). SD-OCT and multicolor fundus imaging as well as histology analysis demonstrated no gross changes in the retinal layers or retinal vasculature. Thrombin activity was 1.5 and 4 fold higher in diabetic mice compared with controls 5 weeks and 4 months following STZ injection (p= 0.016 and p= 0.019, respectively)

Conclusions: STZ induced diabetic mice demonstrated reduced retinal function and increased activity of thrombin in the posterior segment, suggesting that this model is clinically relevant and that PAR-1 activation may be play a role in the retinopathy pathology in this model. Future studies will be aimed at using this model for screening new therapies for diabetic retinopathy

Hybrid Retina: A Novel Concept for Sight Restoration

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Purpose: To overcome the large neuron-electrode distance and the non-selective activation of various retinal pathways (e.g. ON and OFF) which limit the efficiency of currently available retinal prostheses, we propose a novel approach based on coupling glutamatergic neuron to high-density electrode arrays, which we term Hybrid Retinal Prosthesis. The coupled cells will synapse with the host retina and electrical stimulation of the implant induce the activation of retinal circuitry at a cellular resolution with visual restoration at high acuity.

Methods: We generated photoreceptor precursors from human embryonic stem cells, to serve as glutamatergic neurons, by a combination of IWR1e, SAG, CHIR99021 in agarose microwells. COMSOL Multypysics computer modeling was utilized to evaluate and optimize the effect of various geometrical parameters on neurons activation charge. To electro-physiologically characterize the generated cells we employed calcium imaging (rhod2) to visualize intracellular calcium dynamics in response to electrical activation. Finally, optimization and characterization of the neuron-electrode interface were performed by advanced imaging techniques, on electrode arrays which were fabricated by our group.

Results: Cell differentiation efficiency was over 80%, as shown by Fluorescence-activated cell sorting to the photoreceptor marker CRX. Simulations revealed that charge thresholds could be reduced to 0.03nC in a configuration where neurons are sealed in a microwell, as compared to 49nC in a flat electrode configuration. Maturation of neurons was demonstrated by the 3-150 fold increase in the expression of sodium, potassium and calcium voltage-sensitive channels at 12w of differentiation in addition to evidence of voltage-dependent currents observed in voltage clamp recordings. A marked increase and decrease in intracellular calcium was observed following cathodic and anodic electrical pulses, respectively. Finally, surface treatment of electrodes with RGD resulted in a two-fold increase in electrode-neural cells growth area and decreased the electrode-neuron cleft, as revealed by scanning electrode and focused ion beam microscopy.

Conclusions: We propose a new strategy for vision restoration with a hybrid retinal implant composed of a high-density electrode array incorporated with glutamatergic neurons. The hybrid device has the potential to mimic many features of natural vision, and restore high resolution and quality vision.

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