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

PROGRAM & ABSTRACTS

36th Annual Meeting

Kfar Maccabiah

9th-10th March, 2016

תכנית ותקצירים

הכינוס השנתי ה-36

כפר המכבייה

9-10 במרץ, 2016

עריכת התוכנית: פרופ׳ רות אשרי-פדן, פרופ׳ ניצה גולדנברג-כהן, פרופ׳ אירית בכר, פרופ׳ דרור שרון

הפקת הכינוס: כלים שלובים כנסים, ארגון והפקות בע"מ

עיצוב והבאה לדפוס: דבורה מרקס אוחנה

ISRAELI SOCIETY FOR VISION AND EYE RESEARCH
The 36th Annual Meeting, March 09-10, 2016
Program at a glance

Wednesday, March 09, 2016

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Guest lecture- Daniel Palanker	Rayman Center	14:00 – 14:30	17
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Guest lecture- Rachel R. Caspi	Rayman Center	14:00 – 14:30	32
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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

מרצים המקבלים השנה פרס על עבודות שהוצגו בכנס השנה שעברה (הכנס ה-35, 11-12 במרץ 2015)

Award Recipients for the Best Papers Presented at the Previous Annual Meeting (the 35th Meeting, March 11th-12th 2015)

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

1. Ofira Zloto, Goldschleger Eye Institute

A Biological Tissue Adhesive and Dissolvent System for Intraocular Tumor Plaque Radiotherapy: an In-vivo Animal Model Experiment

2. Iris Deitch, Department of Ophthalmology, Rabin Medical Center, Petach Tikva

The protective effect of activated protein C (APC) on cell permeability and laser-induced CNV progression

3. Ruti Sella, Department of Ophthalmology, Rabin Medical Center, Petach Tikva

The Efficacy of Topical Aflibercept versus Topical Bevacizumab for the Prevention of Corneal Neovascularization in a Rat Model

4. Yamit Cohen-Tayar, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel-Aviv University

Pax6 role in the regulation of retinal pigmented epithelium maturation

ARVO CHAPTER AFFILIATE

האגודה הישראלית לחקר העין והראיה
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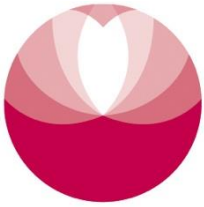

העמותה לחקר בריאות העין
ומניעת עיוורון בישראל (ע"ר)

אודות עמותת לראות

מטרות לראות

- הגברת המאמץ המחקרי ברפואת עיניים בישראל ובעולם
- העלאת המודעות הציבורית לחשיבות רפואת עיניים מונעת

בין יזמות עמותת לראות בשנת 2015:

1. חודש מודעות לבריאות העין ה- 7 , התקיים כנס אינטרנטי ראשון "לראות קדימה" של רופאי עיניים לקהל הרחב.
2. פרויקט הניידת לבדיקות עיניים של קשישים נזקקים–4000 קשישים נבדקו ו20% נצלו מעיוורון!
3. שנה שנייה של מחקר מיפוי גנטי של חולים במחלות ניווניות ברשתית – קונסורציום של 11 מרכזים רפואיים המשתפים פעולה בפרויקט ייחודי בעולם שיקדם רפואה אישית המותאמת לחולה.
4. הקמת אתר לחולי RP, כולל פורומים רפואיים.

תכנית לשנת הפעילות 2016:

1. תכנית למימון מחקרים במוסדות מחקר רפואיים בישראל ובארה"ב
2. מתן יעוץ רפואי ב-7 פורומים של רופאים מומחים ומנהלי מחלקות עיניים
3. ארגון חודש המודעות ה 8 לבריאות העין
4. ניידת בדיקות עיניים לקשישים נזקקים וניצולי שואה בקהילה
5. גיוס חולים למחקר מיפוי גנטי של מחלות רשתית
6. קידום פעילות סקר ראיה לילדים עם הפוטו סקרינר

העמותה לחקר בריאות העין
ומניעת עיוורון בישראל (ע"ר)

המחקרים הממומנים ע"י עמותת "לראות" ב-2015:

השנה כ-9 מחקרים קבלו מימון, כתוצאה מהפעילות של עמותת "לראות".
בין החוקרים המקבלים מענקי מחקר של עמותת "לראות" באמצעות המדען הראשי: **ד"ר חטיב סאמר, פרופ' איתי חוברס, ד"ר אברהם קציר, ד"ר עדי ענבל, ד"ר תמר בן-יוסף, פרופ' איתן גלון ,פרופ' אדו פרלמן, ד"ר מנדל יוסף, פרופ' דרור שרון.**

חברי ועד המנהל של עמותת לראות

אוהד להב, יו"ר

פרופ' אדו פרלמן יו"ר המועצה המדעית

חברי הועד המנהל: פרופ' ארי ברזילי, פרופ' דב ויינברגר, פרופ' ענת לבנשטיין, פרופ' חנא גרזוזי, פרופ' יעקב פאר, פרופ' אהוד אסיה, פרופ' אדו פרלמן, פרופ' דרור שרון, פרופ' יאיר מורד, פרופ' אבי סולומון, ד"ר חני ורבין,ד"ר רונית לוינגר, ד"ר יפית שטרק, גב' איריס שפיגל, מר מרק עמוס, ד"ר ניר ארדינסט, מר יאיר שפר, מר אשר גרינבאום.

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הרצאות אורח בכנס ה- 36

Keynote Speakers at ISVER 2016

Wednesday, March 09 th 2016

Prof. Daniel Palanker

Department of Ophthalmology and Hansen Experimental Physics Laboratory, Stanford University, CA, USA

- Non-damaging laser therapy of the macula: mechanisms and applications

- Photovoltaic restoration of sight in animals with retinal degeneration

Thursday, March 10 th 2016

Prof. Rachel R. Caspi

Chief, Immunoregulation Section; Deputy Chief, Lab. Immunology, NEI, NIH; Bethesda, MD, USA

- Ocular Autoimmunity: a collusion of development and environment

- Commensal microbiota as a potential trigger of autoimmune uveitis.

Wednesday, March 9th 2016

Coffee and Exhibition 8:00 – 8:55

Opening remarks 8:55 – 9:00

Dror Sharon

Imaging 9:00 – 9:45

Moderators:

Dov Weinberger and Ariela Gordon-Shaag

1 9:00 AC

Optic Nerve Head Drusen Prevalence in Normal-Appearing Eyes Using Enhanced Depth Imaging Optical Coherence Tomography p. 43

Alon Skaat (1,2), Mark Ghassibi (2), Jeffrey M. Liebmann (2), Robert Ritch (2), Sung Chul Park (2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, (2) New York Eye and Ear Infirmary of Mount Sinai, New York, NY, USA

2 9:10

Automated Identification of Lesion Activity in nvAMD p. 44

Dafna Goldenberg (1), Usha Chakravarthy (2,3) ,Graham Young (3), Moshe Havilio (4), Omer Rafaeli (4), Gidi Benyamini (4), Anat Loewenstein (1)
(1) Tel Aviv Medical Center, Tel Aviv, (2) Center for experimental medicine, QUB, Belfast, UK, (3) Belfast HSCT, Belfast, UK, (4) Notal Vision Ltd. Tel Aviv

3 9:15

Interchangeability of Two Corneal Topographers in Post Refractive Surgery Patients p. 45

David Markov, Aurelia Elfassi, Sara Shukrun, Einat Shneor
Hadassah Academic College, Department Of Optometry, Jerusalem

4 9:20 AC

Imaging the Suprachoroidal Space with Enhanced Depth Imaging Swept Source OCT p. 46

Joel Hanhart
Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem

5 9:25 AC **Long Term Structural Changes Induced by Macular Argon Laser, Visualized on En-Face OCT** p. 47

Joel Hanhart, Tamar Levi Vineberg, Yaakov Rozenman
Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem

6 9:30 AC **Validation and Repeatability of the Paul Harris Stereotest** p. 48

Liat Gantz, Ariela Gordon Shag, Wedad Sheety, Almaza Haddad, Doreen Hallon, Tzadok Parnas, David Markov, Einat Shneor
Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem

7 9:35 AC **Advanced Multiphoton Methods for *in vitro* and *in vivo* Functional Imaging of Mouse Retinal Neurons** p. 49

Noam Cohen (1), Adi Schejter (1), Nairouz Farah (2), Shy Shoham (1)
(1) Department of Biomedical Engineering, Technion, Haifa, (2) Faculty of Life Science, Bar Ilan University, Ramat-Gan

9:40 **Discussion**

Retina- cell biology

9:45 – 10:45

Moderators:

Ido Perlman and Nitza Cohen-Goldenberg

8 9:45 **Adipose Tissue Derived Mesenchymal Stem Cells Migrate Towards RPE, Rescue Apoptotic RPE under Oxidative Stress, and have the Potential to Differentiate into RPE** p. 50

Aya Barzelay (1,2), Sebastian Katz (1,2), Shira Weisthal (1,2), Moshe Ben-Hemo (1,2), Anat Loewenstein (1,2), Adiel Barak (1,2)
(1) Tel Aviv Medical Center, (2) Sackler School of Medicine, Tel Aviv University

9
9:55
AC

Microarray of Inflammation, Angiogenesis and Coagulation Proteins in a Variety of Retinal Diseases

p. 51

Idit Dan (1,2,3), Alon Zahavi (1,2,3), Yael Nisgav (3), Mor Dachbash (3), Dov Weinberger (1,2,3), Tami Livnat (2,3,4), Rita Ehrlich (1,2,3)
(1) Department of Ophthalmology, Rabin Medical Center, Petah Tiqwa, (2) Sackler School of Medicine, Tel Aviv University (3) Felsenstein Medical Research Center, Rabin Medical Center, Petah Tiqwa (4) The Israeli National Hemophilia Center, Sheba Medical Center, Tel Hashomer

10
10:00
AC

Retinal Toxicity of Intravitreal Injection of Ziv-Aflibercept in Albino Rabbits

p. 52

Dan Ramon (5), Yonathan Shahar (2,1), Amir Massarweh (3), Irit Mann (3), Ido Perlman (3, 4), Anat Loewenstein (1,2)
(1) Sackler Faculty of Medicine, Tel-Aviv University, (2) Department of Ophthalmology, Tel-Aviv Medical Center, (3) Department of Physiology and Biophysics, Technion-Israel Institute of Technology, Ruth & Bruce Rappaport Faculty of Medicine, Haifa, (4) Rappaport Institute, Haifa, (5) Ruth & Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa

11
10:05
AC

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

p. 53

Elena Segal (1), Ronit Heinrich (2), Shadi Safuri (2), Ami Aronheim (3), Naim Shehadeh (1), Ido Perlman (2)
(1) Department of Pediatrics A, Meyer Children's Hospital, Rambam medical Center, Haifa (2) Department of Physiology, Rappaport Faculty of Medicine, Technion, (3) Department of Molecular Genetics, Rappaport Faculty of Medicine, Technion

12
10:10
AC

TAK1 is a Pivotal Player in the Autophagy Process in Human RPE Cells

p. 54

Keren Ben Yaakov, Yaron A. Green, Orit Adir, Ayala Pollack, Zeev Dvashi
Kaplan Medical Center, Rehovot, affiliated with Hadassah-Hebrew University of Jerusalem, Rehovot

13 10:15 AC **Generation of Retinal Pigment Epithelial Cells from Human Induced Pluripotent Stem Cells for the Study of Inherited Macular Degeneration (Best Disease)** p. 55

Oren Ben-Yosef (1), Shadi Safuri (1), Michal Amit (2), Joseph Itskovitz-Eldor (3), Ido Perlman (1)
(1) Department of Physiology, Rappaport Faculty of Medicine, Technion, (2) Accellta Ltd., Technion, (3) Department of Obstetrics-Gynecology, Rambam Hospital, Haifa

14 10:20 AC **Retinal Pigment Epithelium (RPE) Cells Facing Cone Photoreceptors Display Distinct Transciptome with Implications for the Pathogenesis of Age-Related Macular Degeneration (AMD)** p. 56

Shadi Safuri (1), Liat Brenner (1), Anat Loewenstein (2), Ido Perlman (1)
(1)Technion-Israel Institute of Technology, Haifa (2) Tel Aviv Medical Center, Tel- Aviv

15 10:25 AC **Treatment of Corneal Potential Protective Role of the CB2 Cannabinoid Receptor System in the Crosstalk between Autophagy and Cellular Senescence of RPE cells** p. 57

Zeev Dvashi (1), Shimon Ben-Shabat (2), Orit Adir (1), Eli Beit-Yannai (2), Ayala Pollack (1)
(1) Kaplan Medical Center, Rehovot, affiliated with Hadassah-Hebrew University of Jerusalem, (2) Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva

108 10:30 **ERG Oscillatory Potentials Frequency Domain Changes Allow Accurate Recognition of Diabetic Retinopathy Patients** p. 58

Boris Rosin (1,2), David Kohn (1) Eyal Banin (1,2)
(1) Department of Ophthalmology, Hadassah Hebrew University Medical center (2) Department of Medical Neurobiology, Hadassah-Hebrew University School of Medicine

10:35 **Discussion**

Coffee and exhibition 10:45 – 11:45

Therapy 11:45 – 12:30

Moderators:
Yossi Mandel and Michael Belkin

16 11:45 **Phase I Gene Therapy Trial in Israeli Patients with Leber Congenital Amaurosis Caused by a Founder *RPE65* Mutation: Long-Term Follow-up** p. 59

Alexey Obolensky (1), Devora Marks-Ohana (1), Shelly Stika (1), Itzhak Hemo (1), William W. Hauswirth (2), Samuel G. Jacobson (3), Dror Sharon (1), Eyal Banin (1)
(1) Hadassah-Hebrew University Medical Center, Jerusalem, (2) University of Florida, Gainesville, Florida, USA, (3) University of Pennsylvania, Philadelphia, Pennsylvania, USA

17 11:55 AC **Differentiation of Human Embryonic Stem cells into Photoreceptor Precursor – In-Vitro and In-Vivo Study** p. 60

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

18 12:00 **Transplantation of Human Adult Oral Mucosa Stem Cells Ameliorates Retinal Degeneration in a Rat Model of Retinal Dystrophy** p. 61

Ifat Sher (1,2), Nir Levy (1,2), Lea Twito (1), Adi Tzameret (1,2), Shlomo Kotev Emet (3), Ina Arie (4), Sigal Buch (4), Sandu Pitaru (4), Naphtali Savion (3), Ygal Rotenstreich (1,2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel, (2) Sackler Faculty of Medicine, Tel Aviv University, (3) Goldschleger Eye Research Institute, Sackler Faculty of Medicine, Tel Aviv University, Sheba Medical Center, Tel Hashomer, (4) Department of Oral Biology, School of Dental Medicine, Sackler Faculty of Medicine, Tel Aviv University

19 12:05 AC

Measurement and Improvement of Visual Acuity and Reading Capabilities in Simulated Prosthetic Vision with Active Sensing

p. 62

Liron Gerbi Zarfati (1), Chen Abraham (1), Yuval Harpaz (2), Nairouz Farah (3), Zeev Zalevsky (1,4) Yossi Mandel (3,4)
(1) Bar-Ilan University, Ramat-Gan, (2) Faculty of Engineering, (3) Gonda Multidisciplinary Brain Research Center, Faculty of Life Sciences, Optometry Track, (4) Nano Technology Center

20 12:10 AC

Prophylactic Laser Retinopexy in Patients Undergoing Macular Hole and Epiretinal Membrane Surgeries

p. 63

Ran Rutenberg (1), Oded Ohana (1), Elad Moisseiev (1), Zvi Davidovich (2), Adiel Barak (1)
(1) Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, (2) Schneider Children's Medical Center in Israel

21 12:15 AC

Long-Term Treatment with 9-cis-beta-carotene Rich Alga *Dunaliella Bardawil* Inhibits Photoreceptor Degeneration in a Mouse Model of Retinoid Cycle Defect

p. 64

Victoria Edelshtain (1), Ifat Sher (1), Adi Tzameret (1), Dror Harats (2), Aviv Shaish (2), Ygal Rotenstreich (1)
(1) Goldschleger Eye Institute, Sackler Faculty of Medicine, Tel Aviv University, Sheba Medical Center, (2) The Bert W. Strassburger Lipid Center, Sheba Medical Center

22 12:20

A Minimally Invasive Adjustable-Depth Blunt Injector for Delivery of Pharmaceuticals into the Posterior Pole

p. 65

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

12:25 **Discussion**

Guest Lecture 1- Prof. Daniel Palanker

12:30 - 13:00

Department of Ophthalmology and Hansen Experimental Physics Laboratory, Stanford University, CA, USA

Non-Damaging Laser Therapy of the Macula: Mechanisms and Applications

Lunch break

13:00 – 14:00

Guest lecture 2 - Prof. Daniel Palanker

14:00 – 14:30

Department of Ophthalmology and Hansen Experimental Physics Laboratory, Stanford University, CA, USA

Photovoltaic Restoration of Sight in Animals with Retinal Novel Nano Delivery anti-VEGF Strategies for AMD

Animal Models

14:30 - 15:45
Rayman Center

Moderators:

Ruby Shalom-Feuerstein and Ruth Ashery-Padan

23 14:30 AC

Is there a Neovascularization in Diabetic Mouse Model?

p. 66

Tamar Azrad-Leibovitch (3,4), Rinat Ankri (1), Dror Fixler (1), Dov Weinberger (3,5) Nitza Goldenberg-Cohen (2,3,4)
(1) Faculty of Engineering, Institute of Nanotechnology and Advanced Materials, Bar-Ilan University (2) Pediatric Ophthalmology Unit, Schneider Children's Medical Center, (3) Sackler Faculty of Medicine, Tel-Aviv University, (4) Krieger Eye Research Laboratory FMRC, (5) Ophthalmology department, Rabin Medical Center

24 14:40

Six3 Regulates Optic Nerve Development via Multiple Mechanisms

p. 67

Ariel M. Rubinstein, Anat Samuel, Tehila T. Azar, Adi Inbal
IMRIC, The Hebrew University of Jerusalem – Hadassah Medical School

25 14:45 AC

Retinal Degeneration in Fam161a Knockout Mice

p. 68

Avigail Beryozkin (1), Alexey Obolensky (1), Segev Meyer (1), Ayala Ejzenberg (1), Chen Matsevich (1), Yvan Arsenijevic (2), Carlo Rivolta (2), Eyal Banin (1), Dror Sharon (1)
(1) Ophthalmology, Hadassah-Hebrew University Medical Center, (2) University of Lausanne, Switzerland

26 14:50 **Cellular Characterization of the Inflammatory Response Associated with Corneal Neovascularization in a Chemical Injury Model and Potential Therapy** p. 69

Elina Berg (1), David Zadok (1,2), Maayan Cohen (3), Hila Gutman (3), Liat Cohen (3), Rellie Gez (3), Ariel Gore (3), Shlomit Dachir (3), Tamar Kadar (3)
(1) Department of physiology and pharmacology, Sackler Faculty of Medicine, Tel Aviv University, (2) Department of Ophthalmology, Assaf HaRofeh Medical Center, (3) Department of Pharmacology, Israel Institute for Biological Research

27 14:55 AC **Reduced Inflammatory Reaction has a Neuroprotective Effect in Optic Nerve Crush Model** p. 70

Moran Friedman (3,4), Ivan Novitzky (1), Neelan J. Marianayagam (1,4), Shirel Weiss (3,4), Shalom Michowiz (1,3), Nitza Goldenberg-Cohen (2,3,4)
(1) Department of Neurosurgery, Rabin Medical Center, Beilinson Hospital, (2) Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel (3) Sackler Faculty of Medicine, Tel- Aviv University, (4) Krieger Eye Research Laboratory FMRC

28 15:00 AC **Examining the Ability of Resveratrol to Attenuate Disease Progression in Two Rodent Models of Retinal Degeneration and Injury** p. 71

Hamzah Aweidah (1,2), Ayala Ejzenberg (2), Chen Matsevich (2), Eyal Banin (1,2), Alexey Obolensky(1,2)
(1) Department of Ophthalmology and (2) The Center for Retinal and Macular Degenerations, Hadassah- Hebrew University Medical Center

29 15:05 **Clearance of Aflibercept Following Intravitreal Injection in a Rat Model** p. 72

Orly Gal-Or (1), Assaf Dotan (1), Ruti Sella (1,2), Mor Dachbash (3) ,Yael Nisgav (3), Dov Weinberger (1,2,3), Rita Ehrlich (1,2), Tami Livnat (2,3)
(1) Department of ophthalmology, Rabin Medical Center, Petach-Tikva, (2) Sackler School of Medicine, Tel-Aviv University, (3) Laboratory of Eye Research, Felsentstein Medical Research Center, Rabin Medical Center, Petach -Tikva

30 15:10 **Gene Augmentation Therapy Restores Retinal Function and Visual Behavior in a Sheep Model of CNGA3 Achromatopsia – Long Term Follow-up** p. 73

Raaya Ezra-Elia (1), Elisha Gootwine (2), Edward Averbukh (3), Alexey Obolensky (3), Alexander Rosov (2), Hen Honig (2), Shai Sandalon (1), William W Hauswirth (4), Eyal Banin (3), Ron Ofri (1)
(1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, (2) Agricultural Research Organization, The Volcani Center, Beit Dagan, (3) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, (4) Department of Ophthalmology, University of Florida, Gainesville, FL

31 15:15 **Impaired RPE-Mediated Phagosome Turnover as an Early Marker for Ocular Damage in the Cohen Diabetic Rats** p. 74

Shadi Daoud (1), Mirit Cidor (1), Aviram Kogot-Levin (2), Sarah Weksler-Zangen (2), Tal Burstyn-Cohen (1)
(1) The Institute for Dental Sciences, Faculty of Dental Medicine, Hebrew University - Hadassah, Jerusalem (2) The Diabetes Unit, Department of Internal Medicine, Hadassah-Hebrew University Medical Centre, Jerusalem

32 15:20 **Studying Visual Behavior in Barn Owls with a Miniature Head-Mounted Video Camera** p. 75

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

33 15:25 AC **Involvement of NETosis in LPS-Induced Ocular Inflammation in a Mouse Model** p. 76

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

34 15:30 **Pax6 Role in the Regulation of Retinal Pigmented Epithelium Maturation** p. 77

Yamit Cohen-Tayar (1), Pablo Blinder (2), Maria Idelson (3), Benjamin Reubinoff (3), Shalev Itzkovitz (4), Ruth Ashery-Padan (1)
(1) Department of Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel-Aviv University, (2) Department of Neurobiology, Sagol School of Neuroscience, Tel Aviv University, (3) Department of Gynecology, Hadassah-Hebrew University Medical Center, Jerusalem, (4) Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot

15:35 **Discussion**

Pediatric

14:30– 15:45
Rayman East

Moderators:
Chaim Stolovitch and Eedy Mezer

35 14:30 AC **Evaluation of Ocular Motility Deviation Changes Post Cycloplegic Eye Drops versus Prism Adaptation Test in Exotropic Patients** p. 78

Alon Zahavi (1,3), Ronit Friling (2,3), Nitza Goldenberg Cohen (2,3), Yonina Ron (2,3), Miri Ehrenberg (2,3), Moshe Snir (1,2,3)
(1) Ophthalmology Department, Rabin Medical Center – Beilinson Hospital, Petach Tikva, (2) Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petach Tikva, (3) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

36 14:40 AC **Refractive Changes After Unilateral Recess-Resect Strabismus Corrective Surgery: a Case-Control Study** p. 79

Ari Leshno (1), Daphna Mezad–Koursh (2), Tomer Ziv-Baran (3), Chaim Stolovitch (2,4)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer, (2) Department of Ophthalmology Sourasky Tel-Aviv medical center, (3) School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, (4) Assuta Medical Center, Tel-Aviv

38 14:45 **Refractive Changes Induced by Strabismus Corrective Surgery in Adults** p. 80

Daphna Mezad–Koursh (1), Ari Leshno (2), Tomer Ziv-Baran (3), Chaim Stolovitch (1,4)
(1) Tel Aviv Sourasky Medical Center, Tel Aviv,(2) Sheba Medical Center, Tel Hashomer, (3) School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, (4) Assuta Medical Center, Tel Aviv

37 14:50 **A Passive Optical Device for Nystagmus Correction and Resolution Enhancement** p. 81

Dana Gotthilf Nezri, Arkady Rudnitsky, Zeev Zalevsky
Faculty of Engineering, Bar Ilan University, Ramat Gan

39 14:55 **Causes of Visual Impairment and Blindness in Children at a Hospital Based Low-Vision Center in Israel** p. 82

Ibrahim Saadeh (1), Michal Macarov (1), Veronica Tzur (1), Yael Gutman (1), Rachel Dan (1), Orly Wussuki-Lior (1), Anat Blumenfeld (1), Claudia Yahalom (1)
(1) Department of Ophthalmology, Hadassah- Hebrew University Medical Center, Jerusalem

40 15:00 **Measurement of Ocular Torsion with Digital Image Analysis in Face Turn and Head Tilt for Assessment of a Superior Oblique Palsy** p. 83

Joshua M Kruger (1), Niphon Chirapapaisan (2), Joseph F 3rd Rizzo (2), Dean M Cestari (2)
(1) Hadassah Medical Center, Department of Ophthalmology, Jerusalem, (2) Department of Ophthalmology, Harvard Medical School Division of Neuro-Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, MA, United States

41 15:05 AC **Suture Colonization Rate in Adjustable Strabismus Surgery** p. 84

Oriel Spierer (1), Sirinya Suwannaraj (2), Kara M. Cavuoto (2), Darlene Miller (2), Craig A. McKeown (2), Hilda Capo (2)
(1) Department of Ophthalmology, Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (2) Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA

42 15:10 **A Comparison between two Subjective Near Phoria Tests: Maddox Wing Test and Modified Thorington Test** p. 85

Rachel Eichler, Aviva Salomon Cohen, Miriam Lusker, Einat Shneor
Hadassah Academic College, Department Of Optometry, Jerusalem

43 15:15 **Risk Factors for the Development of Cataract in Children with Uveitis** p. 86

Tamar Blum-Hareuveni (1,2), Sophie Seguin-Greenstein (1), Michal Kramer (3,4), Guy Hareuveni (2), Yael Pauker-Sharon (3), Ronit Friling (4,5), Lazha Talat (1,6), Sue Lightman (1,6), Oren Tomkins-Netzer (1,6,7)
(1) Moorfields Eye Hospital, London, UK, (2) Galilee Medical Center, Naharia, (3) Rabin Medical Center, Petah-Tikva, (4) Sackler School of Medicine, Tel Aviv, (5) Schneider Children's Medical Center of Israel, Petah-Tikva, (6) UCL Institute of Ophthalmology, London, UK, (7) Bnai Zion Medical Center, Haifa

44 15:20 **The Role of Pre-Implantation Genetic Diagnosis in Preventing Childhood Blindness** p. 87

Claudia Yahalom (1), Michal Macarov (1), Galit Lazer - Derbeko (2), Gheona Altarescu (2), Dror Sharon (1), Anat Blumenfeld (1)
(1) Department of Ophthalmology, Hadassah- Hebrew University Medical Center, Jerusalem (2) Medical Genetics Institute, Shaare Zedek Medical Center. Jerusalem

45 15:25 AC **Amblyopia and Strabismus: Trends in Incidence and causes among Teenagers in Israel** p. 88

Yinon Shapira (1), Michael Mimouni (1), Yossy Machluf (2), Yoram Chaiter (3), Eedy Mezer (1,4)
(1) Department of Ophthalmology, Rambam Health Care Campus, Haifa, (2) Weizmann Institute of Sciences, Rechovot, (3) Israel Defense Forces, Medical Corps, (4) Bruce and Ruth Rappaport Faculty of Medicine, Technion, Israel Institute of Technology

46 15:30 **OCT Imaging of Papilledema in Pediatric Idiopathic Intracranial Hypertension** p. 89

Yuval Cohen (1), Muhammad Mahajnah (2,3), Rana Hanna (1), Michael Idel (2), Beatrice Tiosano (1,3)
(1) Ophthalmology department, Hillel Yaffe Medical center, Hadera, (2) Pediatric Neurology and Child Development Institute, Hillel Yaffe Medical Center, Hadera, (3) Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa

15:35 **Discussion**

Coffee and exhibition 15:45 – 16:15

Oncology 16:15 – 17:00

Moderators:
Jacob Pe'er and Vicktoria Vishnevskia-Dai

47 16:15 **Retinoblastoma – the Clinical Presentation of Patients with Mosaics** p. 90
Shahar Frenkel, Jacob Pe'er
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

48 16:25 AC **Sub-Retinal Fluid Optical Density in Choroidal Tumors** p. 91
Ari Leshno (1), Vicktoria Dai (1), Adiel Barak (2), Iris Moroz (1), Dina Tzur (2), Shiran Gabai (1,2), Meira Neudorfer (2)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, (2) Department of Ophthalmology Sourasky Tel-Aviv medical center

49 16:30 **Retinoblastoma Treated with Ru-106 Plaque Brachytherapy as a Primary Treatment in Israel** p. 92
Jacob Pe'er, Shahar Frenkel
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem

50 16:35 AC **Malignant Tumors Infiltrating the Optic Nerve** p. 93
Neelan J. Marianayagam (1), Judith Luckman (2), Ruth Huna-Baron (4,9), Helen Toledano (5,9), Shalom Michowitz (6,9), Hadas Stiebel-Kalish (3,9), Nitza Goldenberg-Cohen (7,8,9)
Departments of (1) Neurosurgery and (2) Radiology, (3) Ophthalmology, Rabin Medical Center, Petach Tikva, (4) Ophthalmology, Sheba Medical Center, Tel Hashomer, Units of Pediatric (5) Oncology, (6) Neurosurgery and (7) Ophthalmology, Schneider Children's Medical Center of Israel, Petach Tikva, (8) Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Petach Tikva, (9) Sackler Faculty of Medicine, Tel Aviv University

51 16:40 AC

Using Differential Expression of MicroRNA may Improve Subgrouping of Medulloblastoma for Targeted Treatment

p. 94

Sivan Gershanov (1,2), Shalom Michowiz (3,4), Helen Toledano (3,5), Orit Barinfeld (2,3), Mali Salmon-Divon (1), Nitza Goldenberg-Cohen (2,3,6)
(1) Genomic Bioinformatics, Molecular Biology, Ariel University, Ariel, (2) The Krieger Eye Research Laboratory, FMRC, and (3) Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, (4) Pediatric Neurosurgery, (5) Pediatric Oncology, and (6) Pediatric Ophthalmology, Schneider Children's Medical Center of Israel, Petach-Tikva

52 16:45

Evaluation of the Toxicity of Intravitreal Carboplatin Injection in a Rabbit Model

p. 95

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

52 16:50

The Biomarker TK Predicts Metastases in Uveal Melanoma Patients

p. 96

Vivian Barak (1), Shahar Frenkel (2), Inna Kalichman (1), Jacob Pe'er (2)
(1) Immunology Lab for Tumor Diagnosis.(2) Ophthalmology Dep; Hadassah - Hebrew University Medical Center, Jerusalem

16:55 **Discussion**

Thursday, March 10th 2016

Coffee and Exhibition 8:00 -8:45

Retina 8:45 – 9:45

Moderators:

Ayala Pollack and Ygal Rotenstreich

54 8:45 AC

The Israeli Inherited Retinal Degenerative Diseases Consortium (IIRDC): Mapping Inherited Retinal Degenerative Diseases in the Israeli Population

p. 97

Tamar Ben-Yosef (1), Dror Sharon (2), Eran Pras (3,4), Nitza Goldenberg-Cohen (4,5), Miri Ehrenberg (5), Ohad Birk (6,7), Libe Gradstein (6), Anan Abassi (8), Noam Shomron (4), Hadas Newman (4,9), Rina Leibu (10), Shiri Soudry (10), Haim Levy (6,7), Eyal Banin (2), Ido Perlman (1,9)

(1) Rappaport Faculty of Medicine, Technion, Haifa (2) Hadassah-Hebrew University Medical Center, Jerusalem (3) Asaf Ha'Rofe Medical Center, Rishon Lezion (4) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv (5) Schneider Medical Center, Petah Tikva (6) Soroka Medical Center, Beer Sheva (7) Ben Gurion University, Beer Sheva (8) Bnai Zion Medical Center, Haifa (9)

55 8:55 AC

Anti-VEGF's Effect on Photoreceptor Disruption

p. 98

Asaf Achiron, Ayana Kydyrbaeva, Oded Lagstein, Zvia Burgansky, Oren Blumenfeld, Asaf Bar, Elisha Bartov

Department of Ophthalmology, Edith Wolfson Medical Center, Holon and Sackler Faculty of Medicine, Tel Aviv University

56 9:00 AC

Critical Flicker Frequency and the Relationship to spatial and temporal vision abilities in Healthy and Amblyopic Subjects

p. 99

Auria Eisen (1), Nairouz Farah (1), Zvia Burgansky-Eliash (2), Uri Polat (1), Yossi Mandel (1)

(1) Faculty of life Sciences, Optometry Track, Bar-Ilan University, Ramat-Gan, (2) E. Wolfson Medical Center, Holon

57 9:05 AC

CSR in Women

p. 100

Aviel hadad, Perach Osaadon, Hanin Nasser, Marina Shneck, Itamar Klemperer, Tova Lifshitz, Jaime Levy, Erez Tsumi

Soroka Hospital, Beer-Sheva

58 9:10 **Reversal of CME in a Gyrate Atrophy Patient – Molecular Diagnosis and Treatment Response** p. 101

Dan Heller (1), Assaf Rosenberg (1), Iris Nassie (2), Chen Weiner (2), Isaac Avni (1), Eran Pras (1,2)
(1) Ophthalmology Department, Assaf Harofe Medical Center, Zeriffin, (2) Matlow's Ophthalmogenetic laboratory, Assaf Harofe Medical Center, Zeriffin

59 9:15 AC **Silicone Oil Influence on Macular Thickness** p. 102

Gilad Rabina, Nur Azem, Adiel Barak, Anat Loewenstein, Shulamit Schwartz
Tel Aviv Sourasky Medical Center, affiliated with Tel Aviv University, Sackler School of Medicine

60 9:20 AC **Retinits Pigmentosa and Chronic Granulomatous Disease** p. 103

Miriam Ehrenberg (1), Naama Orenstein (2), Hadas Newman (3)
(1) Ophthalmology Unit, Schneider Children's Medical Center in Israel, Petach Tikva, (2) Genetic Department, Schneider Children's Medical Center in Israel, Petach Tikva, (3) Ophthalmology Department, Tel Aviv Sourasky Medical Center, Tel Aviv

61 9:25 AC **Self-learning the use of Sensory Substitution** p. 104

Menahem Kerem (1), Shachar Maidenbaum (1), Galit Buchs (1), Benedetta Heimler (1), Tomer Behor (1), Amir Amedi (1,2)
(1) Hebrew University of Jerusalem (2) Sorbonne Universités UPMC Univ Paris 06, Institut de la Vision Paris, France

62 9:30 AC **Topical Apraclonidine Reduce Pain after Intravitreal Injections: a Double-Blind Randomized Controlled Trial** p. 105

Oded Lagstein (1,2), Noa Ben-Artzi (2), Asaf Achiron (1,2), Achia Nemet (3), Maroun Khreish (1), Elisha Bartov (1,2), Zvia Burgansky-Eliash (1,2)
(1) The E. Wolfson Medical Center, Department of Ophthalmology, Holon, (2) The Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv (3) The Hebrew University Hadassah Medical School, Jerusalem

63 9:35 AC **Pilot Study of Feasibility of Use of Experimental High Viscosity Silicone Oils** p. 106

Shira Sheen-Ophir, Alexander Rubowitz
Department of Ophthalmology, Meir Medical Center, Kfar Saba

9:40 **Discussion**

Cornea 1

9:45 – 10:30

Moderators:

Avi Solomon and Irit Bahar

64 9:45 **The Beneficial Effects of Aflibercept for Treatment of Corneal Neovascularization in a Chemical Injury Model** p. 107

Shlomit Dachir, Vered Horwitz, Liat Cohen, Maayan Cohen, Hila Gutman, Rellie Gez, Ariel Gore, Tamar Kadar

Department of Pharmacology, Israel Institute for Biological Research, Ness Ziona

65 9:55 **Stiffening of Rabbit Sclera by Bacteriochlorophyll Derivative WST11-D using Near Infrared Light** p. 108

Alexandra Goz (1,2), Efrat Bukelman (3), Jurriaan Brekelmans (4), Alexander Brandis (1), Avigdor Scherz (1), Arie Marcovich (1,2)

(1) Departments of Plant Sciences, The Weizmann Institute of Science, (2) Department of Ophthalmology, Kaplan Medical Center, Rehovot, (3) Tel Aviv Sourasky Medical Center, (4) University Eye Clinic Maastricht, Maastricht, The Netherlands

66 10:00 AC **Repeatability of Corneal Astigmatism Measurements** p. 109

Avner Belkin (1,4), Adi Abulafia (1,2,3), Adi Levy (3), Avi Ohayon (1,4), Douglas D Koch (5), Li Wang (5), Ehud I. Assia (1,3,4)

(1) Sackler School of Medicine, Tel Aviv University, Tel Aviv, (2) Asaf Harofeh Medical Center, Zerifin, (3) Ein Tal Eye Center, Tel Aviv, (4) Department of Ophthalmology, Meir Medical Center, Kfar Saba, (5) Cullen Eye Institute, Baylor College of Medicine, Houston, Texas, USA

67 10:05 **Novel use of SiHy Contact Lens with Prism to Alleviate Binocular Vertical Diplopia in a Patient with Anisometropia and Keratoconus** p. 110

Cyril Kahloun, Liat Gantz, Ariela Gordon-Shaag

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

68 10:10 **Validity and Precision of a novel Instrument that Combines Wavefront Aberrometry, Autofraction and Corneal Topography with a Stationary Scheimpflug Camera** p. 111

Cyril Kahloun, Ariela Gordon-Shaag, Liat Gantz, David Markov, Tzadok Parnas, Tal Ben Yaacov, Rebecca Cohen Levy, Einat Shneor
Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem

69 10:15 AC **Refractive Surgery on the Same Day as the Initial Consultation- Safety, Efficacy and Predictability** p. 112

Assaf Gershoni, Michael Mimouni, Eitan Livny, Irit Bahar
Assuta Optic Laser Center, Tel Aviv

70 10:20 AC **Age Related Changes in Corneal Refractive Parameters** p. 113

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

10:25 **Discussion**

Coffee and Exhibition 10:30 -11:15

Cornea 2

11:15 – 12:15

Moderators:

Tamar Kadar and Arie Marcovich

71 11:15 AC

Very Long Term Success of Pterygium Surgery with Conjunctival Graft

p. 114

Ofira Zloto, Nachum Rosen, Ari Leshno, Mordechai Rosner
Goldschleger Eye Institute, Sackler Faculty of Medicine, Tel-Aviv University, Sheba Medical Center, Tel Hashomer

72 11:25 AC

In-vivo and ex-vivo Corneal Stiffening Induced by WST11-D and Near Infra Red (NIR) Light using a Shortened Irradiation Time and Decreased Total Energy

p. 115

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

73 11:30 AC

ICD vs RoseK2 Lenses for Patients with Keratoconus

p. 116

Liat Gantz, Ronit Engalnoff, Eliran Gavrieli, Lital Naor, Philip Fine
Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem

74 11:35 AC

Induced de-novo Astigmatism after LASIK Surgery in Non-Astigmatic Eyes. H-LASIK vs M-LASIK

p. 117

Lily Karmona (1), Michael Mimouni (2), Tzahi Sela (3), Gur Munzer (3), Igor Kaiserman (3,4)
(1) Department of ophthalmology, Wolfson Medical center, Holon, (2) Department of ophthalmology, Rambam Health Care Campus, Haifa, (3) Care-Vision Laser center Institute, Tel-aviv, (4) Department of ophthalmology, Barzilai Medical center, Ashkelon

75 11:40 **Trends of Bacterial Keratitis Culture Isolates – a 13-Year Analysis** p. 118

Michael Politis (1), Denise Wajnsztajn (1), Colin Block (2), Boris Rosin (1), Ygal Itkin (1), Abraham Solomon (1)
Departments of Ophthalmology (1) and Clinical Microbiology (2) Hadassah-Hebrew University Medical Center, Jerusalem

76 11:45 **Topical Dipyridamole for Treatment of Pterygium and Associated Dry Eye Symptoms: Analysis of User-Reported Outcomes** p. 119

Moshe Rogosnitzky (1,2), Carol A. Bienstock (2), Yitzchak Issakov (1), Aaron Frenkel (2)
(1) Center for Drug Repurposing, Ariel University, Ariel, (2) MedInsight Research Institute, Baltimore, MD, USA

77 11:50 AC **The Effect of Corneal Thickness on the Penetration of Topical Vancomycin** p. 120

Oriel Spierer, Michael Regenbogen, Moshe Lazar, Yossi Yatziv
Department of Ophthalmology, Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

78 11:55 AC **Lineage Tracing of Stem and Progenitor Cells of the Murine Corneal Epithelium in Hemostasis and after Limbal Chemical and Mechanical Injury** p. 121

Rana Hanna (1), Aya Amitai-Lange (2), Anna Altshuler (2), Beatrice Tiosano (1), Ruby Shalom-Feuerstein (2)
(1) Department of Ophthalmology, Hillel Yaffe Medical Center, Hadera, Israel, Affilated to the Technion, Israel Institute of Technology, (2) Department of Genetics and Developmental Biology, The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa

79 12:00 **Fabrication of a Stable and Efficient Antibacterial Nanocoating of Zn-CuO on Contact Lenses** p. 122

Reut Tuby* (1), Shay Gutfreund* (3), Ilana Perelshtein (1), Gabriel Mircus (4), Miriam Ehrenberg (5), Michael Mimouni (6), Irit Bahar (7), Aharon Gedanken (1,2); *- equal contribution
(1) Department of Chemistry and Kanbar Laboratory for Nanomaterials, Bar-Ilan University Center for Advanced Materials and Nanotechnology, Ramat-Gan, (2) Department of Materials Science & Engineering, National Cheng Kung University, Tainan 70101, Taiwan. (3) Department of ophthalmology, Assaf Harofeh Medical Center, Tzrifin, (4) Clinical Microbiology laboratory, Rabin medical center, Petach Tikva, (5) Pediatric Ophthalmology Unit, Schneider Children's Medical Center, Petach Tikva, (6) Department of ophthalmology, Rambam health care campus, Haifa, (7) Department of ophthalmology, Rabin medical center, Petach Tikva

80 12:05 AC **The Effect of Graft-Recipient Collagen Lamellar Axis Discrepancy on Visual Acuity Following Descemet Stripping Automated Endothelial Keratoplasty** p. 123

Yoav Nahum (1,2), Alfonso Iovieno (3), Eugenio Lipari (4), Luigi Fonatana (3), Massimo Busin (5,6)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (3) Ophthalmology, Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia, Italy, (4) Phronema srl, Taranto, Italy, (5) "Villa Igea" Hospital, Department of Ophthalmology, Forlì, Italy, (6) Istituto internazionale per la Ricerca e Formazione in Oftalmologia (IRFO), Forlì, Italy.

81 12:10 **The Therapeutic Effect of Accelerated Photoactivated Chromophore for Infective Keratitis– Corneal Collagen Cross-linking (PACK-CXL).** p. 124

Yonit Krakauer, Tova Lifshitz, Itay Lavy, Alona Petrov, Boris Knyazer
Ophthalmology Department, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva.

12:15 **Discussion**

Awards and ISVER update 12:15 -12:30

Guest lecture - Prof. Rachel R. Caspi 12:30 – 13:00

Chief, Immunoregulation Section; Deputy Chief, Lab. Immunology, NEI, NIH; Bethesda, MD, USA

Ocular Autoimmunity: a Collusion of Development and Environment

Lunch 13:00- 14:00

Guest lecture - Prof. Rachel R. Caspi 14:00 – 14:30

Chief, Immunoregulation Section; Deputy Chief, Lab. Immunology, NEI, NIH; Bethesda, MD, USA

Commensal Microbiota as a Potential Trigger of Autoimmune Uveitis

Genetics

14:30 – 15:45
Rayman Center

Moderators:

Tamar Ben-Yosef and Eran Pras

82 14:30 AC

CHST6 Gene Mutations and in-vivo Assessment of Two Families with Macular Corneal Dystrophy p. 125

Yair Rubinstein, Chen Weiner, Noa Chetrit, Isaac Avni, Adi Einan-Lifshitz, Nadav Shoshany, David Zadok, Eran Pras

Matlow's Ophthalmogenetic Laboratory, Department of Ophthalmology, Assaf Harofe Medical Center, Zerifin

83 14:40

Albinism in the Israeli Jewish population: Causative Mutations and Phenotypes p. 126

Anat Blumenfeld, Efrat Shemesh, Ada Rosenmann, Claudia Yahalom

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

84 14:45

A Combination of Oculopharyngeal Muscular Dystrophy and Inherited Retinal Dystrophy in Bukharan Jews due to Linked Mutations in *PABPN1* and *NRL*

p. 127

Leah Rizel (1), Sergiu C. Blumen (1,2), Itzhak Braverman (1,2), Hadas Newman (3,4), Rana Hanna (2), Beatrice Tiosano (2), Ido Perlman (1,3), Tamar Ben-Yosef (1)
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85 14:50 AC

A Variant of Enhanced S-Cone Syndrome due to a Recessive *NRL* Mutation

p. 128

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86 14:55

Variable Clinical Presentation of X-Linked Dominant Retinitis Pigmentosa Caused by a Nonsense Mutation in RPGR Gene in Two Unrelated Bedouin Israeli Families

p. 129

Libe Gradstein* (1), Jianjun Chen* (2), Zilin Zhong (2), Xiaodong Jiao (2), Eyal Walter (1), Mira Marcus (1), Tova Lifshitz (1), Yonatan Perez (3), Yshaia Langer (3,4), Ohad S. Birk (3,4), J. Fielding Hejtmancik (2)
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87 15:00

Single Nucleotide Polymorphisms in the rs1495965 Locus of IL23R-IL12RB2 Gene is Highly Associated with Behcet's Uveitis, and Vary between Populations, thus Accounting for Differences in Disease Prevalence

p. 130

Michal Kramer (1,2) Murat Hasanreisoglu (3), Shirel Weiss (2,4), Deniz Kumova (3), Michal Schaap-Fogler (1,2), Sezen Ergun-Guntekin (5), Sengul Ozdek (3), Yair Molad (2,6), Gokhan GurMehmet Ali Guntekin (5), Nitza Goldenberg-Cohen (1,2,5), Yoram Cohen (4,5)

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88 15:05 AC

Mild Phenotype of Aniridia: a Missed Diagnosis of a Genetic Blinding Disease

p. 131

Orly Lior, Anat Blumenfeld, Dror Sharon, Claudia Yahalom

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

89 15:10 AC

Whole Exome Sequencing Reveals a Homozygous Splicing Mutation in CEP78 as the cause of Atypical Usher Syndrome in Eastern Jewish Patients

p. 132

Prasanthi Namburi (1), Rinki Ratnapriya (2), Yael Kinarty (1,5), Csilla Lazar (2), Alexey Obolensky (1), Tamar Ben-Yosef (3), Eran Pras (4), Adi Inbal (5), Menachem Gross (6), Eyal Banin (1), Anand Swaroop (2), Dror Sharon (1)

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90 15:15 **Heterozygous and Homozygous *BEST1* and *RDS* Mutations in Israeli and Palestinian Patients with Best Vitelliform Macular Dystrophy** p. 133

Samer Khateb (1), Hanna Bitner (1), Liliana Mizrahi-Meissonnier (1), Rina Leibu (2), Ygal Rotenstreich (3), Yael Birger (4), Itay Chowers (1), Hadas Mechoulam (1), Eran Pras (5), Eyal Banin (1) Dror Sharon (1)

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91 15:20 AC **RS1 Gene Mutations and Clinical Assessment of Four Patients with X-linked Retinoschisis (XLRS)** p. 134

Yair Rubinstein, Iris Nassie, Chen Weiner, Adi Einan-Lifshitz, Nadav Shoshany, Eran Pras

Matlow's Ophthalmogenetic Laboratory, Department of Ophthalmology, Assaf Harofe Medical Center, Zerifin

15:25 **Discussion**

Glaucoma

14:30 – 15:05

Rayman East

Moderators:

Beatrice Tiosano and Alon Skaat

92 14:30 **Novel Method for Laser Suturelysis after Trabeculectomy** p. 135

Assaf Kratz

Ophthalmology department, Soroka University Medical Center, Faculty of health sciences, Ben-Gurion University of the Negev

93 14:40 **Digoxin Derivatives with Selectivity for the α2β3 Isoform of Na,K-ATPase Potently Reduce Intraocular Pressure** p. 136

Dan Heller (1), Adriana Katz (2), Daniel M. Tal (2), Michael Habeck (2), Efrat Ben Zeev (3), Bilal Rabah (4), Yaniv Bar Kana (1), Arie L. Marcovich (4), Steven J.D.Karlish (2)

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94 14:45 AC

Safety and Efficacy of Sub-Conjunctival 5-Fluorouracil Injections after Trabeculectomy Surgery

p. 137

David Uziel (1), Tzvi Tessler (2), Jaime Levy (2), Tova Lifshitz (2), Assaf Kratz (2)
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95 14:50

Diurnal Variation of Intraocular Pressure in EX-Press Valve Surgery

p. 138

Gerardo López (1), Yuval Cohen (1), Rana Hanna (1), Ashraf Masalha (1), Eran Berkovich (1), Bella Gavrilova (1), Jose castaño (1), Beatrice Tiosano (1,2)
(1) Ophthalmology department, Hillel Yaffe Medical center, Hadera, (2) Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa

96 14:55 AC

Through Wnt Signaling Pathway, NPCE Derived Exosomes Modulate Pan-Cadherin Expression in Trabecular Meshwork Cells

p. 139

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

96a 15:00

Evaluation of EX-Press Valve Blebs in Glaucoma Patients by Anterior Segment Optical Coherence Tomography

p. 140

Eran Berkowitz, Yuval Cohen, Cristobal Moctezuma, Ashraf Masalha, Beatrice.Tiosano
Department of Ophthalmology, Hillel-Yaffe Medical Center, affiliated with the Bruce Rappaport School of Medicine, The Technion, Haifa

Cataract

15:05 – 15:45

Rayman East

Moderators:

Ehud Assia and Igor Kaiserman

97 15:05 **A New Zebrafish Model for Studying Molecular Genetic Mechanisms Underlying Fibrotic Cataract** p. 141

Adi Inbal (1), Jeffrey Gross (2), Kineret Taler (1)
(1) IMRIC, The Hebrew University of Jerusalem – Hadassah Medical School, Jerusalem, (2) University of Texas at Austin, Austin, Texas, USA

98 15:15 AC **Predicting Cataract Surgery Time Based on Preoperative Risk Assessment** p. 142

Asaf Achiron, Fady Hadda, Mohammed Gera, Elisha Bartov, Zvia Burgansky
Edith Wolfson Medical Center Holon

99 15:20 AC **Post Cataract Surgery Administration of oral Acetazolamide** p. 143

Ahmed Zuabi (1), Tova Lifshitz (2), Assaf Kratz (2)
(1) Faculty of health sciences, Ben-Gurion University of the Negev, Beer-Sheva, (2) Ophthalmology department, Soroka University Medical Center, Faculty of health sciences, Ben-Gurion University of the Negev, Beer-Sheva

100 15:25 AC **Wound Temperature Profiles of Coaxial Mini-Incision versus Sleeveless Micro-Incision Phacoemulsification** p. 144

Avner Belkin (1,2), Adi Abulafia (1,2,3), Adi Michaeli (2,3,4), Shay Ofir (1,2), Ehud I. Assia (2,3)
(1) Department of Ophthalmology, Meir Medical Center, Kfar Saba, (2) Sackler School of Medicine, Tel Aviv University, Tel Aviv, (3) Ein Tal Eye Center, Tel Aviv, (4) Department of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv

101 15:30 **Laser Capsulotomy Rates Following Implantation of Hydrophilic versus Hydrophobic Acrylic Intraocular Lenses** p. 145

Eitan Livny (1), Yael Sharon (1), Dov Weinberger (1,2), Irit Bahar (1,2)
(1) Department of Ophthalmology, Rabin Medical Center, Petach Tikva, (2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

102 15:35 AC **A Method for the Selection of Cataract Disintegrating Compounds and their use for Reversal of Crystalline Lens Opacification** p. 146

Michael Mimouni (1), Marina Chemerovski-Glikman (2), Yarden Dagan (2), Esraa Haj (2), Lihi Adler-Abramovich (2), Daniel Segal (2), Ehud Gazit (2), Shiri Zayit-Soudry (1)
(1) Department of Ophthalmology, Rambam Health Care Campus, Technion- Israel Institute of Technology, Haifa,(2) Department of Molecular Microbiology and Biotechnology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv

15:40 **Discussion**

Coffee and Exhibition 15:45 -16:15

AMD 16:15 – 16:45

Moderators:
Itay Chowers and Anat Loewenstein

103 16:15 AC **Pharmacogenetic Analysis of Patients with Neovascular Age-Related Macular Degeneration** p. 147

Michelle Grunin (1), Gala Beykin (1), Elior Rahmani (2), Regev Schweiger (2), Gal Barel (2), Shira Hagbi-Levi (1), Batya Rinsky (1), Eran Halperin (2,3,4), Itay Chowers (1)
(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, (2) Molecular Microbiology and Biotechnology, Tel-Aviv University, (3) The Blavatnik School of Computer Science, Tel-Aviv University, (4) International Computer Science Institute, USA

104 16:25 AC **Functional Aspects of Polarized MacrophagesFrom Patients with Age-Related Macular Degeneration** p. 148

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

105 16:30 **Identification of High-Penetrance Rare Genetic Variations Among Israeli Patients Manifesting Early Severe Age-related Macular Degeneration** p. 149

Nadav Shoshany (1,2), Iris Nasie (2), Chen Weiner (2), Noam Shomron (3), Shira Modai (3) Nimrod Dar (4), Isaac Avni (1), Eran Pras (1,2)
(1) Ophthalmology Department, Assaf Harofe Medical Center, Zeriffin, (2) Matlow's Ophthalmogenetic Laboratory, Assaf Harofe Medical Center, Zeriffin, (3) Genomics Intelligence Laboratory, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, (4) Ophthalmology Department, Meir Medical Center, Kfar Saba

106 16:35 AC **Characterizing the Phenotype of Differentiated Macrophages from Patients with Age Related Macular Degeneration** p. 150

Shira Hagbi-Levi, Michelle Grunin, Tareq Jaouni, Liran Tiosano, Batya Rinsky, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center

16:40 **Discussion**

Retina - function

16:45 – 17:15

Moderators:
Tami Livnat and Adiel Barak

107 16:45 **Focal ERG and Focal VEP For Evaluating Localized Retinal Function** p. 151

Tamar Arens-Arad , Adi Gross, Nairouz Farah, Yossi Mandel
Faculty of Life Sciences, Optometry Track, Bar Ilan University, Ramat-Gan

109 16:55 AC **Chromatic Multifocal Pupillometer for Objective Early Diagnosis of Mild Cognitive Impairment** p. 152

Daniel Ben-Ner (1), Ifat Sher (1), Ramit Ravona-Springer (2), Michal Beeri (3), Ygal Rotenstreich (1)
(1) Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, (2) Psychiatry Department A, Sheba Medical Center, Tel Aviv University, (3) Sagol Neuroscience Center, Sheba Medical Center, Tel Aviv University

110 17:00 **Contrast Sensitivity Revealed by Spontaneous Eye-Blinks** p. 153

Yoram Bonneh (1), Yael Adini (2), Uri Polat (1)
(1) Bar-Ilan University, (2) Inst. for Vision Research, Kiron

111 17:05 **The Role of Angiotensin Converting Enzyme in the Diagnosis of Sarcoidosis Related Uveitis** p. 154

Oren Tomkins-Netzer (1,2), Rachael Niederer (1), Ahmed Kasb (1), Sue Lightman (1)
(1) Moorfields Eye Hospital, London, UK, (2) Bnai Zion Medical Center, Haifa

17:10 **Discussion**

Concluding remarks 17:15 – 17:20

Dror Sharon

Abstracts

תקצירים

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

Alon Skaat (1,2), Mark Ghassibi (2), Jeffrey M. Liebmann (2), Robert Ritch (2), Sung Chul Park (2)

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Purpose: To investigate the prevalence of optic nerve head drusen (ONHD) in normal-appearing eyes using enhanced depth imaging (EDI) optical coherence tomography (OCT) and to associate the presence of ONHD with axial length, age, and gender.

Methods: Serial horizontal and vertical EDI OCT scans (interval between scans, ~30 µm) of the optic nerve head were obtained on both eyes of normal subjects. EDI OCT scans were assessed for ONHD by an experienced observer. Signs of ONHD were defined as hyper-reflective bands perpendicular to the OCT beam with or without a signal-poor core. Isolated very short hyper-reflective bands were categorized as suspected ONHD. Associations of ONHD with axial length, age, and gender were assessed.

Results: Among 130 normal subjects with both eyes scanned, ONHD were detected in at least one eye in 18 subjects (13.8%). Of these 18 subjects, 15 (11.5%) showed short horizontal hyper-reflective bands with no signal-poor core, and 3 (2.3%) showed a signal-poor core surrounded by hyper-reflective bands. Four (3.1%) of 130 subjects showed very short hyper-reflective bands only (ONHD suspects). There were no significant differences in age (44 vs 39 years, p=0.22) or gender proportion (56% vs 51% female; p=0.72) between ONHD and non-ONHD subjects. Axial length was measured in both eyes of 70 out of 130 subjects. Of these 140 eyes, the mean axial length of eyes with ONHD (12 eyes; 23.5±0.8 mm) was significantly shorter than that of eyes without ONHD (128 eyes; 24.7±1.5 mm) (p=0.007). A decrease in axial length by 1 mm increased the odds of ONHD two-fold (OR=2.00 [CI, 1.15-3.49]; p=0.015).

Conclusions: Subclinical ONHD may be more prevalent than previously believed, especially in eyes with shorter axial length.

Automated Identification of Lesion Activity in nvAMD

Dafna Goldenberg (1), Usha Chakravarthy (2,3) ,Graham Young (3), Moshe Havilio (4), Omer Rafaeli (4), Gidi Benyamini (4), Anat Loewenstein (1)

(1) Tel Aviv Medical Center, Tel Aviv, (2) Center for experimental medicine, QUB, Belfast, UK, (3) Belfast HSCT, Belfast, UK, (4) Notal Vision Ltd. Tel Aviv

Purpose: To evaluate the accuracy of the Notal OCT Analyzer (NOA) versus retina specialists (RS) in the automated detection of fluid on OCT

Methods: OCT scans of AMD patients were analyzed by the NOA and by three RS for the presence of intra-retinal or sub-retinal fluid. NOA also ranked B-Scans for likelihood of CNV activity allowing a second grading session by the three RS. Outcome measures: NOA's sensitivity and specificity versus the RS grading and NOA's performance in ranking B-scans for activity.

Results: 142 scan sets met the criteria for the primary analysis. On testing the RS grading versus the NOA, the accuracy was 91% (95% CI ±7%), sensitivity was 92% (±6%) and specificity was 91% (±6%). The graders' accuracy when compared to majority of the other graders (including a 4th reader) was 93%. On average, the three graders could identify fluid in 95% of scans by just reviewing a single B-scan with the highest NOA score and 99.5% of scans with fluid by viewing the top three B-scans.

Conclusions: Concordance between the NOA and the RS determination of lesion activity was extremely high. The level of discrepancy amongst RS was similar to the NOA's mismatches. Automated classification of CNV activity is feasible and has the potential to become a powerful clinical tool.

Interchangeability of Two Corneal Topographers in Post Refractive Surgery Patients

David Markov, Aurelia Elfassi, Sara Shukrun, Einat Shneor

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Purpose: Laser Assisted in situ Keratomileusis (LASIK) and Photo Refractive Keratectomy (PRK) are commonly used for corrective refractive surgery. Both are performed on the patient's anterior cornea and it is vital to regularly monitor its shape after the surgery.

Placido disc based corneal topography is the gold standard of anterior corneal imaging. This research will assess the agreement between the CT1000 (SN, Japan), which is a Placido disc based corneal topographer, and the Sirius (CSO, Italy) which is a corneal tomographer, that combines Placido disc topography with rotating Scheimpflug photography, in post refractive surgery corneas.

Methods: Post refractive surgery subjects (14 subjects, 25.7±2.1 years old) recruited from Hadassah Optometry department, participated in the study. Subjects were measured 3 times with the CT1000 and the Sirius by different technicians who were masked to each other's results. Exams were performed in a random order. SimK1 and SimK2 values (mm) were recorded and the mean and standard deviation were calculated. Correlation test and Bland and Altmann analysis (B&A) was used to assess agreement.

Results: There were no significant differences between measurements of subjects who underwent PRK and those who underwent LASIK ($p=0.61$). A good correlation was found between the devices both for SimK1 and for SimK2 ($r = 0.91$ and $r = 0.93$ respectively). However, the mean difference and 95% limits of agreement (LoAs) for SimK1 and SimK2 were 0.08±0.21, LoAs =0.86mm and -0.18±0.18, LoAs =0.71mm respectively, which is a clinically unacceptable disparity.

Conclusions: The CT1000 and the Sirius cannot be used interchangeably in post refractive surgery patients.

Imaging the Suprachoroidal Space with Enhanced Depth Imaging Swept Source OCT

Joel Hanhart

Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem

Purpose: To compare enhanced depth imaging (EDI) and non-EDI swept source OCT (SS-OCT) in their ability to capture the suprachoroidal space (SCS).

Methods: Twenty volunteers with a minimum age of 18 years without any ocular pathology and refractive error below ±2 diopters underwent SS-OCT foveal scanning, with and without EDI. Masked averaged B-scan lines were analyzed for presence of the SCS. When the SCS was seen, the percentage of the scan on which this structure could be unequivocally observed was measured. Scores obtained from the images taken with or without EDI were then compared.

Results: 37 eyes were analysed, since three eyes of three different patients were eliminated, as the outer border of the choroid was insufficiently delineated with both modalities.

The SCS was not detected at all on 14 pictures (37.8%) obtained by non-EDI SS-OCT and 9 pictures (24.3%) obtained by EDI SS-OCT. When the SCS was detected with both modalities, it was observable on 27.2±24.2% of the scan without EDI and 40.4±30.3 of the scan with EDI ($p < .001$).

Conclusions: EDI SS-OCT enables a more frequent and extensive visualization of the suprachoroidal space than non-EDI SS-OCT. This new approach could be considered as the most accurate modality to currently visualize the SCS in vivo.

Long Term Structural Changes Induced by Macular Argon Laser, Visualized on En-Face OCT

Joel Hanhart, Tamar Levi Vineberg, Yaakov Rozenman
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Purpose: We aim to take advantage of en-face optical coherence tomography (OCT) to assess the long-term structural changes induced by macular argon laser.

Methods: We reviewed the records of adult diabetic patients who had undergone macular laser treatment at least 4 years prior to swept source OCT volumetric imaging, recording demographic and clinical relevant data.
En-face images were flattened at the RPE (retinal pigment epithelium) plane. We determined for each eye the retinal surface covered by laser marks and determined the maximal diameter of the largest identified lesion at this plane.
We moved the analysed plane upwards defining the level of neurosensory retinal damage and measuring its distance from the RPE.We measured total retinal thickness at the location of the most superficial lesion and expressed the level of neurosensory retinal damage as a percentage of retinal thickness. We moved the analysed plane towards the sclera until we could not see any specific lesion. We defined the distance between the RPE and the deeper plane at which laser marks were detected as the level of choroidal changes.
Results: 21 eyes of sixteen patients were analyzed. The mean age (±SD) was 61.7±15.5 years (range: 36-84). Patients had undergone macular laser 6.5±2.8 years (range 4-13) prior to entering our study. On en-face view, depending on the selected plane, laser marks appeared as hypo- or hypreflective structures.
In 16 eyes the most superficial laser marks were detected at the inner plexiform/inner nuclear layers. The level of neurosensory retinal damage was 159±48 microns over the RPE (62.6±18.3% of the retinal thickness). The deepest level at which laser marks were retrieved was 125±110 microns below the RPE.
A positive moderate correlation was observed between time since laser and the surface of retina covered by laser marks at the RPE (Pearson's correlation coefficient=0.36; p=0.1), the deeper level of detected laser marks (Pearson's correlation coefficient=0.35; p=0.1) and the level of neurosensory retinal damage as a fraction of the retinal thickness (Pearson's correlation coefficient=0.25; p=0.2).

Conclusions: With time, argon laser marks expand horizontally and vertically. The damage induced by argon laser in the neurosensory retina often reaches inner layers.

Validation and Repeatability of the Paul Harris Stereotest

Liat Gantz, Ariela Gordon Shag, Wedad Sheety, Almaza Haddad, Doreen Hallon, Tzadok Parnas, David Markov, Einat Shneor
Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem

Purpose: The Paul Harris (PH) Randot test is a vectographic booklet for measuring stereopsis that, similarly to the TNO stereotest but unlike the Titmus stereofly and traditional Randot (tRandot) tests, is devoid of monocular cues. This prospective observational study investigated the intra-test repeatability and inter-test agreement for the PH Randot test compared with the other clinical stereotests.

Methods: Seventy subjects (mean age: 24±7, range: 18-53, 54 female) with normal binocular vision were measured three times with each stereotest, in random order. Thirty subjects were re-measured after a week. Bland-Altman (B-A) analysis and a repeated measures ANOVA with one factor, determined the interchangeability between the PH Randot and other stereotests by determining the mean difference between the measurements of two stereotests ($m_{diff\text{-}tests}$) and their confidence intervals. Intra-test repeatability was assessed by comparing the mean difference between the 1st and 2nd measurements ($m_{diff\text{-}measurements}$) and their standard deviation ($stdev_{measurements}$).

Results: Mean stereothreshold measurements differed significantly between the TNO and PHRandot and the other booklets (mean stereothresholds-TNO: 51.3±14.5", Stereofly: 36.0±15.5", tRandot: 33.6±16.8",PHRandot: 22.7±5.7"; $F_{(df=3,69)}$=77.8, p<0.0001, Tukey HSD<0.01). The Titmus and tRandot were not significantly different from one another. B-A analysis found that the PHRandot yielded systematically lower thresholds in subjects with stereopsis lower than 40", which may be due to a difference in step sizes between the booklets. Nevertheless, the $m_{diff\text{-}tests}$ between the PHRandot and the tRandot (11") and Titmus (13") was lower than the minimal step size (20") and over 94% of the observations were within ±20" of each other. This was not the case for the TNO ($m_{PHRandot\text{-}TNO}$=28"). The comparison between the 1st and 2nd measurement sessions yielded the smallest m_{diff} and $stdev_{measurements}$ for the PH Randot test (PHRandot= 2.72" ± 11.4", tRandot = 10.61± 40.8, Titmus= 18.28 ± 33.3, TNO=-14.39 ± 68.1), indicating better repeatability.

Conclusions: Normal subjects with above normal stereopsis often achieve lower thresholds using the PHRandot stereotest than with other stereotests. Nevertheless, the PHRandot test can be used interchangeably with the tRandot and Titmus tests but not with the TNO test. The PHRandot yielded the best inter-test repeatability, indicating more precision.

Advanced Multiphoton Methods for *in vitro* and *in vivo* Functional Imaging of Mouse Retinal Neurons

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Purpose: Studying the responses of retinal ganglion cell (RGC) populations is of major importance to the fields of neuroscience and vision research. Multiphoton excitation of optogenetic probes has recently become the leading imaging approach for recording fluorescence signals in neural populations and has specific advantages for imaging retinal activity during visual stimulation, because it leads to reduced direct excitation of the photoreceptors. However, multiphoton imaging of retinal activity is not straightforward: point-by-point scanning leads to repeated neural excitation, while optical access through the rodent eye for *in vivo* imaging has proven highly challenging. Here, we present two enabling optical designs that facilitate multi-photon imaging of responses to visual stimuli in mouse retinas expressing GCaMP6 calcium probes.

Methods: For rapid functional imaging of retinal activity, we scan an isolated retina expressing the genetically encoded indicator (GECI), GCaMP6, with a temporally focused line rather than a point, increasing the scan speed and reducing the impact of repeated excitation, while maintaining high optical sectioning. Furthermore, in order to acquire functional recordings from the retina *in vivo* we integrate offset lenses before the objective lens of a custom two-photon microscope. By utilizing an electronically tunable lens (ETL) controlled by the computer, it is possible to depth-scan the retina without translating any of the microscope parts.

Results: First, we present an imaging solution based on Scanning Line Temporal Focusing (SLITE) for rapidly imaging neuronal activity *in vitro* and demonstrate our ability to capture the neural behavior of RGCs population in reaction to different visual patterns. Second, we present the first demonstration of *in vivo* of two-photon imaging of RGC activity in the live mouse retina. Following a design based on optical modeling, we were able to obtain images of retinal structures with sub-cellular resolution and without the need for incorporating adaptive optics. The properties of two-photon excitation, together with our optical design, enable to obtain high-resolution images at different depths.

Conclusions: The new optical designs presented here overcome a number of outstanding obstacles, allowing the study of rapid calcium signals both in vitro and in vivo, thereby bringing us a step closer toward distributed monitoring of retinal neural activity during vision.

Adipose Tissue Derived Mesenchymal Stem Cells Migrate Towards RPE, Rescue Apoptotic RPE under Oxidative Stress, and have the Potential to Differentiate into RPE

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(1) Tel Aviv Medical Center, (2) Sackler School of Medicine, Tel Aviv University

Purpose: Oxidative stress plays a cardinal role in the pathophysiology of AMD, and leads to apoptosis of RPE. Adipose tissue derived mesenchymal stem cells (ASCs) may serve as a therapeutic tool to regenerate RPE. Here we evaluated the activity of ASCs when exposed to RPE under oxidative stress in vitro; we assessed their migratory capacity towards injured RPE, and their ability to prevent apoptosis of RPE. We also studied the differentiation potential of ASCs into RPE.

Methods: Human ASCs were harvested from subcutaneous fat of patients undergoing abdominoplasty. Primary cultures of human RPE cells were subjected to oxidative stress by exposure to 1.5mM hydrogen peroxide (H2O2). Conditioned medium of “stressed” RPE was collected. The migratory capacity of ASCs towards conditioned medium of “stressed” RPE or towards conditioned medium of normoxic RPE was determined by a scratch assay. In order to study the preventive effect of ASCs on apoptosis of RPE, “stressed” RPE were treated with ASCs’ conditioned medium or with standard, non-conditioned medium. H2O2 induced RPE apoptosis was measured by Annexin V/propidium iodide staining and flow cytomtery analysis. Finally, the differentiation potential of ASCs into RPE was evaluated by culturing ASCs with 10nM nicotine amide.

Results: ASCs exhibited enhanced migration towards RPE that were subjected to oxidative stress (193%±0.4 increase cells per area, $p<0.05$). Treatment of “stressed” RPE with ASCs’ conditioned medium prevented H2O2 induced apoptosis (50±0.7% decrease cells number, $p <0.05$). After two weeks in differentiation medium, ASCs underwent marked morphological changes forming spheroid bodies in culture and upregulating early eye field markers (PAX6 2.2±0.1, RX 2.1±0.8, BF1 4.7±0.7, NestinA 2.3 ±0.38 folds).

Conclusions: ASCs migrate towards RPE under oxidative stress and reduce H2O2 induced apoptosis of RPE. Moreover, ASCs demonstrate a differentiation potential into RPE evident by a morphological change and upregulation of eye field markers. These data may imply to a therapeutic potential of ASCs in regenerating RPE.

Microarray of Inflammation, Angiogenesis and Coagulation Proteins in a Variety of Retinal Diseases

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Purpose: To evaluate the activity of the inflammation, angiogenesis and coagulation systems in the vitreous of patients with different vitreo-retinal pathologies with microarray.

Methods: Vitreous samples were collected from 28 consenting patients during pars plana vitrectomy surgery. The vitreo-retinal pathologies were divided into three groups:
1) Control (N=10) which included patients with macular holes (MH) or epiretinal membranes (ERM);
2) Rhegmatogenous retinal detachments (RRD) (N = 9);
3) Vitreous hemorrhages (VH) due to proliferative diabetic retinopathy (N=9).
P-selectin, IL-6, G-CSF, D-Dimer, Thrombomodulin, Tissue Factor, TFPI, VEGF and IL-8 were selected to serve as key biomarkers for inflammation, coagulation and angiogenesis. The proteins levels were measured using a Quantibody Array.

Results: Significant higher levels of P-Selectin, IL-6 and D-Dimer was found in the RRD group as compared to control. In the VH group the levels of P-Selectin, D-Dimer, IL-8 and VEGF were significantly higher in comparison to control. For all the remaining proteins no significant difference between the groups was found.
Using post-hoc ANOVA analysis we found that RRD patients had higher levels of inflammation proteins whereas VH patients had higher levels of angiogenic proteins. As for the coagulation proteins, both RRD and VH groups had no significant difference compared to control.

Conclusions: In our study we have found that patients with RRD manifest higher activity of the inflammatory system and patients with VH exhibit higher activity of the angiogenesis system.

Retinal Toxicity of Intravitreal Injection of Ziv-Aflibercept in Albino Rabbits

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Purpose: Ziv-aflibercept (Zaltrap, Sanofi-aventis U.S. LLC, Bridgewater, NJ), a drug indicated for patients with colon cancer, acts as a soluble receptor that binds to human Vascular Endothelial Growth Factors 1 and 2, and to human Placental Growth Factor. Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) the Intravitreal equivalent of ziv-aflibercept, is an FDA approved drug for the treatment of neovascularization in age-related macular degeneration, of macular edema following retinal vein occlusion and of diabetic macular edema. The aim of this study is to evaluate retinal toxicity of ziv-aflibercept.

Methods: A total of 18 albino rabbits were injected intravitreally with 0.1 ml of ziv-aflibercept solution into the experimental eye and 0.1 ml saline into the control eye. Twelve were used for electroretinogram (ERG) 4-weeks follow-up (one of these died) and 6 were used for histological and glial fibrillary acidic protein (GFAP) immunocytochemistry during follow-up. ERG responses were recorded 3 days, 1-, 2-, and 4-weeks after injection. The visual evoked potential (VEP) was recorded after 4 weeks. Immunohistochemical and histological studies were performed throughout the follow-up period and after the termination of the follow-up period.

Results: the ERG responses of the experimental eyes did not show any significant difference from the responses of the control eyes, either in amplitude or in pattern, throughout the follow-up period. The flash VEP responses of the experimental eyes were of normal pattern and amplitude and were similar to those recorded by stimulation of the control eyes. Histologic studies of both experimental and control eyes did not show any signs of structural damage. However, GFAP immunocytochemistry showed activation of retinal Müller cells, indicating mild retinal gliosis.

Conclusions: Ziv-aflibercept was found to be non-toxic to the retina of rabbits based on electrophysiological testing and histologic examination. However, GFAP immunocytochemistry suggests mild retinal stress caused by the drug. Therefore, application of intravitreal ziv-aflibercept in patients needs caution and additional considerations.

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

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Purpose: Specific mutations in Bestrophin1 (Best1) gene result in different retinal phenotypes, including juvenile-onset Best Vitelliform Macular Dystrophy, adult-onset Vitelliform Macular Dystrophy, Autosomal Dominant Vitreoretinochoroidopathy and Autosomal Recessive Bestrophinopathy. The expression of Best1 is confined to the retinal pigment epithelium (RPE), responsible for phagocytosis of photoreceptors outer segments (POS). We have recently found that mutated Best1, expressed in ARPE-19 cells, alter POS phagocytosis compared to the wild type. We hypothesize that Best1 modulates POS phagocytosis via protein-protein interactions with regulatory proteins.

Methods: Ras recruitment system is based on the ability of Ras mutant to be localized to the plasma membrane through the interaction between two proteins. Best1 was fused to Ras whereas human RPE cDNA library was fused to v-Src membrane localization signal. Ras membrane localization via protein-protein interaction results in the complementation of a yeast temperature sensitive mutant strain in the Ras guanyl nucleotide exchange factor, Cdc25-2 (*Aronheim, 2001a+b*). The screening was performed as follows: Best1 was prepared on Met-425 plasmid whereas the library was constructed on galactose inducible plasmid. Met-425 promoter was repressed in the presence of methionine, thus Best1 expression was induced when cells were grown on a medium lacking methionine. Library expression was induced in medium containing galactose and repressed in the presence of glucose. In order to induce the expression of Best1 and library, cells were grown on galactose medium lacking methionine. Candidate clones were further analyzed by DNA extraction and sequencing, and screened with 4 different Best1 mutations.

Results: Mapping protein-protein interactions of wild type Best1 and RPE library resulted in 13 candidates, from which two DNA sequences analyzed by BLAST were consistent with 2 different proteins that may potentially interact with Best1. These 2 proteins failed to interact with Arg47His and Arg200X mutated Best1.

Conclusions: Our findings suggest that Best1 may interact with 2 different proteins, previously reported to regulate cell signaling, and that those interactions may be altered by mutations, thus contributing to disease manifestation.

TAK1 is a Pivotal Player in the Autophagy Process in Human RPE Cells

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Purpose: Autophagy is an evolutionarily conserved intra-cellular housekeeping mechanism that removes damaged organelles and protein aggregates that are unnecessary or dysfunctional to the cells. This process is activated in response to environmental stress such as hypoxia and oxidative stress, and is crucial for maintaining cellular homeostasis. The aim of this study was to evaluate the role of Transforming Growth Factor β-Activated Kinase 1 (TAK1) in the autophagy process in retinal pigment epithelial (RPE) cells.

Methods: The effect of TAK1 activity on autophagy was examined in two different RPE cell lines, ARPE-19 and D407. Cells were treated with Rapamycin or H_2O_2 to induce autophagy, and activation of TAK1 was determined by western blot (WB) analysis and immunostaining. Next, pharmacological or genetic inhibitions of TAK1 were applied in RPE cells prior to autophagy induction, and the level of the autophagy marker LC3A/B-II was determined by WB analysis and immunostaining. Finally, the proliferation rate of RPE cells treated with Rapamycin and TAK1 inhibitor was determined by XTT analysis.

Results: Treatment of RPE cells with the autophagy inducers Rapamycin or H_2O_2 resulted in phosphorylation and activation of TAK1. Pharmacological or genetic inhibition of TAK1 prior to Rapamycin or H_2O_2 treatment caused a significant decrease in the autophagy process, manifested by a reduced expression of the autophagy marker LC3A/B-II. Finally, inhibition of TAK1 activity together with Rapamycin treatment significantly reduced the proliferation rate of RPE cells compared to Rapamycin alone.

Conclusions: Our results suggest that TAK1 is involved in the regulation of autophagy in RPE cells, and aberrant activity of this kinase impairs autophagy and cell viability. Since autophagy is a cellular mechanism to cope with damaged proteins and organelles accumulating under stress conditions, controlling TAK1 activity may delay retinal pathologies, and may be a target for drug development.

Generation of Retinal Pigment Epithelial Cells from Human Induced Pluripotent Stem Cells for the Study of Inherited Macular Degeneration (Best Disease)

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Purpose: Best disease is an autosomal dominant macular degeneration disease caused by mutations in Vitelliform Macular Dystrophy 2 (VMD2) gene, causing disruptions in the Bestrophin protein. Bestrophin is expressed solely in the retinal pigment epithelium (RPE), which is the cell layer in the retina responsible for phagocytosis of photoreceptor outer segments. Our goal was to derive RPE cells from pluripotent cells (iPSC) of patient suffering from Best macular dystrophy in order to study the role of mutated bestrophin in POS phagocytosis by the RPE cells.

Methods: iPSCs were first established by Yamanaka et al (2007) by virally transfecting somatic cells with four transcription factors: c-myc, Klf4, Sox2, and Oct3/4. Differentiation of iPSCs to RPE cells was done by medium manipulation. Determination of the electrical properties of the differentiated RPE cell cultures was possible by cultivation of iRPE cells on Millicell™ plates. This system allowed the creation of a confluent polarized monolayers and measurement of the trans-epithelial potential (TEP) and resistance (TER). Phagocytosis assays were performed by exposing the confluent iRPE monolayers to bovine FITC-labeled POS and examining them under microscope and plate reader.

Results: iPSCs were created and characterized. The VMD2 N296S mutation was present throughout the process, from fibroblasts to induced RPE. iPSCs were successfully differentiated into RPE-like cells. Best Disease BDiRPE showed a significant reduction in TEP and TER compared to healthy cells (HiRPE). A significant increase in phagocytosis was observed in the BDiRPE cells compared to HiRPE.

Conclusions: Our findings suggest that the reduced TEP and TER in BDiRPE is probably connected to Bestrophin's role as a Ca^{+2} dependant Cl^{-} channel (CaCC). This is also a likely cause for the diminished EOG Light Peak in Best disease. Increased phagocytosis by BDiRPE will contribute to the progression of Best disease, due to the RPE inability to fully recycle the POS toxic content.

Retinal Pigment Epithelium (RPE) Cells Facing Cone Photoreceptors Display Distinct Transciptome with Implications for the Pathogenesis of Age-Related Macular Degeneration (AMD)

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Purpose: RPE Cells interact with photoreceptors in a variety of ways acting together as a functional unit. As the retinas of most animal models used in retinal research are dominated by rods, little is known about RPE cells facing cones - the dominant type of photoreceptors at the human macula. This study tested whether the transciptome of RPE cells facing cones differ from that of RPE cells facing rods in a manner that may explain macular susceptibility and pathogenesis of AMD

Methods: The retina of NRL knock-out (NRL-ko) mouse is composed of cone-like photoreceptors, while the retina of wild type (WT) mouse contains mainly rod photoreceptors. RPE cells were harvested from eyes of both WT and NRL-ko mice (6 weeks old). RNA samples were hybridized to Illumina MouseWG-6 v2.0 whole-genome array. After applying filters, including a fold change of 1.7, and dynamic statistical stringency criteria iteratively modified to obtain a manageable list size, a list of 108 genes was generated. From this list, the expression of 25 genes of special interest was validated using Nanostring's nCounter technology.

Results: Several genes that were up regulated in RPE facing cones were previously reported to be associated with macular degenerations when mutated. Genes coding for proteins serving along the phagocytosis process, from binding down to degradation, were up regulated, suggesting a unique phagocytosis process for shed cone outer segment compared to that of rods. Several genes coding for proteins serving in the complement system were altered in a manner consistent with shift in balance toward the classical pathway. Several other genes were altered, including genes involved in cellular adhesions, protection from oxidation, visual transduction and retinol metabolism.

Conclusions: We show that the transciptome of RPE cells can be modulated by the photoreceptors located adjacent to them. Some of the genes have relevance to the physiology of RPE-photoreceptors interactions and others may be of relevance to AMD pathogenesis, including genes coding for proteins of the complement system. We suggest that gene expression of RPE cells facing cones can explain, at least partially, macular susceptibility to age related lesions.

Treatment of Corneal Potential Protective Role of the CB2 Cannabinoid Receptor System in the Crosstalk between Autophagy and Cellular Senescence of RPE cells

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Purpose: Accumulation in the retinal pigment epithelial (RPE) cells of A2E, a pyridinium bis-retinoid, has the potential to cause RPE cell death and may contribute to the RPE cell atrophy observed in AMD. The cannabinoid receptor system is present in human RPE cells and is intimately involved in the oxidative damage process, including that associated with AMD. It has been shown that levels of endocannabinoids are significantly increased in retinal tissue from AMD donors. This study aimed to investigate the crosstalk between autophagy and cellular senescence of RPE cells, on the in vitro AMD-A2E model in the presence and absence of cannabinoid (HU-308, a specific agonist of CB2).

Methods: By using A2E-loaded RPE cells we can mimic the oxidative stress taking place in AMD. The presence of autophagy and activation of the signalling pathway were assessed in the presence and absence of HU-308, a specific CB2 receptor agonist, by Western-blot analysis, flow-cytometry, ELISA and confocal microscope.

Results: Following oxidative stress (100μM H2O2) A2E significantly reduced LC3-I and LC3-II, Bcl-2 ($p<0.05$) and p65 (*$p<0.002$)* and MAPKs activity, compared to cells treated with H2O2 alone. In contrast HU-308 significantly increased LC3-I and LC3-II, p65 and MAPKs activity indicating proper activation of the autophagy process. Higher positive SA-B-Gal staining was found in A2E treated cells vs. control. This effect was significantly increased when H_2O_2 was added, while HU-308 successfully blocked the increase in SA-β-Gal staining halting the process of cellular senescence in these RPE cells.

Conclusions: This research demonstrates that A2E alone might induce cellular senescence of RPE cells and have negative affect on these cells. Moreover, these results demonstrate that the CB2 cannabinoid receptor system may attenuate AMD generated by the accumulation of A2E. This study demonstrates that HU-308 as a candidate therapeutic compounds that may contribute to delaying or arresting A2E-related toxicity to the RPE cells.

ERG Oscillatory Potentials Frequency Domain Changes Allow Accurate Recognition of Diabetic Retinopathy Patients

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

Methods: We examined the frequency domain properties of OPs of normal versus DR patients using wavelet analysis. Retrospective analysis of 15 normal and 10 DR patients was performed, and further data collection is ongoing. We assessed the frequency domain activity of the OPs at various frequency bands using wavelet analysis employing real Morlet wavelet functions. Wavelet analysis was chosen because of the intermittent nature of the OPs, requiring high resolution in both the time and frequency domains for proper characterization. The Frequency Separation Ratio (FSR) was defined as the mean normalized power of frequency above 250Hz divided by that between 100 and 250 Hz. The cut-off value was set to 0.2 and the average FSR values were calculated for both groups. The results were compared using the student's t-test. All analyses were performed using Matlab 2015b (The MathWorks Inc., Natick, MA).

Results: The average values for the oscillatory activity normalized power above 250 Hz was 0.07 (SEM 0.03, n=15) in the normal vs 0.64 (SEM 0.24, n=10) in the DR group, with the difference proving to be significant ($p < 0.01$). All normal subjects had a FSR of < 0.2, and all diabetic subjects had an FSR of > 0.2.

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

Phase I Gene Therapy Trial in Israeli Patients with Leber Congenital Amaurosis Caused by a Founder *RPE65* Mutation: Long-Term Follow-up

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Purpose: Gene therapy of human patients with Leber congenital amaurosis (LCA) due to mutations in the *RPE65* gene became a reality following demonstration of safety and efficacy in *RPE65*-mutant dog and mouse models. Our phase I clinical gene therapy trial in Israeli patients, launched in February 2010, was the fourth of its kind worldwide (NCT00821340). The purpose of this report is to describe the results of long-term follow-up in three Israeli patients treated with gene augmentation therapy.

Methods: Gene therapy was performed in three LCA patients (ages 21-29 years) who harbor a homozygous splicing mutation (c.95-2A>T; IVS2-2A>T) in the *RPE65* gene. Subretinal injection of an AAV2-h*RPE65* viral vector carrying the normal human *RPE65* gene was carried out after vitrectomy in one or two sites, avoiding the foveal area. Visual function and structure were evaluated repeatedly as per protocol using clinical eye exams, computerized light- and dark-adapted perimetry, Goldmann perimetry and non-invasive color, infrared, OCT and autofluorescence imaging.

Results: Five years of follow-up data are available for the first treated patient, 2.5 years for the second, and 4 years for the third. The second patient was lost for follow-up 2.5 years following treatment. No toxicity or complications were observed in any of the patients. Post-operative data indicates stable visual acuity and increased sensitivity to light in the treated regions in all patients, to varying degrees. In the first patient up to 100-fold increases persisted through the five year exam. The third patient also reports and objectively shows significant functional improvement in the treated area. The treatment effect in the second patient was slow to occur and is less pronounced. Long-term follow-up showed attenuation of sensitivity to light in non-treated regions. In patients 1 and 3, at the 4 and 5 year timepoints, partial loss of the previously improved sensitivity in some of the treated areas was also observed. OCT revealed continued loss of photoreceptors in all retinal regions.

Conclusions: Long-term (> 4years) follow-up in two Israeli *RPE65*-LCA patients treated with gene augmentation therapy demonstrated long-lasting improvement in sensitivity of photoreceptors. However, at the latest timepoints, the data suggests that gene augmentation failed to fully arrest progression of retinal degeneration in these patients.

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

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Purpose: Herein, we studied photoreceptor precursor generation from human embryonic stem cells (hESC) in two-dimensional (2D) (*Gregory-Evans K., 2013*) or a three-dimensional (3D) (*Yoshiki Sasai, 2012*) cell culture models. In addition, we studied the retention of these human photoreceptor precursors in the subretinal space of rats by fluorescence imaging of the retina.

Methods: hESC (H9, US National Stem Cell Bank) differentiation into photoreceptor precursors was investigated in two cell culture models: a 2D model where photoreceptor differentiation was induced in monolayer cultures over 17 days using media including Dkk1, Noggin and IGF1, or a 3D model, where differentiation was induced in suspension cultures over 21 days with media containing endo-IWR 1, SAG, CHIR 99021. Differentiation was characterized by mRNA expression (CRX,VSX2,PAX6), immunostaining (CRX, PAX6) and FACS analysis (CRX). The differentiated cells were labeled by infection with GFP-expressing adenovirus and injected into the subretinal space of Long-Evans rats (100,000 cells/8 µl). The retention of the cells was studied over a month by repeated fluorescence imaging of the retina using a Micron-IV Phoenix rodent imaging system.

Results: Many hESC differentiated into photoreceptor precursors in both models as assayed by immunostaining or expression of CRX transcripts. Higher efficiency was found for the 3D model as compared to the 2D, with up to 80 percent of cells viewed in the microscope stained for CRX, confirmed by FACS analysis. Transplanted cells spread evenly in the subretinal space without producing cell clumps. Retention of cells was low, however, with less than 10% of the transplanted cells being be detected by fluorescence imaging at 1 month post-transplantation.

Conclusions: Both 2D and 3D protocols were efficient in photoreceptor precursor generation with some advantage of the 3D over the 2D method. Retention of injected cells differentiated from hESC in the subretinal space of rats was poor. Further studies should be conducted in order to improve the transplantation protocol.

Transplantation of Human Adult Oral Mucosa Stem Cells Ameliorates Retinal Degeneration in a Rat Model of Retinal Dystrophy

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Purpose: To examine the effect of transplantation of human oral mucosa stem cells on retinal function and structure in Royal College Surgeon (RCS) rat model of retinal dystrophy.

Methods: Epithelial oral mucosa stem cells from 4 healthy human donors were transplanted into the extra vascular spaces of the choroid (EVSC) of one eye of RCS rats at age of 4 weeks. Retinal function was tested by electroretinogram (ERG) before and following transplantation for 16 weeks.

Results: Transplantation of oral mucosa stem cells derived from 3 donors (ages 20, 29 and 61 years) significantly increased retinal function of RCS rats. Thus, four weeks following cell transplantation, the mean maximal scotopic ERG b-wave amplitude recorded in transplanted eyes was 54.2± 6.7 microvolts. By contrast, the mean maximal scotopic ERG b-wave amplitude recorded in control eyes was 19.8± 2.7 microvolts ($p<0.001$). Retinal function was significantly higher in transplanted compared with control eyes up to 16 weeks following transplantation ($p<0.018$). Transplantation of stem cells from a forth donor (age 59 years) that demonstrated an in vitro slower proliferation rate than the other donors, did not result in increased ERG response in transplanted eyes. No immunosuppressants were used and no adverse effects on general health were detected in any of the transplanted animals.

Conclusions: Transplantation of human oral mucosa stem cells in the EVSC compartment preserved retinal function in RCS rats for 16 weeks. Our findings suggest that oral mucosa stem cells may possibly be an effective and safe treatment for retinal dystrophies. In vitro and in vivo functional screening of stem cell derived from different donors is recommended prior to transplantation.

Measurement and Improvement of Visual Acuity and Reading Capabilities in Simulated Prosthetic Vision with Active Sensing

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Purpose: Retinal prosthesis is a promising technology for vision restoration in patients blinded by various outer retinal degeneration. Various image processing and similar methods are suggested in order to improve prosthetic vision capabilities. In this research we study the effect of active sensing, in the form of scanning and zoom, on visual performance in a model of prosthetic vision simulation.

Methods: In order to test the effect of active sensing in prosthetic vision in subjects with normal vision, we used a simulated prosthetic vision based on presentation of phosphenized (2D Gaussian) visual objects, E chart for measurement of visual acuity and words on a computer screen. Visual acuity was tested by a staircase method with and without scanning while the E-letter sizes ranged from 0.8 to 1.8 logMAR. In order to simulate various electrode densities, phosphene density ranged from 0.5 to 3 cpd. We examined the effect of scanning on visual acuity. Reading capabilities were evaluated by measuring words recognition rate and reading speed of random words presented in various phosphene densities (0.75 to 2 CPD), 10 words per each phosphene density. The effect of active and passive scanning, font size, contrast (ranging between 25 to 100 percent) and active zoom on reading capabilities were evaluated in each individual session.

Results: E-letter acuity increased linearly with simulated phosphene density. Reading recognition rate increased sigmoidally with simulated phosphene density and reached a plateau at CPD 1.75, corresponding to 5.25 cycles per letter. Reduced contrast and small letter size were associated with decreased reading performance. Active zooming of text size was associated with significant increase in reading performance. Active scanning had a suggestive improvement on reading speed in low phosphene density (0.75-1 CPD).

Conclusions: In simulated prosthetic vision, good reading performance is achieved at a phosphene density corresponding to 5.25 cycles per letter. The use of active sensing in the form of active zoom improved visual acuity and the reading capabilities. Further studies are needed in order to evaluate the effect of active scanning modalities on reading performance in prosthetic vision.

Prophylactic Laser Retinopexy in Patients Undergoing Macular Hole and Epiretinal Membrane Surgeries

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Purpose: To investigate the effect of prophylactic circumferential laser retinopexy for the prevention of retinal detachment in patients undergoing pars plana vitrectomy for the treatment of macular hole (MH) and epiretinal membrane (ERM).

Methods: Historic cohort design including 200 consecutive patients operated in the years 2006 – 2010 for MH or ERM at Tel Aviv Sourasky Medical Center. Exclusion criteria were previous retinal detachment, lack of follow-up or lack of data regarding the use of laser retinopexy. The baseline characteristics and risk of retinal detachment were compared between patients who underwent circumferential laser retinopexy during the main surgery and those who did not.

Results: Initial results include 87 eyes of 84 patients (target population is 200 eyes) divided into 2 groups: 51 eyes that had prophylactic laser retinopexy and a control groups of 30 eyes that did not have the retinopexy. 6 eyes were excluded. Baseline characteristics were similar for the two groups. The incidence of retinal detachment was 5.9% and 6.7% for the laser and control groups, respectively. Based on Kaplan-Meier survival analysis, circumferential laser retinopexy was not associated with a significant decrease in the risk for retinal detachment (log-rank p=0.18).

Conclusions: Initial results show that performing prophylactic circumferential laser retinopexy in patients undergoing MH and ERM surgeries has no significant benefit. However, completion of the current study (due February 2016) is required for better assessment of the investigated procedure.

Long-Term Treatment with 9-cis-beta-carotene Rich Alga *Dunaliella Bardawil* Inhibits Photoreceptor Degeneration in a Mouse Model of Retinoid Cycle Defect

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Purpose: To examine the therapeutic effect of oral treatment with 9-cis β-carotene rich alga *Dunaliella bardawil* on retinal function and structure in Rpe65rd12 mice, a model of genetic defect in retinoid cycle.

Methods: Thirteen RPE65rd12 mice at age of 28 days were fed with Teklad Global 18% Protein Rodent Diet (control diet), vitamin A deficient diet (VAD) or VAD diet supplemented with powder of 9-cis β-carotene rich *Dunaliella bardawil* alga (DUNA, 8% w/w) for 14 months. Retinal function was recorded once a month in both eyes simultaneously by electroretinograph (ERG). Histological analysis and immunofluorescence staining with anti- M opsin antibody were used to determine retinal structure.

Results: At 14 months, mice fed with DUNA presented significantly higher maximal a-wave compared with mice fed with VAD or control diet (30μV [SE=5] vs. 5 μV [SE=3] p=0.006 and vs. 3 μV [SE=2] p=0.007, respectively) and significantly higher maximal b-wave compared with mice fed control diet (82μV [SE=8] vs. 30 μV [SE=10] p=0.002). These results are associated with histological analysis revealing increased number of M-opsins in retina of mice treated with DUNA.

Conclusions: Long term oral treatment with *Dunaliella bardawil* powder rich in 9-cis β-carotene preserves retinal function and rescues M-cones from degeneration in Rpe65rd12 mice. Our findings suggest that 9-cis β-carotene may possibly be an effective treatment for retinal dystrophies involving the retinoid cycle.

A Minimally Invasive Adjustable-Depth Blunt Injector for Delivery of Pharmaceuticals into the Posterior Pole

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Purpose: To investigate the feasibility and safety of a novel minimally-invasive adjustable-depth blunt injector for pharmaceuticals delivery into the posterior segment.

Methods: Indocyanine Green (ICG) and iron oxide nanoparticles (IONPs) were injected using the new injector into the extravascular spaces of the choroid (EVSC) compartment of rabbits and cadaver pig eyes. Spectral Domain Optical Coherence Tomography (SD-OCT) imaging and histology analysis were performed for assessment of injection safety and efficacy.

Results: ICG and IONPs were detected across the EVSC in rabbit eyes, covering 70.5±10 percent of the posterior eye surface. Injected IONPs were retained in the EVSC for at least two weeks following injection. No retinal detachment, choroidal hemorrhage or inflammation were detected in any of the injected eyes. In cadaver pig eyes, ICG was detected across the EVSC.

Conclusions: This novel minimally invasive delivery system may be used to safely deliver large volumes of pharmaceuticals into a new treatment reservoir compartment -the EVSC which can serve as a depot, in close proximity to the retina, covering most of the surface of the back of the eye without insertion of surgical instruments under the central retina. This system is predicted to enhance the therapeutic effect of treatments for posterior eye disorders.

Is there a Neovascularization in Diabetic Mouse Model?

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Purpose: Muller cells play a critical role in the pathogenesis of diabetic retinopathy (DR). These cells react to high glucose levels in the blood by unregulated over-expression of VEGF that leads to pathological neovascularization (NV). Yet, NV was not well detected in mouse models of DR. In this study we examined the expression levels of VEGF in the retinae of type-1 and type-2 diabetic mice (NOD and db/db mice, respectively). We further used novel histological methods to demonstrate normal and pathological retinal vessels, using spherical gold nanoparticals (GNP).

Methods: Glucose blood levels were measured weekly in NOD mice, until developing hyperglycemia (>600mg/dL). The db/db mice were sacrificed at the age of 4 months, after developing DR for at least 8 weeks. Retinae were extracted for expression of mRNA levels of VEGF as measured by RT-PCR. Fundus photography, fluorescein angiography (FA), as well as the feasibility of OCT-angiography with and without GNPs in mice was tested in-vivo. The mice were sacrificed, following perfusion with Indian ink, fluorescence gel or GNPs. Flat mount retinae were analyzed under different microscopes including hyperspectral and special air scan electron microscope.

Results: Decreased levels of VEGF were detected in both NOD and db/db mice. In vivo imaging did not show NV. Only mild leakage was detected on FA. OCT angiography failed to demonstrate mouse retinal vascularization. Intravenous injection of GNP did not improve the OCT detection. Flat mount retinae revealed NV showing accumulation of GNPs by hyperspectral microscopy and scan electron microscope. Histological section demonstrated intravitreal tufts of pathological vessels.

Conclusions: Neovascularization is difficult to detect in mice with the current technologies. Despite high glucose level, reduction of VEGF expression was showed. Although the lack of in vivo detection of NVE, and the reduced VEGF levels, we managed to demonstrate NVE in diabetic flat mount retinae using novel intravenous perfusion and GNPs injection. Under specific microscopes, flat mount retinae demonstrated detailed vessels with some growing into the vitreous. This technique improves the detection of the NVs. Having a model of PDR in mice may improve molecular characterization of the pathology underlying neovascularization**.**

Six3 Regulates Optic Nerve Development via Multiple Mechanisms

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Purpose: To identify the mechanisms underlying Six3-mediated eye malformations. Six3 is a transcription factor essential for eye and forebrain development in vertebrates. One mutant SIX3 allele in humans may cause holoprosencenphaly (HPE), a congenital syndrome that includes forebrain malformation, ventral forebrain midline deficiencies and various eye malformations including cyclopia, anophthalmia, microphthalmia and coloboma.

Methods: We used zebrafish to generate a new model for Six3 loss of function, in which, unlike previous models, eyes develop beyond early stages. We analyzed the development of the eyes and optic nerve using various imaging and molecular techniques..

Results: The mutant embryos exhibit mild microphthalmia, optic disc coloboma and deficiencies in the ventral forebrain midline. The optic nerve is highly abnormal, showing defasciculation, failure to form a normal optic chiasm and abnormal projections to the ipsilateral tectum and telencephalon. Consistent with these abnormalities, mutant embryos show reduced visual performance but are not completely blind. Analyses of the molecular mechanisms underlying aberrant optic nerve formation identify multiple abnormalities in expression of genes required for normal optic nerve development in the eye, optic stalk and ventral diencephalic midline. Additionally, differentiation of photoreceptors and retinal ganglion cells (RGCs) that send axons of the optic nerve is delayed. Comparison of gene expression profiles between normal and mutant eyes by RNA-Seq identifies abnormal expression of genes involved in cell cycle regulation. Analysis of cell cycle dynamics suggests a prolonged cell cycle and delayed cell cycle exit.

Conclusions: Our findings reveal new roles for Six3 in eye development and are consistent with known phenotypes of reduced SIX3 function in humans. Hence, the new zebrafish model for Six3 loss of function can provide inroads into better understanding mechanisms underlying optic nerve development and SIX3-mediated eye and forebrain malformations.

Retinal Degeneration in Fam161a Knockout Mice

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Purpose: *FAM161A* mutations are the most common cause of inherited retinal degenerations in Israel. In addition, *FAM161A* is an excellent candidate for gene therapy: the open reading frame is relatively short and all reported mutations are null. Our main purpose is to generate a line of knockout mice in which there is no Fam161a expression and examine the effect on retinal function and structure.

Methods: Mice with a heterozygous non-activated conditional construct were produced and used to generate a knock out line of mice that are homozygous for the activated allele by Cre activation. Mice were examined at different ages (1, 3 and 6 months). The cellular retinal expression of the construct was evaluated by LacZ staining. Retinal function was evaluated by electroretinography (ERG) in scotopic and photopic conditions and retinal structure was studied by optical coherence tomography (OCT) and histological analysis.

Results: As part of the process of generating the KO line, we identified a known *CRB1* mutation in the breeding colony and bred the mice with C57BL/6J mice in order to filter out this mutation. Subsequently, the mice were inbred with Cre mice aiming to create a line with an activated construct resulting in the deletion of the major Fam161a exon (exon #3). LacZ staining revealed that Fam161a is expressed in the ganglion cells, inner and outer nuclear layer in these mice. In photoreceptors, LacZ expression was noted in the inner and outer segments. ERG analysis revealed decrease in a- and b-wave amplitudes comparing to WT mice at ages 1, 3, and 6 months (n=8 animals per group) in a progressive manner. Light-adapted ERG showed lower responses that are correlated with light intensity. OCT analysis of the same tested animals at ages 3 and 6 months showed a minor difference between KO and WT animals in outer nuclear layer (ONL) thickness while major differences were observed at the age of 6 months. Retinal histology analysis revealed a progressive degeneration of photoreceptors along time.

Conclusions: The results indicate that a homozygous Fam161a frameshift mutation affects retinal function and cause retinal degeneration. This model will be used for gene therapy treatment in the future.

Cellular Characterization of the Inflammatory Response Associated with Corneal Neovascularization in a Chemical Injury Model and Potential Therapy

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Purpose: To further investigate the inflammatory response as the leading factor for the development of corneal neovascularization (NV) and limbal stem cell deficiency (LSCD) following sulfur mustard (SM) exposure and to evaluate potential therapy in rabbits.

Methods: Chemical burn was induced in the right eyes of NZW rabbits, using SM vapor. Clinical examination was performed and NV was evaluated. Inflammatory cells (neutrophils, macrophages, antigen presenting cells and T cells) were identified immunohistochemically. LSCD was verified using Impression Cytology (IC) and PAS stained paraffin sections. In accordance with the above characterization, Tacrolimus, a potent immunomodulator was tested. Treatment with Tacrolimus (Prograf, Teva, 0.25 mg / 50 µl sub-conjunctival injection) was started either before (72 hrs) or after (4 weeks) the appearance of NV and was given once a week for 3-4 weeks. Eyes were clinically examined and the effect on T cells was studied.

Results: Corneal NV, associated with LSCD, developed starting from two weeks after exposure. Neutrophil levels were elevated compared to naïve eyes, mainly in the limbus. Migration and accumulation of T cells was observed in the limbus of neovascularized eyes at all time points (1-4 weeks), forming focal infiltration, and in some eyes T cells infiltrated into the cornea. Simultaneously, numerous antigen presenting cells were seen in the limbus and cornea. Macrophages were not identified. Treatment with tacrolimus was not effective in reducing the clinical signs including NV severity and corneal thickness. Moreover, immunohistochemical staining revealed that the treatment was not helpful in diminishing T cell levels.

Conclusions: Long term injuries associated with SM exposure are accompanied by chronic inflammation. Antigen presenting cells, key players in T cell activation, and T cells, capable of orchestrating specific immune responses, were found in the limbus and cornea of exposed eyes. Nevertheless, the T cell suppressor Tacrolimus did not reduce the amount of T cells and was not beneficial against the corneal injury.

Reduced Inflammatory Reaction has a Neuroprotective Effect in Optic Nerve Crush Model

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Purpose: Based on the inflammatory cells infiltration to stroke areas in the brain, we measured the neuroprotective effect of reduced inflammatory reaction in transgenic mice, TNFα receptors 1&2 (TNFR1&2) knock-out (KO) mice following optic nerve crush (ONC) induction.

Methods: ONC was induced to the right eye of all mice. The left eye served as an internal control. Histological and Immunohistochemistry analysis of the optic nerves and retinae were performed. Included were TNFαR1 KO (n=3), TNFαR2 KO (n=6) and wild type (WT, n=7) mice. Retinal thickness was measured and the number of RGCs was calculated and compared to the healthy control eye and to WT. Immunostaining with CD45, Vimentin and GFAP was performed. Molecular analysis was previously shown.

Results: On day 21, in the WT mice thinning of the retina was measured from 217 (±6) control retina to 186µm (±3) following ONC induction. Significant RGCs loss (25%) was detected in the right WT eyes. The TNFαR1&2 KO mice had thinner control retinae of 177µm (±4) and showed minimal thinning to 174µm (±4) post ONC induction, and minimal RGCs loss (8%). GFAP and vimentin immunostaining showed reactive gliosis in the WT group as compared to the TNFαR1&2 KO mice. CD45 staining for inflammatory cells was similar in both groups.

Conclusions: After ONC injury, both TNFαR1/2-KO mice showed a neuroprotective effect on histology in comparison to the WT mice. Blocking TNFαR1 or TNFαR2 immediately after trauma might facilitate vision preservation.

Examining the Ability of Resveratrol to Attenuate Disease Progression in Two Rodent Models of Retinal Degeneration and Injury

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Purpose: Oxidative injury is presumed to play a role in retinal and macular degenerations such as Retinitis pigmentosa (RP) and age-related macular degeneration (AMD), and light-induced formation of oxygen free radicals has been proposed as the underlying mechanism of photic retinal injury.
Resveratrol (3,5,4-trihydroxystilbene), one of dietary polyphenols found in red wine and grape skin, is known to have strong antioxidant effects. It has been reported to exhibit various bioactivities including anti-tumorigenic, anti angiogenic, and neuroprotective effects.
In this study we tried to evaluate the ability of Resveratrol to attenuate disease progression and enhance photoreceptor survival in the rd10 mouse model of genetic retinal degeneration as well as in a mouse model of photic injury.

Methods: Thirteen rd10 mice with a mutation in the phosphodiesterase gene, a well established rodent model of RP, were used in this study. From post-natal day 3, seven animals received PO Resveratrol (100 mg/kg) via gavage 6 times weekly, while six control animals were subjected to gavage of BSS according to the same protocol. At the age of 3 and 4.5 weeks retinal function was assessed by electroretinographic (ERG) recordings, and retinal structure was examined histologically.
The possible role of Resveratrol in retinal photic injury was investigated by treating 10 adult BALB/c albino mice with Resveratrol (100 mg/kg) by daily gavage for 7 days prior to exposure to intense fluorescent light (8500 lx) for a duration of 150 minutes. Treatment was then continued for 7 additional days, at which time ERG recordings were performed and eyes taken for histological processing and analysis. Eight BALB/c mice that were administered BSS according to the same protocol served as controls.

Results: In both the rd10 model of hereditary retinal degeneration and the photic injury model, retinal function as measured by the ERG and degree of photoreceptor injury on histology did not differ between the Resveratrol-treated and BSS-administered animals.

Conclusions: Under the conditions described, Resveratrol did not seem to provide a protective effect against retinal degeneration and injury in the two rodent models tested.

Clearance of Aflibercept Following Intravitreal Injection in a Rat Model

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Purpose: Aflibercept is known as a potent anti vascular endothelial growth factor (anti-VEGF), though little is known regarding its clearance mechanism following intravitreal injection to the eye. Our purpose was to characterize the localization and clearance of intravitreally injected Aflibercept in the eye in a rat model.

Methods: Choroidal neovascularization (CNV) was induced by diode laser photocoagulation on the right eye of 8 Brown Norway rats.
3µl Aflibercept (25mg/ml) was injected intravitreally on day 3 from CNV induction. Immediately after Aflibercept injection and 3,6,24 and 48 hours later, animals were euthanized and eyes were enucleated for immunofluorescence staining. Donkey anti-human IgG labeled with Alexa Fluor® 488 was used for Aflibercept immunoreactivity detection. Untreated eyes were used as negative control. Anti CD31 antibody was used as a marker for schlemm's canal's endothelial cells. Intensity of the immunofluorescence staining was analyzed qualitatively.

Results: Aflibercept immunoreactivity was detected in the cornea, iridocorneal angle, and the retina immediately after injection, and declined in a decremented manner within the following hours.
Forty eight hours from the injection no Aflibercept staining was detected in the structures mentioned above.

Conclusions: Our study demonstrated the immediate accumulation of intravitreally injected Aflibercept in retina, cornea and iridocorneal angle and its presence there at least for 24 hours.
Clearance of Aflibercept molecules from the eye through the iridocorneal angle and retina were shown to take place within 48 hours.

Gene Augmentation Therapy Restores Retinal Function and Visual Behavior in a Sheep Model of CNGA3 Achromatopsia – Long Term Follow-up

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Purpose: Recently we reported that unilateral subretinal delivery of an adeno-associated virus serotype 5 (AAV5) vector carrying either mouse (mCNGA3) or human (hCNGA3) cDNA results in recovery of photopic vision in CNGA3-mutant dayblind sheep. Following recent reports that the efficacy of gene therapy in LCA patients starts declining after 6-12 months, our aim was to evaluate long-term treatment efficacy in our treated sheep cohort.

Methods: Animals that underwent mCNGA3 (n=4) or hCNGA3 (n=5) gene augmentation therapy 3.8±0.5 and 3.0±0.2 years ago, respectively, were studied. Photopic vision was evaluated by maze navigation. Cone function was evaluated by light adapted, full-field flash electroretinography. Flicker responses to eight increasing frequencies were recorded and the critical flicker fusion frequency (CFFF) determined.

Results: Mean±SD passage time of mCNGA3- and hCNGA3-treated animals was 4.7±0.6 and 4.0±0.5 seconds, respectively, without any collisions with obstacles. However, when the treated eye was covered, average passage time increased significantly ($P<0.0005$) to 24.2±9.4 and 23.3±7.3 seconds, respectively, and the number of collisions increased to 1.6±1.3 and 5.8±2.2 in mCNGA3- and hCNGA3-treated animals, respectively. The CFFF of mCNGA3 and hCNGA3-treated eyes was 70±8.2 and 65±5.8 Hz, respectively, compared to 25±5.8 and 32.5±25 Hz in the untreated control eyes ($p<0.0005$).

Conclusions: A single, subretinal injection of a AAV5 carrying the CNGA3 cDNA resulted in significant improvement in photopic vision and cone function, lasting over 3 years. Our results confirm long-term efficacy and safety of CNGA3 gene therapy in our dayblind sheep model, paving the way for clinical trials in achromatopsia patients.

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Impaired RPE-Mediated Phagosome Turnover as an Early Marker for Ocular Damage in the Cohen Diabetic Rats

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Purpose: Ophthalmic manifestations severely impairing vision are a leading cause of blindness among diabetic-patients. Often, damage is detected at a relatively late stage, with unknown etiology. Perturbations to RPE cells via oxidative stress and damaged Bruch's membrane could impair RPE function. The Cohen-rats are a model of diet induced diabetes, developing hyperglycemia when exposed to a diabetogenic-diet but maintaining normoglycemia on regular chow diet. Diabetic Cohen-rats were shown to develop diabetic retinopathy, with prominent degeneration of photoreceptors. We examined RPE phagocytic function at the pre-diabetes and diabetes stages in the Cohen rat model.
Methods: The dynamics of RPE uptake and recycling of photoreceptor outer segments (POS) was assessed by phagosome quantification at 9AM and at 13PM. Oxidative stress induced protein carbonylation of RPE proteins was detected by the oxyblot method and function of recycling pathways were assessed by western blot. Overall viability of photoreceptors was assessed by hematoxylin-Eosin staining.

Results: POS uptake by RPE in diabetic rats at 9AM was similar to that of normoglycemic rats. The clearance and turnover of phagosomes was severely delayed in RPE cells of diabetic rats, with numerous phagosomes that failed to clear away at 1PM. RPE cells of hyperglycemic rats showed elevated levels of oxidative stress-induced protein carbonylation. While the proteasome-degradation pathway was not affected in these cells, the lysosomal/autophagy degradation pathway was significantly inhibited. Notably, these abnormalities were detected with the onset of diabetes, and prior to photoreceptor cell death.

Conclusions: Our data indicate that RPE stress and dysfunction observed at diabetes onset could result from cellular accumulation of oxidative damage and inhibition of the lysosomal/autophagy degradation pathway occurring at the pre-diabetes stage. With the development of advanced imaging techniques, we propose phagosome uptake and recycling could be used to assess ocular damage during early stages of diabetes, and prior to retinal damage.

Studying Visual Behavior in Barn Owls with a Miniature Head-Mounted Video Camera

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Purpose: Study visual search in barn owls.

Methods: We trained barn owls (*Tyto alba*) to search for stimuli presented on an LCD computer screen. To track their performance a lightweight wireless video camera ("Owl-Cam", 30 frames per second (fps), ~60º view angle) was mounted on the owls' head. The camera is self-assembled from a miniature micro-camera combined with a video broadcasting chip (900 MHz), and a rechargeable lithium-polymer battery. We trained the owls to fixate a red oval in the screen center to initiate the trial. Then the center oval disappeared and a target oval made of elongated dense texture appeared in one of five locations around the screen center. The owl was rewarded for switching and maintaining gaze on the target. Two backgrounds were tested: one gray and a second made of dense elongated texture similar to but oriented orthogonally to the target's texture. This made the target appear camouflaged. The point of gaze was identified as the point on the video frame with the highest probability to acquire the red oval (functional fovea).

Results: The owls consistently fixated the target on a single point on the retina. Thus although owls do not contain an anatomical fovea they have a functional fovea. The owls significantly responded to the targets indicating detection of targets in both backgrounds. No side preference was observed ($\chi 2=3.928$, $p=0.416$, $\chi 2=2.615$, $p=0.624$; gray and dense elongated texture respectively). In addition we found that the reaction time was significantly longer when the background was similar to the target compared to when it was gray ($Z = -3.199$, $p = 0.001$).

Conclusions: This study demonstrates that it is possible to train owls for visual search tasks on a computer screen and that information about their visual perception can be extracted by tracking the gaze point. Furthermore we show that owls can detect patches that are characterized by different dominant orientation from the background.

Involvement of NETosis in LPS-Induced Ocular Inflammation in a Mouse Model

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Purpose: NETosis is a process of microbial killing where neutrophils form Neutrophil Extracellular Traps (NETs). NETs are net-like structures comprised of DNA, histones, and antimicrobial proteins which create a net that captures and eliminates the pathogen. The occurrence of NETosis in ocular inflammatory conditions has not been explored yet. We therefore aimed to evaluate the involvement of NETosis in lipopolysaccharide (LPS)-induced ocular inflammation in a mouse model.

Methods: Inflammation was induced in the right eye of 20 C57BL/6J male mice by intravitreal injections of 100 ng/1µl/mice lipopolysaccharide (LPS) from E.*coli*. Control eyes were injected with saline. Eyes were clinically evaluated for inflammation progression at 0, 3, 6, 24 and 48 hrs post injection using slit lamp and indirect ophthalmoscope. At each time point eyes were enucleated, fixed and stained with H&E for histopathology. Presence of neutrophils and NETs was evaluated using immunofluorescence staining using the following markers; CD11b - a marker for neutrophils, neutrophil elastase (NE) – a serine protease with high affinity to DNA which helps destroy bacteria, myeloperoxidase (MPO) – expressed in neutrophils and helps to carry out the antimicrobial activity and Citrullinated Histone 3 (CitH3) –citrullinated chromatin, a common marker for proper NET existence.

Results: Clinical and histological signs of inflammation were observed as early as 3 hrs and peaked at 24 hrs post immunization, which was associated with massive influx of inflammatory cells to the vitreous. The inflammatory cells were positive for CD11b+ thereby indicating the presence of activated neutrophils. A subpopulation of these cells excreted to their surroundings an extracellular net-like structure positive for NE, MPO and CitH3, components that are positive markers for NETosis and powerful anti-microbial agents.

Conclusions: Our study shows for the first time elevation of NETosis markers associated with inflammation induced in murine eyes. Our results suggest that neutrophil recruitment and NETosis may play a role in inflammatory processes in the eye.

Pax6 Role in the Regulation of Retinal Pigmented Epithelium Maturation

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Purpose: Haploinsufficiency of Pax6 was long shown to cause aniridia and was reported to involve neovascularization of the cornea. However, Pax6 involvement in vascularization remained elusive and lack of imaging techniques for the choroid vasculature limited further inquiry regarding the effect on this tissue. This research aims to determine the molecular mechanism in which Pax6 regulates retinal pigmented epithelium (RPE) maturation and choroid development using somatic mutagenesis in mouse models and RPE cells derived from human embryonic stem cells (hES-RPE).

Methods: To this purpose, conditional mutations are induced in mice and gain of function analysis is conducted using sub-retinal injections followed by electroporation. Quantitative expression levels are measured using single molecule FISH and the choroidal phenotype is analyzed using a novel perfusion technique. Further investigation of the molecular mechanism involved in this regulation is performed using hES-RPE cells and includes chip-seq, RNA-seq and knockdown using viral infections.

Results: Pax6 deletion in the specified RPE resulted in a phenotype of aniridia and among the changes in gene expression we observed an up-regulation in Sox9 expression level, a key transcription factor in organogenesis which is related to late stages of RPE differentiation. Pax6 and Sox9 expression patterns were determined in course of RPE differentiation in wild type mice and mice with Pax6 specific ablation from the RPE. Quantitative expression analysis illustrated opposite correlation and gain of function analysis confirmed this observation since Pax6 miss-expression resulted in inhibition of Sox9 expression.

Conclusions: This study is the first to document Pax6 role in timing RPE differentiation through its regulatory relations with Sox9. Future efforts are aimed to elucidate the molecular mechanism of this regulation and examine a possible effect on the choroid vasculature.

Evaluation of Ocular Motility Deviation Changes Post Cycloplegic Eye Drops versus Prism Adaptation Test in Exotropic Patients

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Purpose: To evaluate ocular motility deviation changes post cycloplegic eye drops against prism adaptation changes (PAT) in exotropic patients.

Methods: We performed a retrospective chart review of patients with exotropia examined at a pediatric ophthalmology unit from 2013 to 2015. Inclusion criteria were all patients who had undergone strabismus surgery for the first time in their life without other ophthalmic, neurological or systemic pathology. Data analysis included demographic details, medical history, orthoptic and ophthalmic examination. Ocular motility changes were noted immediately after instillation of cycloplegic eye drops and after 10 and 20 minutes. Findings were compared with PAT readings.

Results: Twenty-two males and 21 females, aged 13.7±9.1 years participated and met the inclusion criteria of the study. Ten patients had esotropia and 33 had exotropia. All patients were evaluated using both methods described above. Post cycloplegic ocular motility deviation changes compared to baseline measurements were not statistically significant in patients with exotropia for distance/near ($p=0.584$, $p=0.468$, respectively). Comparison of changes between primary deviation and immediately after PAT were not statistically significant for distance/near in patients with exotropia ($p=0.002$, $p=0.01$, respectively) and for PAT after 10 minutes for near deviation ($p=0.011$). Comparison between cycloplegic drops to PAT ocular motility deviation changes for distance/near demonstrated the superiority of the immediate PAT ($p=0.001$, $p<0.001$, respectively) and even after 10 minutes for near vision ($p=0.036$).

Conclusions: Surgical correction in exotropic patients with estimation of the post-operative results depends on the maximal ocular motility deviation changes according to both methods. It would seem that in exotropic patients, the PAT is superior to cycloplegic eye drops for the evaluation of the distance/near motility changes.

Refractive Changes after Unilateral Recess-Resect Strabismus Corrective Surgery: A Case-Control Study

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Purpose: To evaluate the change in refractive error induced by a unilateral homogenous strabismus surgery by comparing it to the non-operated sound eye.

Methods: Retrospective chart review of patients treated with unilateral horizontal lateral rectus recess medial rectus resect procedure for exotropia. The preoperative refraction was mathematically subtracted from the postoperative refraction for both the operated eye and sound eyes, and the induced refractive changes were averaged and statistically compared. The proportion of clinically significant refractive change was evaluated as well.

Results: Overall 28 cases at median age of 14 years (range 4-48 years) met the inclusion criteria. Although refractive changes were observed in both eyes at one month postop, the magnitudes of these changes was significantly higher in the operated eye compared to the sound eye ($P < 0.005$) and especially in terms of cylinder (0.35 ± 0.38 in the operated eye compared to 0.06 ± 0.23 in the sound eye, $P = 0.001$). In addition, The proportion of cases with clinically significant change in sphere and cylinder power was significantly higher in the operated eyes compared to the sound eyes (48% versus 14%, OR = 12.0, $P = 0.006$ and 31% versus 10%, OR = 8.0, $P = 0.046$ respectively).

Conclusions: Refractive changes should be anticipated after strabismus surgery. Therefore postoperative measurements are important to reduce the risk of amblyopia. Longer follow-up studies are needed to determine whether these are transient or constant changes.

Refractive Changes Induced by Strabismus Corrective Surgery in Adults

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Purpose: To investigate refractive changes after strabismus correction procedures among adults

Methods: Retrospective chart review of adult patients operated for strabismus with preoperative and one month postoperative cycloplegic refraction measurements.
The preoperative refraction was mathematically subtracted from the postoperative refraction, and the induced refractive changes were averages and statistically analyzed. Vector analysis was used to examine the magnitude of the toric change. In cases of single eye surgery the changes in refractive status of the operated eye and the sound eye were compared. The proportion of clinically significant refractive change was evaluated as well.

Results: Twenty-six eyes from 18 subjects met the criteria and were included in the final analysis. Spherical equivalent was significantly different between the two measurements ($P < 0.0001$). A significant postoperative refractive change towards myopia and surgical induced positive astigmatism with the rule were observed. In a subset of 9 cases a third cycloplegic refraction measurement demonstrated stable refraction compared to the 1-month postoperative measurement. In 7 cases of single eye surgery, significant refractive changes were observed only in the operated side. The induced surgical refractive change was of clinical significance (≥0.5D) in 10 out of 18 patients.

Conclusions: As refractive changes are a significant side effect of strabismus corrective surgery among adults, patients should be informed about it prior to surgery and should be re-refracted in the postoperative period.

A Passive Optical Device for Nystagmus Correction and Resolution Enhancement

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Purpose: To present a future solution that will allow central (foveal) vision to nystagmus patients, by centering the image on the fovea, using a passive device composed of a rigid contact lens, which moves together with the eyeball, and spectacles. The patients will wear both.

Methods: In order to compensate for the involuntary movements of the eyeball and the retina caused by nystagmus, the patient will wear a rigid contact lens and an ophthalmic lens (spectacles). Due to the uncontrolled movement of the eyeball, there is a relative shift between the two lenses: the contact lens, which moves together with the eyeball and the fixed spectacle. We are about to prove that this relative shift is equivalent to generation of a prism which will cancel (when the optical parameters are properly chosen) the movement of the image on the retina caused due to the non-controlled movement of the eyeball. We built an experimental setup composed of two lenses representing the spectacles (f=+40mm), and the contact lens + eye (f=-50mm), and a camera attached to computer, represents the retina. We imitated the movements of the eye as happens in nystagmus and checked the movement, or lack of movement of the image on the retina.

Results: The uncontrolled movement of the eyeball existing in nystagmus patients is compensated by a passive optical device composed of a rigid contact lens and spectacles. Movements can be compensated in the X axis, Y axis or on both axes simultaneously, as required by the nature of the nystagmus in each case. When the patient moves his head, and/or his eyes, the angle between the contact lens and the spectacles is changed, yet, the focus on the retina is obtained in the same central position.

Conclusions: The proposed configuration always centers the image at the center of the retina (the fovea), thus in order to read or to construct a large field of view, the nystagmus patients will have to turn their head. Nevertheless, the proposed solution will allow them to read in enhanced resolution and to function in the daily life tasks. The proposed procedure of treatment can be done, beginning at a young age in children having nystagmus, in order to prevent the development of amblyopia.

Causes of Visual Impairment and Blindness in Children at a Hospital Based Low-Vision Center in Israel

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Purpose: To assess the epidemiologic characteristics of children with severe visual impairment and blindness followed through our hospital based low-vision center in Israel. Our center includes a multidisciplinary team composed by optometrists, ophthalmologists, social worker and genetic counselor. The team works through a comprehensive approach including diagnosis, rehabilitation, prevention and treatment.

Methods: A retrospective review of the medical records of visually impaired children aged 0-18 seen through our clinic from 2010 till 2014. The following data was collected: ocular diagnosis, visual acuity, presence of strabismus and/or abnormal head posture (AHP), blind certificate, sex, and associated deficiencies.

Results: A total of 897 patients were included, 58% male (n = 522) and 42% female (n =375). The mean age was 9.6 years. Associated non-ophthalmic disorders were present in 23% of patients. The most prevalent disorders causing severe visual impairment were albinism (30.8%), retinal dystrophies in 20.5%, cortical visual impairment (CVI) in 11% and optic atrophy (11%). Inherited eye diseases accounted for 51.3 % of all diagnoses.
Legal blindness was present in 273 (30.4%) of the studied children. CVI was the most common cause of blindness with 76/273 (27.8%), closely followed by retinal dystrophies 73/273 (26.7%).
From the 897 patients included in the study, 218 (24.3 %) children had strabismus and 189/897 (21%) had AHP.
Ocular pathology that accounted for the poorest mean visual acuity included retinopathy of prematurity (6/90), Leber's congenital amaurosis (6/90) and achromatopsia (6/60).

Conclusions: The leading causes of childhood severe visual impairment and blindness, in our patient cohort were genetic eye diseases (mainly retinal dystrophies and albinism) with 36.6% of confirmed inherited ocular pathologies among legally blind children. CVI also accounted for one of the commonest causes of childhood blindness in our patients; its rate is in rise during the last years among industrialized countries around the world.
Our findings suggest that in Israel the incidence of inherited ocular diseases is even higher than the reported by other developed countries. Efforts for preventing childhood blindness should

Measurement of Ocular Torsion with Digital Image Analysis in Face Turn and Head Tilt for Assessment of a Superior Oblique Palsy

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Purpose: The superior oblique intorts the globe, and its paresis results in pathologic excyclotorsion. Abnormal torsion can be clinically detected by fundus assessment. Typically fundus torsion is assessed in primary position. We hypothesized that additional assessment of fundus torsion in face turn and head tilt would improve diagnostic accuracy.

Methods: Study participants underwent a full neuro-ophthalmic and sensorimotor examination. Fundus images of each eye were taken for primary position, 45 degrees face turn (right and left), and 15 degrees of head tilt (right and left). Torsion was assessed by an experienced strabismus specialist and by digital analysis software, measuring the angle between the fovea and the center of the optic nerve.

Results: Fifteen normal subjects and twenty-five patients with clinical features of a unilateral superior oblique palsy were recruited. In primary position the mean torsion for normal subjects was 6.4 degrees of excyclotorsion (SD 3.6). Only 9 of the 21 superior oblique cases demonstrated abnormal torsion in primary position, and an additional 4 cases had abnormal torsion only in the contralateral eye. There was significant correlation with double-maddox readings (p 0.01) and high correlation with the subjective fundus assessment of the expert ($p < 0.0001$). The degree of torsion in side gaze was not significantly different from primary position in either population. Relative to the sagittal axis of the skull, ipsilateral and contralateral head tilt produced a significant but slight change in torsion for both normal subjects and superior oblique palsy cases but there was no significant variation between the two populations.

Conclusions: A significant amount of patients with clinical findings of a superior oblique palsy have normal fundus torsion. An experienced strabismus surgeon is able to accurately assess fundus torsion. Additionally evaluating torsion in side gaze or head tilt does not add diagnostic value.

Suture Colonization Rate in Adjustable Strabismus Surgery

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Purpose: To document the colonization rate of sutures used in adjustable strabismus surgery.

Methods: A prospective, non-interventional, laboratory-based study of all patients over the age of 18 years who underwent strabismus surgery with an adjustable suture technique was done. At the end of the adjustment, a 1 cm section length of the polyglactin 6-0 suture, adjacent to the adjustable knot was trimmed and placed in a tube containing 2 ml of trypticase soy broth (TSB). The TSB tube was then transferred to the microbiology laboratory and monitored for bacterial growth. In case of bacterial growth, susceptibility patterns and Minimal Inhibitory Concentrations (MIC, mcg/ml) for common antimicrobials were evaluated. The MIC value was interpreted using the E-test. Antimicrobial susceptibilities were determined according to the Clinical and Laboratory Standards Institute (CLSI).

Results: Over the six month study period, 59 adjustable sutures from 59 consecutive patients were collected. Bacterial growth occurred in 39 of 59 (66.1%) sutures. There were 47 bacterial isolates from these 39 sutures. Eight of the 39 sutures (20.5%) showed growth of two bacterial species. Nine bacterial species were identified. *Staphylococcus epidermidis* was the most predominant isolation, accounting for 72.3% (34/47) of bacterial isolates. Seven of the 34 (20.6%) isolates were Methicillin-resistant *S. epidermidis*, 2/34 (5.9%) were Methicillin-resistant *S. aureus* and 7/34 (20.6%) were fluoroquinolone resistant. All the isolates tested were highly sensitive to gentamicin (100%, n=46). Among the fluoroquinolones, susceptibility rates were between 84.1-84.8% (n=44-46). The highest resistant rates of bacterial isolates were to erythromycin (52.17%, n=46). The mean age of patients with positive cultures was higher than those with negative cultures: 56.2 vs. 41.7 years old (p=0.03). Time interval of the adjustment from the surgery did not influence the suture-contamination rate (p=0.31).

Conclusions: Suture colonization rate in adjustable strabismus surgery is high. Results may help guide selection of post-operative antibiotic prophylaxis.

A Comparison between two Subjective Near Phoria Tests: Maddox Wing Test and Modified Thorington Test

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Purpose: Phoria describes the natural position of the eyes in the absence of fusion. Clinically, one can categorize a phoria according to its deviation and distance from the fixation target (near or far). In the literature there are different methods of measuring the subjective phoria at near: Von Graeffe, Modified Thorington and Maddox Wing, Maddox rod and one objective -the alternate Cover test.

In this research, we compared the horizontal phoria results with the Maddox Wing test vs. the Modified Thorington test. Both tests use a set scale to determine the phoria. However, the Maddox Wing test uses a septum for disassociating the eyes while the Modified Thorington test uses a Maddox lens.

Methods: Two different examiners performed the experiment and were blind to each others results. Half the participants were first examined with the Maddox Wing technique and then with the Modified Thorington technique. The second half of participates were examined in the opposite order. Data was analyzed using the correlation test and Bland & Altman analysis (1986).

Results: Thirty subjects (6 men and 24 women) between the ages of 21-31, with average age of 24.12±2.46 years, participated in the study. Subjects had near visual acuity of at least J1 (Jaeger chart), stereopsis of at least 40 SOA (Stereopsis Randot) and refractive error up to 5.00D sphere and 2.00D cylinder. A significant correlation was found between both tests R=0.81. However, the average of the difference between the tests was 0.84D with high standard deviation (SD=±2.74D)

Conclusions: The Maddox Wing test and Modified Thorington test for measuring the near phoria are not interchangeable.

Risk Factors for the Development of Cataract in Children with Uveitis

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Purpose: To evaluate risk factors for the development of cataract in children with uveitis of any etiology.

Methods: A cross sectional cohort study (2013-2014).
140 children (249 eyes) with uveitis in 2 tertiary centers : * Moorfields Eye Hospital – London, * Rabin Medical Center – Tel Aviv.
Demographic, clinical and therapeutic data were collected from the children files.
Main Outcome Measures: *Prevalence of cataract in our cohort (and distribution by anatomical diagnosis) *Incidence of cataract in our cohort.
*Time to cataract development using Kaplan-Mayer survival. *Risk factors for cataract development using multivariate Cox regression analysis.
Risk factors investigated: anatomical diagnosis, posterior synechia at presentation, CME, use of systemic corticosteroids, second line immunosuppressive therapy, local steroid injections, time of treatment with topical steroids (>3 drops/day) and number of flares per year.

Results: The prevalence of cataract in our cohort was 44.2%.
The prevalence distribution by anatomical diagnosis was: AAU- 12.9%, CAU- 48.3%, IU- 48%, PostU- 16.7% and PanU- 77.1%.
The overall incidence of newly diagnosed cataract was 0.09/eye-year.
The estimated time to cataract development was 129.5 months.
Eventually 69% of eyes will develop cataract.
The risk factors that were strongly associated with early development of cataract were: number of flares per year, CME, posterior synechia and local steroid injections.
Treatment with systemic steroids, IMT and treatment with more than 3 drops of steroids per day were not associated with early cataract development.

Conclusions: In this study we found that formation of cataract is common among eyes treated for uveitis, but may develop over several years.
Risk factors related to cataract formation include presence of PS, CME, the number of flares per year and local steroid injections.
Interestingly, once adjusted for other risk factors, treatment of uveitis with local (>3 drops/day) or systemic steroids was not a significant risk factor.
Therefore disease control must be the clinicians primary goal, flares should be avoided, even in the face of long treatment with frequent topical steroids.

The Role of Pre-Implantation Genetic Diagnosis in Preventing Childhood Blindness

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Purpose: Knowledge about inherited eye diseases has increased dramatically during the last twenty years. Although there are no global statistics on the extent of the burden of inherited visual impairments, it is clear that inherited eye diseases represent a significant percentage of the causes of blindness in industrialized countries. In Israel, the 2014 statistics from The Center for the Blind shows that out of 122 children who received blind certificate, 22% were secondary to genetic eye diseases (mainly albinism and retinitis pigmentosa), while another 27% were secondary to possible genetic diseases like congenital cataract, glaucoma, optic atrophy, nystagmus and more. The purpose of our study was to report the value of pre-implantation genetic diagnosis (PGD) in preventing inherited eyes diseases causing childhood blindness.

Methods: Retrospective study of 37 non-related mothers who underwent PGD of embryos procured through in vitro fertilization by cell biopsy genetic analysis. Chromosomal analysis or DNA analysis was done to detect specific gene mutations. Healthy embryos (having no mutations or healthy carriers) were implanted to their respective mothers. Patients details were collected from medical charts from the two main hospitals in Jerusalem, from 2006 till 2015.

Results: Genetic counseling and preimplantation genetic testing were performed in 37 unrelated families, suffering from different genetic ocular diseases: 10 families with albinism, 5 with retinitis pigmentosa (RP), 3 with retinoblastoma (RB), 2 with achromatopsia, 2 with aniridia, 2 with blue cone monochromatism (BCM), and 2 with optic atrophy, as well as additional minor diagnoses. All propositi in respective families had poor vision or were legally blind. Causative mutation was identified in all families and they decided to proceed for in vitro fertilization with PGD in order to prevent further potentially blinding genetic eye disease in their families. Fourteen healthy children were born till today from 37 completed IVF + PGD treatments.

Conclusions: Genetic diseases are responsible for a high proportion of childhood blindness in Israel. The importance of PGD in preventing the transmission of the different mutations from parents to their offspring should be enhanced. We recommend that PGD will be offered to those couples who are at risk of having a child with severe genetic eye disease as a way to prevent childhood blindness, particularly given the limited treatment options available for inherited ocular diseases.

Amblyopia and Strabismus: Trends in Incidence and causes among Teenagers in Israel

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Purpose: To estimate the prevalence of amblyopia and predisposing factors among teenagers in Israel, and analyze time trends.

Methods: The records of 112,726 teenagers born between 1971 and 1994 were reviewed. Amblyopia was defined as best-corrected visual acuity (BCVA) of <0.67 in either eye or as an inter-ocular difference of ≥2 lines. The prevalence across birth years was analyzed. Additionally, trends in the severity as well as the potential causes of amblyopia, including anisometropia (anisohyperopia >+1.5 diopters (D), anisoastigmatism >2D, or anisomyopia >|-3D|), isoametropia (hyperopia >+4D, myopia >|-5D|, astigmatism>2D) and strabismus were examined.

Results: The prevalence of amblyopia decreased from 1.2% in subjects born before the year 1985 to 0.8% among those born after 1985 (R2=0.84, p<0.0001). This was mostly due to a decrease in unilateral amblyopia (R^2=0.91, p<0.0001). Bilateral amblyopia did not significantly change over the years (p>0.05). The incidence of mild amblyopia declined from 0.7% to 0.4% (p<0.0001), moderate amblyopia declined from 0.35% to 0.2%, while severe amblyopia remained in 0.2% of the population over the years (p>0.05). Anisometropia ranged between 16-20% among unilateral amblyopic teenagers across the different birth years, without a significant trend (p>0.05), while strabismus ranged between 6-13% across the different birth years, with no significant trend (p>0.05). Among bilateral amblyopes there was no significant trend in isoametropia (hyperopic, myopic, or astigmatic), ranging together between 49-60% (p>0.05). The incidence of strabismus in the entire population decreased over the years, from 1.4% in subjects born in earlier years to 0.6% in those born in the later years (R^2=0.75, p<0.0001). Amblyopia occurred in 4-15% of strabismic subjects, and increased over the birth years (R^2=0.91, p<0.01). The increase over the last years was mostly attributed to higher proportion of mild amblyopia (0.5-10%) in teenagers with strabismus (R^2=0.73, p<0.01). Moderate amblyopia (1.5%-3.4%) and severe amblyopia (0.8%-3.4%) did not change significantly over the birth years (p>0.05).

Conclusions: The incidence of amblyopia and strabismus decreased among teenagers in Israel over a generation (24 years). Among strabismic teenagers the incidence of amblyopia increased in later years.

OCT Imaging of Papilledema in Pediatric Idiopathic Intracranial Hypertension

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Purpose: To compare the mean retinal nerve fiber layer (RNFLT) and total retinal thickness (TRT) and 12 segmentation analysis of the optic nerve of newly diagnosed IIH children to a control group. Additionally, the change in RNFLT/TRT was measured during 3 months of IIH treatment with acetazolamide and weight reduction.

Methods: We used spectral domain optical coherence tomography (sdOCT) to evaluate retinal nerve fiber layer thickness (RNFLT) and total retinal thickness (TRT) of children presenting with clinically suspected IIH. Patients were evaluated by a pediatric neurologist, ophthalmologist and underwent sdOCT exam before and after Lumbar puncture (LP), and after one and 3 month of follow-up. IIH was diagnosed based on Dandy Criteria. We compared the RNFLT and TRT of clinically diagnosed IIH children to an age matched controls group that did not have papilledema on fundoscopic exam.

Results: Thirty one children were included (N=16 for the IIH group, N=17 for the control group). The mean RNFLT was 135.1±19.7 vs. 113±8.9 µm for the IIH and control groups (p=0.001), respectively. Segmental analysis of RNFLT showed that the nasal region was significantly different between the groups. Intracranial pressure (range between 21-52 cmH2O) measured in the IIH group was directly correlated with RNFLT at the nasal segment (r=0.64, p=0.03). Following 1 and 3 months of IIH treatment, RNFLT and TRT gradually decreased to 117.1±8.6 µm, and most patients returned to normal thickness.

Conclusions: The nasal part of the optic nerve was the most sensitive segment in detection of papilledema in IIH. We suggest that sdOCT could be used as a non-invasive method for diagnosis and follow-up of pediatric patients with IIH.

Retinoblastoma – the Clinical Presentation of Patients with Mosaics

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Purpose: The clinical presentation of retinoblastoma differs between those with somatic and germline mutations in the RB1 gene. Extensive analysis is required to find mosaics who are at a risk for second and secondary malignancies as patients with germline mutations. We describe the clinical presentation of retinoblastoma in patients with mosaics vs. germinal and somatic cases.
Methods: We examined a cohort of 295 RB patients who underwent genetic counseling and molecular analysis and evaluated the clinical presentation among the three groups. IRB approval was obtained to review patient information.
Results: Nine patients were found to have 10-30% mutated cells in the peripheral blood. All but one had a stop codon. Five were diagnosed over 1 year of age (mean 35 months) and 4 under 1 year (mean 4 months). Six had unilateral disease. Three presented with strabismus and the rest with leukocoria, although none had macular involvement. There was a wide variability in the grouping of the eyes.
Conclusions: Older kids with unilateral disease and no macular involvement should be carefully assessed for mosaics.

Sub-Retinal Fluid Optical Density in Choroidal Tumors

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Purpose: We investigated the optical density characteristics and clinical relevance of sub-retinal fluid (SRF) of choroidal tumors and choroidal metastasis.

Methods: Patients with optical coherence tomography (OCT) at diagnosis prior to any type of intervention, and whose OCT scans showed sufficient SRF for sampling, were included. The highest quality B-scan containing SRF was analyzed. Optical density (OD) measurements were obtained using ImageJ. Optical density ratios (ODRs) were calculated as SRF OD divided by vitreous OD. Non-parametric tests for independent samples were used to detect differences in ODR between groups.

Results: Overall 25 cases of choroidal tumors met the inclusion criteria, of which nine were diagnosed as metastases and 16 as malignant melanoma. Measurement of ODR was significantly lower in metastases (median 0.69, range 0.41-0.96) compared to melanoma cases (1.01, 0.54-3.2, $p<0.05$). There was no significant difference in age, OCT acquisition and quality parameters or vitreous OD between the groups.

Conclusions: ODR might be used in order to differentiate between choroidal melanoma and choroidal metastases.

Retinoblastoma Treated with Ru-106 Plaque Brachytherapy as a Primary Treatment in Israel

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Purpose: Retinoblastoma is responsive to radiation treatments. External beam radiotherapy (EBRT) bears extensive complications, especially when performed unilaterally, more so under 1 year of age. The aim of this study is to describe the use of brachytherapy for retinoblastoma with its strengths and weaknesses.

Methods: We examined a cohort of retinoblastoma patients who underwent brachytherapy with a Ru-106 plaque as a primary treatment in unilateral unifocal tumors. The planned apical dose was 50Gy. IRB approval was obtained to review patient information.

Results: Over the past eight years, 13 children (6 girls) were treated with primary brachytherapy for an isolated retinal tumor. The mean age of diagnosis was 16.6 months (range 3-63 months, median 11 months, but only four children were diagnosed over one year of age). Eight eyes had group B tumors, 4 had group C tumors, and 1 had a group D tumor. The tumor was located in the macula in half the cases. All the tumors responded to treatment without local recurrence. No complications were noted. In the youngest child, additional tumors emerged in both eyes months after the brachytherapy. An RB1 mutation was detected in 3/7 cases were mutation analysis was completed.

Conclusions: Ru-106 brachytherapy is an effective primary treatment for monofocal retinoblastoma even for larger tumors and helps to avoid enucleations or EBRT in unilateral cases.

Malignant Tumors Infiltrating the Optic Nerve

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Purpose: Malignant optic nerve tumors are rare, diagnosed late, cause poor vision and have dismal survival. We aim to describe 7 patients who lost vision and died as a result of malignant tumor infiltrating their optic nerves.

Methods: In this study, seven individuals were included, age 14-75 years old (2 children, 5 adults), all underwent repeated neuro-imaging and were followed in two tertiary centers between the years 2003-2013. The medical files were reviewed for demographic and clinical findings. Imaging studies were reviewed and tumor localization, size and progression were documented. The correlations between patients' symptoms and signs, imaging and progression of disease were analyzed from diagnosis until end of follow-up.

Results: Symptoms at presentation included acute monocular (3), progressive binocular (2) loss of vision, bitemporal hemianopia (1) and homonymous hemianopia (1). The two children had been previously treated for a brain tumor (recurrent ependymoma and PNET) while all the adults were previously healthy, with no pathological findings on first neuroimaging in two of them at diagnosis. One was diagnosed with a compressive tumor of the right sinus and the other with enhancement of the optic nerve later diagnosed as lymphoma. Progressive deterioration of vision and visual fields was observed in 4. Six died within 6-24 months from diagnosis of visual pathway involvement. Four underwent biopsy, revealing malignant ganglioglioma, glioblastoma (2) and PNET metastasis. One had lymphoma. The other two had known metastatic ependymomas and sinus rhabdomyosarcoma. Clinical findings and imaging studies suggested malignant infiltration of tumor to the optic nerves in 6 patients, and inconclusive compression or infiltration in one.

Conclusions: Malignant infiltration of the optic nerve is rare and difficult to diagnose. Vision deteriorates prior to findings on imaging. The delay of weeks to months in diagnosis causes difficulties in treatment with often unnecessary workup. Currently, treatment rarely improves outcome and the prognosis is poor.

Using Differential Expression of MicroRNA may Improve Subgrouping of Medulloblastoma for Targeted Treatment

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Purpose: Medulloblastoma (MB), the commonest malignant brain tumor of childhood, is divided into four tumor subgroups representing distinct clinical, biological and molecular entities. Treatment should be designed according to the specific subgroup. MicroRNAs (miRNAs) are involved in carcinogenesis and tumor progression by regulating post-transcriptional gene expression. However, the miRNA-mRNA regulatory network is far from being fully understood. The aim of the study is to identify novel miRNA subgroup biomarkers and their target mRNAs for rapid, specific and cost effective diagnosis by analyzing integrated mRNA-miRNA transcriptome sequencing from tumors.

Methods: Total RNA was extracted from fresh frozen tumor tissue, collected from MB patients during surgery of their primary tumor. RNA sequencing was performed using HiSeq 2500 sequencer (Illumina). RNA-seq and miRNA-seq expression counts were normalized to library size following Trimmed Mean of M values (TMM) normalization using edgeR package. Voom transformation and differential expression analysis was performed using linear modeling implemented at the R limma package. Integrated analysis was done using QIAGEN's Ingenuity® Pathway Analysis.

Results: 10 MB tumors were analyzed, 867 mature miRNAs were identified in at least a single MB sample, of them 462 were common to all 4 subgroups. 25 (2.5%) of all expressed miRNAs appeared to be significantly differentially expressed between the medulloblastoma subtypes (FDR<0.1). Namely, upregulation of hsa-miR-224-5p and hsa-miR-449c-5p was found exclusively among WNT, while downregulation of hsa-miR-135b-5p characterized SHH. Among groups 3 and 4, hsa-miR-20a-5p was upregulated or downregulated, respectively. RNA-seq from the same tumor samples identified 500 genes that vary between the four subtypes (q value <0.05), among which 69 (13.8%) have anti-correlated miRNA-mRNA interactions with the 25 detected miRNA biomarkers. The predicted mRNAs targets of these miRNAs are associated with different signaling pathways, known to have a role in MB biology.

Conclusions: MiRNAs are readily detectible and are highly specific to distinct MB subgroups. Understanding the involvement of miRNAs and their targets in MB related signaling pathways may improve diagnosis and advance the development of targeted treatment for MB

Evaluation of the Toxicity of Intravitreal Carboplatin Injection in a Rabbit Model

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

Methods: Ten New Zealand male rabbits (1800-2000 gram) were injected with a single carboplatin intravitreal injection each, in decreasing dosage (8-3 µg) / 0.1 ml in one eye. The second eye was used as control .
The animals were evaluated clinically by Intraocular pressure (IOP) measurement, slit lamp examination and indirect ophthalmoscopic fundus examination, immediately post Injection, on day one day 7, day 14, day 30 and before euthanasia (day 45).
In addition to the clinical ophthalmic examinations, toxicity was evaluated using baseline and repeated (days 14, 30, 45) Electroretinogram (ERG), Optical Coherence Tomography (OCT) and Ultrasound (US) examinations .
After euthanasia the eyes were fixed and submitted for histopathological evaluation .
All the animals were holed, anesthetized and euthanized with accordance to the ARVO protocols.

Results: All the eyes had normal repeated IOP, anterior segment and fundus examinations at all the examination points .
All the eyes had normal repeated OCT and US examinations at all the examination points in the study and the control eyes.
All the eyes were normal in histopathological evaluation in the study and the control eyes .
No significant ERG changes were noted under 3 and 4 µg carboplatin. ERG was decreased under 5-8 µg of intravitreal Carboplatin injections.

Conclusions: Intravitreal carboplatin injection appears to be safe in the dosage of 3- 4 µg/0.1 ml in a rabbit model. Dosage of 5-8 µg/0.1 ml decreases the ERG reading but resulted in no anatomical ocular changes.

The Biomarker TK Predicts Metastases in Uveal Melanoma Patients

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Purpose: Thymidine kinase (TK) is an enzyme involved in DNA synthesis and leaks into the blood as a result of high cell turnover, particularly in case of cancer. We and others have shown previously that serum TK levels can be used for distinction between low and high grade disease, monitoring of Leukemia and Lymphoma patients, as to response to various treatments and for their prognosis. The purpose of this study was to evaluate the potential of the TK Biomarker in Uveal Melanoma (UM), mainly in predicting metastasis.

Methods: Sera from a total of 58 UM patients (pts), including 19 pts with Disease Free 10y (DF) and 39 pts with Metastases (Mets), before and after Mets detection were analyzed and compared with 43 healthy Controls. A TK ELISA from DIASORIN, Italy, was used.

Results: Significantly (p=0.008) higher TK levels were detected in Mets, compared to DF and Controls, which were similar. The Mean +SE levels (ng/ml) of TK were: DF: 5.4 ± 0.75 (min 0.9 -12 max), Mets:10.3 ±0.15

(min 1.5 -37.5 max), Controls: 5.8 ± 0.3 (min 3.2-13 max). In about half of Mets UM pts, an increase in TK levels was found at Mets diagnosis.
Conclusions: The results of this preliminary TK evaluation indicate that TK can provide valuable information as to distinction between DF and Mets pts and may predict Mets formation in UM patients. Evaluation of more pts is required to obtain firm results.

The Israeli Inherited Retinal Degenerative Diseases Consortium (IIRDC): Mapping Inherited Retinal Degenerative Diseases in the Israeli Population

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Purpose: To recruit and genetically diagnose the vast majority of Israeli patients with Inherited Retinal Degenerative Diseases (IRD).

Methods: A consortium, IIRDC (the Israeli IRD consortium) was established, including ophthalmologists and geneticists from research universities and academic hospitals, covering the entire state of Israel, from Beer Sheva in the South to Haifa in the North. The consortium consists of 11 research groups: 6 genetic centers, 4 units for clinical electrophysiology of vision, and a bioinformatics lab. The clinical electrophysiology centers are responsible to diagnose IRD patients and refer them to the genetic centers, which recruit and genetically analyze patients; the bioinformatic center analyzes exomes of patients referred by the genetic centers.

Results: Our current cohort of recruited IRD families contains over 1900 families including patients with various IRDs, the most common one is retinitis pigmentosa (RP). We performed different genetic analyses on this set of patients and were able to identify the cause of disease in 40% of families. Since the establishment of IIRDC, we were able to scale up the rate of recruitment. In addition, IIRDC members identified a relatively large number of novel IRDD-causing genes and founder mutations.

Conclusions: This is a unique consortium given the national-wide spread, the availability for testing populations from all backgrounds, and to offer genetic testing throughout Israel. The immediate expected outcomes include an epidemiological overview of IRD distribution and etiology in the Israeli population, identification of novel causative genes and mechanisms, and genotype-phenotype correlations. The main expected long-term outcome is a significant reduction in the prevalence of IRD in Israel. This will be achieved by a combination of prevention, by genetic screening and counseling among high-risk populations, and treatment, by identification of patient groups with shared genetic diagnoses, who can be recruited to clinical trials for evaluation of various treatment strategies.

Anti-VEGF's Effect on Photoreceptor Disruption

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Purpose: Assessing changes in photoreceptor integrity following intravitreal anti-VEGF treatment may serve as a prognostic marker in patients with macular edema (ME).

Methods: Prospective longitudinal study. Sixteen eyes belonging to newly diagnosed patients with ME were included in this study. Foveal photoreceptor microstructure (FPM) integrity was evaluated by measuring fragmentations COST and IS/OS lines in the central 0.48 mm height. The main outcome measures were associations between FPM, visual acuity (VA), metamorphopsia and central macular thickness (CMT) after treatment of the first anti-VEGF injections series

Results: Treatment led to a significant improvement of 27.5% in mean VA and to a 23.9% reduction in the mean CMT. A larger FPM defect was associated with a lower VA, both pre- and post-treatment. Patients with a larger FPM defect at baseline had a smaller VA improvement ($r=-0.53, p=0.03$). Improvement in FPM defect integrity was associated with VA improvement ($r=0.63, p=0.008$), as every 100 µm recovery in FPM contributed to a gain of 0.04 logMar. Patients with a final VA worse than the mean VA (0.83 logMar) had significantly larger FPM defect then patients with VA better than the mean (1587µm vs. 519µm, $p=0.027$). Final VA was correlated with baseline VA ($r=0.82, p<0.001$) and with baseline Mscore ($r=0.536, p=0.03$).

Conclusions: Recovery of FPM post anti-VEGF treatment was significantly associated with a VA improvement. Direct measurement of photoreceptor integrity might provide a better assessment of retinal function and treatment response in patients newly diagnosed with ME. An FPM defect at baseline may be a predictor for treatment response

Critical Flicker Frequency and the Relationship to spatial and temporal vision abilities in Healthy and Amblyopic Subjects

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Purpose: Critical Flicker Frequency (CFF), the frequency at which a flickering light is perceived as a continuous light, is the measure of choice for evaluating visual temporal resolution. CFF is serving as an important diagnostic tool and follow up measure of drug efficacy. To date, the agreement between the measured CFF obtained from the various available methods is not known. In this study we developed a system that enabled us to compare between three methods used to measure CFF and studied the effect of stimuli illumination, age and amblyopia on CFF.

Methods: We developed a novel laptop based CFF testing system based on custom written Matlab software and an analog data output device, to drive a LED stimulation, control the flickering frequencies and analyze the perceived CFF. We designed our experiments to evaluate three types of psychophysical tests: the methods of limits, where stimuli with increasing or decreasing flickering frequency were projected to the subject until the subject reported on perceiving the stimuli as constant or flickering; the method of constant stimuli, where stimuli flickering at various frequencies were presented to the subject, in a random order, in a two-choice paradigm and threshold was calculated as a 75 percent correct responses; and the staircase method, performed in a 3/1 paradigm.

Results: The CFF could be measured reliably with all three methods, with high repeatability. Correlation between the various methods was highest between constant stimuli and staircase (r=0.90) followed by the two other methods pairs (r=0.83). Increasing stimuli illumination increased CFF significantly with saturation at 25 cd/m^2. Amblyopia and age were associated with decreased CFF in all three methods. Time to complete the test was significantly longer in constant stimuli (mean 25.4 min, STD 2.2 min) as compared to the two other methods (mean 2.5 min, STD 0.62 min, mean 1.8 min, STD 0.25 min, for staircase and methods of limits, respectively).

Conclusions: Evaluation of CFF by a staircase method is reliable and significantly faster than the constant stimuli method. Stimuli illumination is associated with increased CFF up to illumination levels of about 25 cd/m^2. Amblyopia and age are associated with lower CFF. Our system for measuring CFF was found to be easy to use and reliable and could be utilized to study the effect of various parameters on CFF.

CSR in Women

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Purpose: To report the clinical features and natural course of central serous chorioretinopathy (CSR) in women.

Methods: Medical records of women with CSR diagnosed at Soroka University Medical Center between 2008-2014 were retrospectively analyzed. Ophthalmological assessment included measurement of best corrected visual acuity, slit lamp biomicroscopy, color and red free fundus photography, fluorescein angiography and retinal optical coherence tomography. CSR in men and in women was analyzed separately.

Results: During the study period, a total of 27 men and 9 women were followed up in our department. Median age was 41.7 +- 11 years in men and 55.3 +-7.86 years in women (p value>0.02).Mean follow- up period was 40 +- 7 weeks. Presenting visual acuity was 0.28 logMAR in men and 0.25 logMAR in women (p value =0.69). 10 men and 6 women had comorbidities at presentation (P value =0.1). Final visual acuity was 0.2 logMAR in men and 0.25 logMAR in women (p value 0.45).

Conclusions: In our study population, women with CSR present with almost equally visual acuity and had more comorbidities than men. Studies with a larger sample size are warranted to validate our findings.

Reversal of CME in a Gyrate Atrophy Patient – Molecular Diagnosis and Treatment Response

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Purpose: Gyrate atrophy (GA) of the choroid and the retina is an inherited autosomal recessive disorder characterized by progressive vision loss, myopia, cataract formation and peripheral visual field reduction up to tunnel vision. This disorder is related to mutations in the ornithine-aminotransferase gene (OAT) which result in hyperornithinemia. Some patients are responsive to pyridoxine treatment which reduces blood ornithine levels, without any known clinical influence. Low arginine intake is also associated with reducing ornithine blood levels, and might slow down progression. Only two case reports of the rare combination including GA and optic nerve astrocytic hamartoma, and a few cases of GA and cystoid macular edema (CME) were previously published in the literature. We describe a unique case of GA with astrocytic hamartoma of the optic nerve and CME, with good clinical response to low arginine diet and pyridoxine supplement.

Methods: A 28 years old female with GA, optic nerve astrocytic hamartoma and CME was treated and followed up in our clinic. Clinical findings including slit-lamp examinations, color photos, SD-OCT and Ornithine blood levels were measured and recorded prior to and after two months of treatment with low arginine diet and per os 500mg pyridoxine supplement qd. Sequencing of the OAT gene was conducted.

Results: After two months of treatment, blood ornithine levels dropped from 700 µmol/l to 500 µmol/l. BCVA improved from 6/120 to 6/30 in the right eye and from 6/120 to 6/21 in the left eye. Central macular thickness measured with SD-OCT improved from 666µm to 404µm in the right eye and from 535µm to 421µm in the left eye, with significant improvement in the intraretinal and subretinal fluid levels. Previous treatment with NSAIDS (NEVANAC) did not improve BCVA nor CME. Sequencing revealed a novel mutation, OAT c.159delC; p.H53Qfs7*, It is a homozygous single nucleotide deletion of C which changes the aa Histidine at position 53 to Glutamine, and a frame shift of 6 aa until a stop codon occurs at 7 aa after the change.

Conclusions: To our knowledge this is the first case report in the literature which combines these 3 rare findings of GA, optic nerve astrocytic hamartoma and CME, as well as the first reported case in which CME improved clinically following treatment with low arginine intake and pyridoxine supplement. A novel mutation, OAT c.159delC; p.H53Qfs7*, might be responsible for this unique combination of findings and clinical behavior

Silicone Oil Influence on Macular Thickness

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Purpose: To evaluate the influence of silicone oil (SO) on macular thickness in patients who underwent an anatomically successful retinal detachment (RD) surgery with SO tamponade.

Methods: Retrospective, interventional, comparative case series. We reviewed the medical charts of 96 consecutive patients who underwent pars plana vitrectomy for retinal detachment and were left with a SO tamponade (5500 or 1300 centistokes), between 2013-2015. SO was removed few months later in a second planned operation. Optical Coherence Tomography (OCT) was performed with the SO tamponade and one month after SO removal (SOR). Central macular thicknesses (CMT), internal and external layers thickness were measured in the operated eye and in the fellow healthy eye in each patient over the study period of time. Patients with insufficient or poor quality images or with macular pathologies were excluded. Main outcome was the change in macular thickness before and after SOR compared to the healthy eyes.

Results: Twenty-two patients (15 females and 7 males) were included in the study. Average age was 55.4±12.2 years. In 54% (12 eyes) of patients the macula was detached at presentation and SO 5500cs was used in 50% (11 eyes) of patients. Average SO tamponade duration was 153±54 days. We found a statistically significant increase in the mean CMT with 249µm before compare to 281µm after SOR ($p<0.0001$). Mean CMT after SOR was similar to the mean CMT of 279µm of the normal fellow eyes ($p<0.0001$).The increase in mean CMT was mainly attributed to changes in the mean thickness of the internal layers with 168µm before compare to 196µm after SOR ($p<0.0001$). CMT in the eye with SO tamponade was strongly correlated with the CMT after SOR ($r=0.847$). A positive correlation was found between SO duration and the mean change in CMT ($r=0.432$). No correlation was found with macula status, silicone type or age ($p=0.880$, 0.898, 0.775 respectively).

Conclusions: We found that macular thickness decreases in eyes with SO tamponade, mainly in the internal layers. After SOR, the CMT resembles the fellow healthy eyes suggesting a mechanical effect of SO on the retina.

Retinits Pigmentosa and Chronic Granulomatous Disease

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Purpose: We hereby present, for the first time, a case of autosomal recessive chronic granulomatous disease (CGD, OMIM #306400) in combination with retinitis pigmentosa, diagnosed in an eight years old boy.

CGD is a primary immunodeficiency disease, manifested by repeated bacterial and fungal infections. The disease is the outcome of a genetic defect in the NADPH oxidase complex of phagocytes most commonly originating of an X-linked mutation in the *CYBB* gene, however 3 more autosomal recessive (AR) gene mutations may cause CGD: *CYBA, NCF1* and *NCF2* genes. Retinitis pigmentosa (RP) was described in some patients with the X-linked form of CGD but no case of RP and AR CGD was described so far. We summarize the ocular findings in CGD and discuss the relevant findings with the case presented. We will further discuss the genetic link between the two diseases.

Methods: The patient underwent complete ophthalmic examination, including best-corrected visual acuity, clinical examination, optical coherence tomography (OCT), and fundus autofluorescence. Detailed electroretinography (ERG) testing was conducted including expanded ISCEV protocol for light-adapted and dark-adapted.

Results: Ophthalmic exam revealed best-corrected visual acuity of 6/24 OD and 6/15 OS, with moderate myopia, normal anterior segments and lens, typical perivascular chorioretinal punched out lesions, but also "bulls eye" macular appearance, enhanced in fundus auto-fluorescence images. OCT enabled the view of discontinuity of the ellipsoid zone in the perifoveal/foveal regions. Full field ERG demonstrated a generalized rod-cone dysfunction.

Conclusions: Physicians treating inherited retinal degenerations and retinal diseases should be aware of the possible linkage between CGD and RP. Patients with CGD should be monitored for RP signs and symptoms, independent of the genetic cause.

Self-learning the use of Sensory Substitution

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Purpose: One of the main bottlenecks to the adoption of Sensory Substitution Devices (SSDs) by blind users is the difficulty to learn their use. Here we test the efficacy of a dedicated self-train program developed in our lab for the EyeMusic SSD and compare different training strategies within it.

Methods: The EyeMusic visual-to-auditory SSD scans a visual and returns a soundscape.
We developed a self-learning program for learning the EyeMusic SSD (available online at amedilab.com). In this program, participants perform pre-post identical 4-AFC exams, with training sessions between them. This task was performed by a group of sighted participants (N=17).
Participants were divided into two groups. In the first (n=9) “visual” group, participants heard the soundscape of the image for two times, then saw the original visual image, and then heard the soundscape again. In the second (n=8), “non-visual” group, instead of seeing the original image, participants read its textual description. Following each such lesson, a small exam was administered.

Results: Before training but after explanation of the algorithm, all participants (in both groups) answered correctly 40% of questions on the EyeMusic soundscape, already significantly above chance ($p<1.14E-3$), chance at 25%). Training lead to a significant ($p<8.18E-6$ improvement) with post-test success rate of 61%.
When comparing the two modes of training participants in the “visual” group answered 65% ($P < 2.4E-3$ compared to the pre-scores) of the exam's questions correctly, while participants in the “non-visual” group achieved a rate of 70% ($p < 4.4E-5$ compared to the pre-scores) correct answers. No significant difference was found ($p=1.68E-2$), though a trend was observed towards the “visual” group.

Conclusions: This experiment demonstrates that it is indeed possible to self-learn a whole-scene visual-to-auditory SSD, and that within an hour, while still far from perfect, scores significantly improve.
Furthermore we demonstrate that while visual access to the images during training improves the final score, the difference is not significant, demonstrating the potential efficacy of such self-training also for blind users.
In addition, this experiment supports previous evidence reporting the intuitive comprehension of SSD, showing a high rate of accuracy of participants answering questions on the soundscape, without any training.

Topical Apraclonidine Reduce Pain after Intravitreal Injections: a Double-Blind Randomized Controlled Trial

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Purpose: To evaluate the efficacy of topical Apraclonidine in reducing the frequency and severity of subconjunctival hemorrhage and pain after Intravitreal injections.

Methods: A prospective, randomized, double-blinded single-center study. Thirty-nine patients receiving two consecutive monthly Intravitreal injections of 1.25mg/0.05cc Bevacizumab, delivered by a 30-gauge needle, were included. All patients were examined twice, once at each monthly injection (a total of 78 examinations). Patients were randomly assigned to receive 0.05cc of topical Apraclonidine 0.5% or placebo (NaCl 0.9%) to the treated eye, 30 minutes before the injection. At their next Injection appointment, patients received the other type of intervention. Every patient received a standard anesthesia and disinfection regime, 5 minutes prior to the procedure. Thirty minutes after the injection, patients were examined by an examiner blinded to the treatment. Subconjunctival hemorrhage was assessed by slit-lamp microscopy. Subconjunctival hemorrhage size was calculated by multiplying the width and length (in millimeters) of the affected area. Pain was assessed by the NRS-11 psychometric response scale (1-10).

Results: Mean NRS-11 pain score was 1.69 (SD ± 1.44) in the Apraclonidine group and 3.28 (SD ±2.27) in the control group ($p<0.001$). Phakic patients experienced more pain when treated by placebo ($p=0.16$) and had a larger delta of pain score size after topical Apraclonidine ($p<0.001$). Subconjunctival hemorrhage occurred in 16 eyes (41%) in the Apraclonidine group and in 20 eyes (51.3%) of the control group ($p = 0.503$). Mean subconjunctival hemorrhage size was 1.71 mm_2 (SD ±5.83) in the Apraclonidine group and 3.25 mm_2 (SD ±6.41) in the control group ($p=0.253$). Older patients tended to bleed less when treated by placebo ($p=0.002$). Patients with CNV had a smaller delta of subconjunctival hemorrhage size after topical Apraclonidine ($p=0.003$), as did patients with hypertension ($p=0.044$). Phakic patients had a larger delta of subconjunctival hemorrhage size ($p=0.048$) after topical Apraclonidine.

Conclusions: Topically applying 1 drop of Apraclonidine 0.5%, 30 minutes before intravitreal injections, decreased pain, especially in phakic patients. It may also decrease subconjunctival hemorrhage size in non-hypertensive, non-CNV diagnosed phakic patients. Topical application of Apraclonidine could increase patients' satisfaction and compliance to treatment.

Pilot Study of Feasibility of Use of Experimental High Viscosity Silicone Oils

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Purpose: Polydimethylsiloxanes ("silicone oils"), currently used in retinal surgery as long term endotamponade have viscosities between 1000 and 5000 cS, and share problems such as recurrent detachments and emulsification.

The Purpose of this pilot study is to evaluate the feasibility of use of experimental high viscosity silicone oils, with respect to both suitability of use with a currently available vitrectomy system, as well as their toxicity and safety.

Methods: We performed vitrectomies on 8 rabbit eyes, and filled their vitreous cavities with silicone oil, two with commercially available 5500cS silicone oil, 3 with 12,500cS oil, and 3 with 30,000cS oil. After 3 months, the eyes were examined histopathologically. We also evaluated the feasibility and time needed to inject 5cc's of the 3 oils using a commercially available system (Alcon VFCPac).

Results: Retinal histopathology, was comparable in all 8 eyes, with no excess toxic effect or damage seen in the eyes with the 2 experimental oils. Both experimental oils were also readily injectable with the VFCPac system.

Conclusions: Experimental silicone oils with higher viscosities otherwise have the same chemical and physical properties, therefore their toxicities are expected to be similar. In a small pilot sample of 8 eyes filled with silicone oil for 3 months, we showed identical histopathology in eyes with 2 experimental high viscosity oils and a commercially available medical grade silicone oil. We also confirmed the feasibily of injecting these oils using available current vitrectomy equipement. The use of new high viscosity silicone oils may offer several advantages over currently available oils in ertain case

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The Beneficial Effects of Aflibercept for Treatment of Corneal Neovascularization in a Chemical Injury Model

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Purpose: To examine the ability of aflibercept (Vascular Endothelial Growth Factor, VEGF-trap, R_1R_2, EYLEA®) to ameliorate corneal neovascularization (NV) in rabbits and to compare its effects to bevacizumab (Avastin).

Methods: Chemical burn was induced in the right eye of NZW rabbits by exposure to sulfur mustard (SM) vapor. Aflibercept (25 mg/ml, 50µl) was applied once to neovascularized eyes by subconjunctival injection at 4 weeks after exposure. Non-treated exposed eyes served as controls. A clinical follow-up including pachymetry was performed up to 10 weeks following exposure. Digital photographs of the cornea were taken for continuous measurement of blood vessels, using image analysis software. Vascular endothelial growth factor (VEGF) expression was studied by immunohistochemistry and ELISA. The anti-angiogenic effect of aflibercept was compared to the effect of bevacizumab (25 mg/ml) subconjunctival injections administered twice a week, for 3 weeks.

Results: Corneal NV developed, starting as early as two weeks after exposure, and was associated with increased levels of corneal VEGF and delayed development of Limbal Stem Cell Deficiency (LSCD). A symptomatic treatment with single injection of aflibercept, significantly reduced the extent of NV, while at the same time the NV in the control eyes continued to increase. Measurement of NV length indicated a significant decline in the aflibercept group already one week following injection and it lasted for several weeks. Although aflibercept had no effect on corneal thickness, it was more potent in reducing the NV than bevacizumab or topical steroid (0.1% dexamethasone, Dexamycin®).

Conclusions: Symptomatic treatment with aflibercept decreased corneal NV in a rabbit model of chemical injury. These findings are in accordance with previous results in the literature, showing the anti-angiogenic efficacy of aflibercept in other models, and demonstrate the advantage of aflibercept over bevacizumab as a therapy for corneal NV.

Stiffening of Rabbit Sclera by Bacteriochlorophyll Derivative WST11-D using Near Infrared Light

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Purpose: To compare the scleral stiffening efficacy of the photosensitizer WST11 combined with dextran-500 20% (WST11-D) and NIR illumination applied for either 5, 10, or 30 minutes on enucleated rabbit eyes for the treatment of progressive myopia

Methods: Twenty seven rabbit eyes were enucleated post mortem and treated topically with WST11-D 2.5 mg/ml for 20 minutes on the superior or inferior sclera, followed by external illumination with NIR at 10mW/cm2 for either 30 minutes (n=9), 10 minutes (n=9) or 5 minutes (n=9) using a diode laser at 755nm. The opposite side of the sclera served as control. After the treatment, the eye was dissected to superior and inferior halves. Scleral equatorial strips, 4±0.2mm in width, were cut with a self-constructed double-blade cutter. Stress-strain measurements were performed using a micro-computer controlled biomaterial tester (Minimat, Rheometric Scientific GmbH, Germany).

Results: : Ultimate stress increased by 40.6%, 68.6% and 30% ($p < 0.05$) following 5, 10, and 30-minutes of NIR illumination, respectively. Young's modulus increased by 38%,90% and 77% ($p < 0.05$) following 5,10 and 30 minute of NIR illumination, respectively. No statistical difference was noted in the ultimate stress ($p > 0.35$) nor in the Young's modulus ($p > 0.427$) between the 3 groups.

Conclusions: WST11-D/NIR treatment with illumination of 10 mW/cm2 at 755 nm significantly increases the biomechanical strength of rabbit sclera even after 5 or 10 minutes of illumination. This novel treatment with reduced illumination time and overall illumination energy may induce scleral stiffening and halt the progression of degenerative myopia

Repeatability of Corneal Astigmatism Measurements

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Purpose: To compare the repeatability of the astigmatism measurements taken by various devices

Methods: We performed two sets of corneal measurements on 28 right eyes of 28 healthy volunteers at an interval of five to ten days. All exams were done by a single experienced optometrist, and all measurements adhered to strict validation criteria. Inclusion criteria were age ≥ 18 years, no known ocular pathology, no contact lens wear, and no previous ocular surgery. Corneal measurements were performed using IOLMaster 500, Lenstar LS 900, NIDEK ARK-530A, Atlas topographer and Pentacam HR. Repeatability was evaluated by comparing the differences between the two measurements for the J0 and J45 vectors.

Results: The lowest variances of the differences in measurements (J0 and J45) were seen with the Lenstar and the Pentacam, P=0.026. Using the Lenstar 78.6% of eyes had an absolute power difference of the measured corneal astigmatism which was smaller or equal to 0.25 Diopter, followed by the Pentacam (71.4%), the Nidek (60.7%), the IOLMaster (42.9%) and the Atlas (35.7%) devices.

Conclusions: The repeatability of corneal astigmatism measurements can vary among different devices. The implications of these findings should be considered for surgical planning and monitoring postoperative astigmatic outcomes.

Novel use of SiHy Contact Lens with Prism to Alleviate Binocular Vertical Diplopia in a Patient with Anisometropia and Keratoconus

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Purpose: To use Silicone hydrogel (SiHy) toric tri-monthly (prism ballast and back surface toric) contact lenses (Soflex, Israel) with an integrated Base Down (BD) prism to manage anisometropia, vertical diplopia and keratoconus (KC).

Methods: A 46 year-old woman presented with keratoconus, presbyopia and right hypophoria secondary to anisometropia. After ensuing diplopia with a spectacle and a rigid-gas permeable (RGP) contact lens approach, SiHy toric tri-monthly Filcon V3 lenses with 74% water, 8.1mm base curve, and an integrated 2.5 prism diopter (p.d.) BD prism in the OS only, were custom-made for the patient, based on empirical data (OD: -4.00/-2.25 X 30, 14.5 mm diameter, central thickness: 0.18mm; OS: -0.75/-1.25 X 150, 15.0 mm diameter, central thickness: 0.26 mm).

Results: Spectacle correction with prisms caused diplopia and nausea. RGP diagnostic lenses resulted in good visual acuity but caused diplopia. The visual acuity (VA) with the SiHy contact lenses was acceptable for the patient's needs (measured distance VA- OD: 20/30-, OS: 20/25, OU: 20/25) and alleviated the diplopia. Slit lamp findings showed no desiccation and minimal staining after lens removal. An associated phoria of 1 prism diopter Base Up in the OD was diagnosed. At the one month follow-up, the patient reported wearing the lenses for 8 hours a day and experienced almost no diplopia.

Conclusions: To the best of our knowledge, this case is the first example of correcting vertical deviation with a SiHy contact lens that incorporated a BD prism.

Validity and Precision of a novel Instrument that Combines Wavefront Aberrometry, Autofraction and Corneal Topography with a Stationary Scheimpflug Camera

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Purpose: To evaluate the validity and precision of a novel instrument, the VX120 (Visionix Luneau, Chartres, France), that combines wavefront based autorefraction with stationary Scheimpflug imaging of the anterior chamber.

Methods: In this prospective study, subjects were recruited from healthy first year students at Hadassah Academic College, ages 18-38. Subjects were measured 3 times with the Sirius rotating Scheimpflug camera (CSO, Italy) and the VX120, by different technicians. Subjective refraction was carried out by one qualified optometrist. The optometrist and technicians were masked to one another's results and exams were performed in a random order. A subset of subjects was tested one week later for repeatability evaluation. Bland and Altmann analysis was used to assess agreement and precision. Only the right eye was included for analyses.

Results: 61 subjects (42 women) participated in the refraction validation study (24.36±7.29 years old). The mean difference between subjective refraction and the VX120 autorefraction for sphere, spherical equivalent (SE) and astigmatic vectors J0 and J45 was 0.14±0.47D, 0.01±0.34D, 0.10±0.18D and 0.047±0.17D, respectively. Repeatability was assessed on 37 patients. Intra-test repeatability showed small within-subjects standard deviation (Sw=0.38 to 0.39) and inter-test repeatability showed no statistically significant difference between the first and the second session for all parameters (p>0.33). 71 subjects (49 women) participated in the Scheimpflug imaging validation study (24.30±6.61 years old). The difference between the VX120 and Sirius for central corneal thickness (CCT), iridocorneal angle and anterior chamber depth (AD) were 26.12±11.46µm (-3.51±11.46µm with calibration offset), 0.93 ± 3.83° and -0.005 ± 0.118mm, respectively. Repeatability was assessed on 35 subjects. Intra-test repeatability showed small Sw of 2.85, 1.08 and 0.21 for CCT and iridocorneal angle and AD, respectively. Inter-test repeatability showed no statistically significant difference for any of the anterior chamber parameters measured by the VX120 (p>0.25).

Conclusions: The VX120 shows good agreement and repeatability values.

Refractive Surgery on the Same Day as the Initial Consultation- Safety, Efficacy and Predictability

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Purpose: The purpose of the study is to compare the safety, efficacy, predictability and clinical outcomes of refractive operations for the correction of myopia of different severities that were made on the same day as the initial consultation ("first visit surgery") to those performed on a later visit. The refractive procedures which were examined were Transepithelial Photorefractive Keratectomy (Trans-PRK) and Ziemer-Laser In Situ Keratomileusis (Z-LASIK).

Methods: We retrospectively reviewed the medical records of all patients who underwent corrective eye surgery for the treatment of myopia in our institution, between 1/1/2013 and 31/10/2014. The collected data includes age, sex, operating physician, operation date and whether it was a "first visit surgery", follow-up time, patient's refractive status and visual acuity prior to surgery and throughout the available follow-up, operative data, corneal thickness and post-operative complications.

Results: Of 3531 eyes that met the inclusion criteria 2652 eyes were treated with Transepithelial Photorefractive Keratectomy (Trans-PRK), 629 of which had first visit surgery and 2023 had surgery on a later visit. The safety index in the first visit surgery group was 0.96 ± 0.16 and 0.95 ± 0.15 in the later visit group (P=0.743). The efficacy index in the first visit group was 0.93 ± 0.19 and 0.94 ± 0.17 in the later visit group (P=0.153). The final spherical equivalence was -0.00 ± 0.79 and -0.01 ± 0.68, respectively (P=0.721).

879 eyes out of 3531 were treated with Ziemer-Laser In Situ Keratomileusis (Z-LASIK), 160 of which had first visit surgery and 719 had surgery on a later visit. The safety index in first visit surgery group was 0.99 ± 0.15 and 0.99 ± 0.12 in the later visit group (P=0.717). The efficacy index in the first visit group was 0.97 ± 0.15 and 0.98 ± 0.13 in the later visit group (P=0.633). The final spherical equivalence was -0.09 ± 0.58 and -0.18 ± 0.55, respectively (P=0.076).

Conclusions: In this study, first visit refractive surgery for the treatment of myopia showed almost identical results to those of surgery performed on a later visit, with both groups displaying excellent safety, efficacy and predictability profiles.

Age Related Changes in Corneal Refractive Parameters

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Purpose: To analyze and describe the changes in the corneal refractive parameters with age for myopic and hyperopic patients.

Methods: A retrospective study of patients who underwent laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) between January 2005 and December 2014 at the Care-Vision Laser Centers, Tel-Aviv, Israel. The following parameters were obtained for each group: sphere, cylinder, axis, BCVA, UCVA, Flat K, Steep K, Average K, corneal pachymetry, J0 and J45.

Results: Overall, 62,422 eyes of 31,211 patients were included in the final analysis of this study. Several parameters significantly correlated with age, particularly in patients > 40 years or age. In the myopic group the following parameters had a positive correlation with age: sphere (0.044, $p<0.001$), axis (0.019, $p<0.001$) while the other parameters had a negative correlation with age – cylinder (-0.087, $p<0.001$), BCVA (-0.039, $p<0.001$), flat K (-0.089, $p<0.001$), steep K (-0.063, $p<0.001$), average K (-0.065, $p<0.001$), J0 (-0.048, $p<0.001$).
For hyperopic patients – cylinder (0.346, $p<0.001$), BCVA (0.11, $p<0.001$), Flat K (0.3, $p<0.001$), Average K (0.143, $p<0.001$), pachymetry (0.1, $p<0.001$) correlated positively with age, while sphere (-0.23, $p<0.001$), axis (-0.12, $p<0.001$), J0 (-0.31, $p<0.001$), and blur (-0.312, $p<0.001$) had a negative correlation with age.

Conclusions: In the hyperopic group BCVA began to increase after the 40s while changes in the spherical equivalence and blur component were not significant until the 40s to 50s**.**
For myopic patients BCVA began to decrease after the 40s compared to changes in the spherical equivalence and blur component that were not patent until the 50s to 60s**.**
This findings could be explained by the decreasing optical quality of the human eye in elderly persons. Clinically, these changes could have an impact on the best visual acuity of myopic and hyperopic patients.

Very Long Term Success of Pterygium Surgery with Conjunctival Graft

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Purpose: To examine to the very long term prognosis (16 years in average) of pterygium surgery with superior versus inferior conjunctival graft.

Methods: Clinical data for patients that underwent pterygium surgeries with conjunctival graft by 2 surgeons at the Goldschleger Eye Institute, Sheba Medical Center, Israel, between the years 1997-2001 were retrieved from medical records. For all the included patients, data about their eye examinations was retrieved and a phone questionnaire was done.

Results: Twenty four patients were included in the study. Eleven with superior conjunctival flap (Group 1), and thirteen with inferior conjunctival graft (Group 2). In group 1, there was one surgery for recurrent pterygium, and in group 2 there were two cases operated for recurrent pterygium. In all cases the grafts were sutured and Mitomycin C was not used. No recurrence of pterygium was found in either group. No eye complications or side effects were found after sixteen years in average.

Conclusions: After a very long follow-up of almost two decades there are no recurrences of pterygium or complications when using upper conjunctival flap or lower conjunctival graft during the surgery. It seems that lower graft is as good as upper flap for preventing recurrence of pterygium. Larger studies are required in order to confirm these results.

In-vivo and ex-vivo Corneal Stiffening Induced by WST11-D and Near Infra Red (NIR) Light using a Shortened Irradiation Time and Decreased Total Energy

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Purpose: Literature is not conclusive about the efficacy of available shortened high fluency corneal cross-linking (CXL) protocols. In a previous study our group established the safety and efficacy of a novel corneal stiffening technique using WST11-D/NIR with parameters similar to the Dresden protocol that is commonly used in Riboflavin/UVA CXL. In this in-vivo and ex-vivo laboratory study we set out to evaluate the stiffening effect of a shortened WST11-D/NIR protocol, as we irradiate rabbit corneas for 1, 5, or 30 minutes.

Methods: Forty-five New Zealand White rabbits, aged 3 months, were treated in-vivo (n=18) and ex-vivo (n=27) according to three different protocols (1, 5, or 30 minutes of irradiation). Corneal strips were biomechanically tested, either immediately (ex-vivo) of one month after treatment (in-vivo), to obtain the elastic modulus. From each pair one cornea served as an untreated control, and one cornea was de-epithelialized, topically impregnated with 2.5mg/mL WST11 (Steba-Biotech, France) containing 20% Dextran-500 (WST11-D) for a period of 20 minutes. The impregnated corneas were irradiated with NIR light from a 755nm diode laser (CeramOptics, Israel) at 10mW/cm^2 for 30, 5, or 1 minute.
Central strips of 4±0.2mm in width containing sclera on both ends, were cut to be biomechanically tested using a biomaterial tester (Minimat, Rheometric Scientific GmbH, Germany). From the obtained stress-strain curves, the tangent elastic modulus was calculated. Statistical analysis was done using paired Student T-tests and linear mixed modelling (SPSS,IBM Corp, Armonk, NY).

Results: The tangent elastic modulus increased significant ($p<0.001$) in all three irradiation groups, by over 100%, ex vivo. In-vivo treatment resulted in a significant ($p<0.05$) increase of approximately 70% and 35% after 30 and 5 minutes irradiation respectively, but did not change significant in the 1 minute treatment group.

Conclusions: Both in-vivo and ex-vivo a significant corneal stiffening is obtained after only 5 minutes of irradiation, without increasing the light intensity. It has yet to be elucidated what the cause is for the difference between the effects in-vivo and ex-vivo. This novel WST11-D/NIR treatment provides an ultra-fast and safe alternative CXL technique, also suitable for thin corneas that would be excluded with RF/UVA CXL.

ICD vs RoseK2 Lenses for Patients with Keratoconus

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Purpose: This clinical non-dispensing case series compared visual outcomes obtained with irregular corneal design (ICD) and RoseK2 contact lenses.

Methods: Patients with keratoconus cones of 5 mm diameter or less, determined using Sirius topography (Schwind, Italy), were included in the study. Lenses were fit according to manufacturer recommendation, in random order. Distance and near Snellen visual acuity (VA) in LogMAR values, maximum contrast sensitivity (CS) and spatial frequency (SF) of the maximum CS (Fact Chart, Stereo Optical, USA) obtained with both lenses were compared using paired, two-tailed, Bonferroni-corrected t-tests.

Results: Seven eyes (5 female, 1 male, mean age: 35±14) were included in the study. Both lenses significantly improved outcomes compared with uncorrected (Unc) values in distance VA (Unc:0.10±0.05, ICD:0.80±0.16, RoseK 2:0.65 ±0.33), CS(Unc: 27.38±26.45, ICD: 78.13±26.20, RoseK2:56.75±25.49%) and SF(Unc:2.44±1.59, ICD: 7.50±2.78, RoseK2:6.75±3.49 cpd) but were not significantly different from each other. The ICD lens was preferred by four participants in terms of subjective visual quality and comfort.

Conclusions: Based on this small sample, ICD and RoseK2 provide similar visual outcomes, with ICD providing superior subjective comfort.

Induced de-novo Astigmatism after LASIK Surgery in Non-Astigmatic Eyes. H-LASIK vs M-LASIK

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Purpose: To compare the surgically induced astigmatism by H-LASIK vs M-LASIK in patients with no pre-operative refractive astigmatism.

Methods: A retrospective study of patients who had H-LASIK and M-LASIK during 2005-2014 at the Care-Vision Laser Center, Tel-Aviv, Israel. We calculated the mean absolute surgically induced astigmatism and performed risk factor analysis for induced astigmatism of more than 0.5 D. Differences between H-LASIK and M-LASIK were analyzed.

Results: 3877 eyes that underwent M-LASIK and 549 eyes that had H-LASIK were non-astigmatic pre-op, received a non astigmatic treatment and met the inclusion criteria. The mean age of the patients was 32.8 ± 19.7 SD (range 17-55 years). The induced astigmatism was determined by the post-op manifest refraction astigmatism as all cases were non-astigmatic preoperatively. 6 months after surgery, hyperopic treatment induced more SIA than myopic treatment: the mean induced astigmatism was 0.49± 0.48 D in the H-LASIK group and 0.36 D±0.4 in the M-LASIK group (P<0.001). In the H-LASIK group, the risk factors for induced astigmatism of >0.5 D were: younger age (47.8 ± 9.9 years old VS 49.8 ± 8.2 years old ; p=0.05), higher preoperaive refractive error (p=0.003), and larger treated optic zone (7 mm VS 6 mm). In the M-LASIK group, eyes with SIA tended to have steeper corneas (43.8 ± 1.5 D VS 43.6 ± 1.4 D; p=0.001), higher refractive spherical equivalent (3.43±1.53 VS 3.07±1.45 p<0.001), and smaller treatment optic zones (6 mm VS 7 mm).

Conclusions: There was a consistent trend toward more SIA in hyperopic LASIK vs myopic LASIK, and in higher refractive error correction. In H-LASIK we found larger optic zones to induce more SIA and in M-LASIK we found smaller ones to cause it.

Trends of Bacterial Keratitis Culture Isolates – a 13-Year Analysis

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Purpose: To describe the trends in pathogens and antibacterial resistance of corneal culture isolates in infectious keratitis during a period of 13 years at Hadassah-Hebrew University Medical Center.

Methods: A Prospective analysis of bacterial corneal isolates was performed during the months of January 2002 to December 2014 at Hadassah Hebrew University Medical Center. Demographics, microbiological data and antibiotic resistance and sensitivity were collected.

Results: A total of 943 corneal isolates were analyzed during a 13 years period. A pathogen was recovered in 452 samples (48%), and bacteria were present in 92% out of the total pathogens recovered. The Annual incidence was 34.78 ± 6.54 cases. The most common isolate was *coagulase-negative staphylococcus*, which had a significant decrease in trend through out the study period (APC=-8.1, p=0.002). Methicillin-resistant Staphylococcus aureus (MRSA) appears to have a decrease trend (APC=-31.2, P=0.5). There was a trend toward decrease in the susceptibility of *pseudomonas aeruginosa* to ceftazidime for the study period (APC=-0.96, p=0.01). There was an increase in the resistance trend of *coagulase-negative staphylococci* to penicillin (APC=5.0, P=<0.001). None of the pathogens had developed any resistance to Vancomycin. (P=0.88). An inverted correlation between average monthly temperatures and number of cases was found. In the cold months there was an increase in the incidence of bacterial keratitis (P=0.009).

Conclusions: Coagulase negative staphylococci were the predominant bacteria isolated from patients with keratitis. There was no significant change in the annual incidence of cases of bacterial keratitis seen over the past 13 years. Keratitis caused by MRSA appeared to decrease in contrast to the reported literature. Ceftazidime activity against Pseudomonas aeruginosa decreased significantly during the study period.

Topical Dipyridamole for Treatment of Pterygium and Associated Dry Eye Symptoms: Analysis of User-Reported Outcomes

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Purpose: A recent review article (Rogosnitzky et al.) demonstrated the benefits of dipyridamole in treating various posterior segment eye disorders. Pterygium, a proliferative disorder, is associated with viral causation (HPV), oxidative damage (UVB radiation), overexpression of VEGF, MMP9, and is usually accompanied by dry eye symptoms. Dipyridamole possesses multiple therapeutic mechanisms including, inhibition of viruses, VEGF & MMP9, and anti-proliferative and anti-oxidant properties, thereby having applicability in both pterygium and its associated dry eye symptoms. Following a case report (Carlock et al.) demonstrating pterygium regression through topical administration of dipyridamole, ophthalmologists have begun prescribing dipyridamole eye drops prepared by compounding pharmacies. Our aim was to analyze data provided directly by patients in order to assess subjective symptomatic improvement and objective pterygium regression.

Methods: Fifty patients participated in a baseline symptom survey that included the Ocular Surface Disease Index (OSDI). Of these, 25 patients participated in follow-up, providing comparison survey data. Photographs were provided by some patients and were visually assessed for indicators of change.

Results: The maximum percent change achieved from baseline OSDI severity scores during the course of treatment was a reduction of 52.4% (+/- 27.5). [Mean OSDI scores were 37.7 (+/- 20.2) at baseline and 18.7 (+/-15.2) at maximum response.] Treatment endpoint (at time of data analysis) averaged 137 (+/-95) days. Visual inspection of photos revealed marked anti-angiogenic and anti-hyperemic benefit, resulting in thinning out and/or regression of pterygium tissue.

Conclusions: Significant improvement in OSDI scores was achieved, as well as marked photographic evidence of pterygium regression, demonstrating promise for topical dipyridamole in treating pterygium. The topical dose being used is very small, at a ratio of approximately 1:25,000 of the standard daily oral dose of this drug. Insignificant systemic absorption, if any, would be expected from such a low topical dose. In comparison, the ocular/oral ratio of ophthalmic drugs is usually much higher, as with Restasis® (cyclosporine) at 1:400 and Vigamox® (moxifloxacin) at 1:700. Clinical trials are necessary to confirm these benefits, clarify the precise mechanisms of action and identify conditions that may benefit most from this novel treatment.

The Effect of Corneal Thickness on the Penetration of Topical Vancomycin

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Purpose: To study the influence of corneal thickness on intraocular penetration of topical ophthalmic drops, using vancomycin 50 mg/ml drops as a model.

Methods: The study included 58 eyes of 58 patients undergoing phacoemulsification cataract extraction. The central corneal thickness was measured by ultrasonic pachymetry on the day of surgery. Thirty minutes prior to the surgery, one drop of topical vancomycin 50 mg/ml was instilled 3 times with 10-minute intervals: 30 minutes, 20 minutes, and 10 minutes before the surgery. At the beginning of surgery, a small specimen of aqueous humor was aspirated and sent to the laboratory for measurement of drug concentration in order to determine the effect of corneal thickness on vancomycin concentration in the anterior chamber.

Results: There was insufficient amount of aqueous humor for analysis in 9 samples, leaving a total of 49 samples. The mean central corneal thickness was 539.7 ± 39.5 microns (range 458-635). The mean vancomycin concentration in the anterior chamber was 0.220 ± 0.209 mcg/ml. There was no significant association between vancomycin concentration and corneal thickness (r=-0.07, p=0.62, Pearson correlation). When patients were divided into 3 groups based on the mean central corneal thickness ±1 SD, no significant differences in vancomycin concentrations (mcg/ml) were encountered: 0.267 ± 0.247 (for corneal thickness <500.2 microns), 0.209 ± 0.212 (for corneal thickness of 500.2-579.2 microns) and 0.200 ± 0.160 (for corneal thickness >579.2 microns) (p=0.73, ANOVA).

Conclusions: Corneal thickness does not influence the penetration of topically applied vancomycin into the anterior chamber. The effect of corneal thickness on penetration of other topical drugs warrants further investigation.

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

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Purpose: To describe a new mouse model that allows for multicolor lineage tracing of limbal and corneal cytokeratin 14 positive (K14+) cells.

Methods: We performed lineage tracing experiments using R26R-Confetti mice to follow K14+ corneal/conjuncival epithelial cells stochastically induced to express one out of four fluorescent genes. We also conducted a controlled alkali burn to the limbus and used long-term live-imaging experiments to follow wound healing.

Results: In hemostasis, radial limbal stripes of slow migrating cells proceeding toward the corneal center were observed. Corneal cells, however, significantly contributed to mild corneal wound repair while large limbal streaks appeared within a week following severe wounding that coincided with partial loss of corneal transparency. Following controlled alkali burn to the limbus, LSC loss resulted in total corneal opacity, neovascularization, and corneal scarring that developed a week after the injury. Eight days post injury large stripes of cells emerged from the conjunctiva reaching the center of the cornea.

Conclusions: This study resolves the conflict and shows unequivocally that the limbus is the major if not only source of corneal regeneration under homeostasis and severe corneal wounding. Following limbal destruction by alkali burn cojunctival stripes ingrowth coincided with clinical deterioration. In conclusion, this model may be efficiently used for better understanding of the mechanisms of corneal regeneration in homeostasis and may aid to developing novel strategies for therapy.

Fabrication of a Stable and Efficient Antibacterial Nanocoating of Zn-CuO on Contact Lenses

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Purpose: To study the efficiency of nanoparticles of zinc doped copper oxide (Zn-CuO) as an antibacterial coating for silicon hydrogel contact lenses.

Methods: By sonochemical deposition process silicone hydrogel contact lenses (BAUSCH & LOMB® PureVision™) were coated with nanoparticles of zinc doped copper oxide. 0.4 wt% and 0.2 wt% coating concentrations were evaluated against Streptococcus epidermidis and Pseudomonas aeruginosa. Coated and uncoated contact lenses were incubated in a bacterial suspension for 24h and then washed thoroughly to remove non-adherent microbes. Following 10-fold serial dilutions, each dilution was plated on a nutrient agar. After appropriate incubation, the numbers of colony forming units of bacteria from coated and uncoated lenses were enumerated. All experiments were repeated three times.

Results: Both of the coating concentrations showed statistically significant reduction in adhesion of P.aeruginosa ($p=0.043$) and S.epidermidis ($p=0.011$).In the adhesion assay of P.aeruginosa there was almost a 100% reduction in adhesion in both the medium and high coating concentrations with a mean reduction of 4.64 logs and 4.95 logs respectively. There was no statistical significance between the two coating concentrations ($p=0.817$).In the adhesion assay of S.epidermidis there was a 100% reduction in bacterial adhesion with a mean reduction of 2.72 logs with no bacterial adhesion seen in both concentrations of coated lenses in all three experiments.

Conclusions: Nanocoating of Zinc doped copper oxide shows promising results in-vitro as an antibacterial coating for contact lenses. Physical properties such as refractive index, oxygen permeability and biocompatibility of the coated lenses have to be further evaluated.

The Effect of Graft-Recipient Collagen Lamellar Axis Discrepancy on Visual Acuity Following Descemet Stripping Automated Endothelial Keratoplasty

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Purpose: To evaluate whether a discrepancy between the orientation of graft and recipient collagen lamella can significantly affect visual acuity following Descemet Stripping Automated Lamellar Keratoplasty.

Methods: A multicenter cohort study of eyes that underwent DSAEK for Fuchs' endothelial dystrophy or pseudophakic bullous keratopathy between May 2008 and January 2013 at Villa Serena-Villa Igea private Hospitals (Forlì, Italy) and at Santa Maria Nuova public hospital, (Reggio Emilia, Italy). We have included eyes with distance corrected visual acuity of 8/10 or better, no ocular comorbidities, and clear cornea. The main outcome measure was graft-recipient axis discrepancy of lamellar orientation around the visual axis as assessed by means of polarimetric intereferometry.

Results: Twelve eyes were included in this study. Eight eyes had a spectacle corrected distance visual acuity of 8/10, three eyes had 9/10 and one had 10/10. In 8/12 (66.7%) eyes, two discernable axes of collagen lamellar orientation, were identified and were all 30 degrees or more apart (range 30-90). In two eyes only one axis was identified and in another two eyes, two axes 20 and 17 degrees apart were identified. The eye with 10/10 visual acuity presented a discrepancy of 17 degrees between lamellar axes.

Conclusions: A discrepancy between the lamellar orientation of the graft and the recipient is compatible with excellent visual acuity following DSAEK.

The Therapeutic Effect of Accelerated Photoactivated Chromophore for Infective Keratitis– Corneal Collagen Cross-linking (PACK-CXL)

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Purpose: To evaluate the therapeutic effect of ultraviolet A (UV-A)-corneal crosslinking (CXL) with riboflavin on therapy-refractory infectious keratitis.

Methods: Eleven patients with moderate-severe infectious keratitis associated with corneal melting were treated with accelerated CXL (30 $mW/cm^{2)}$ at the department of the Soroka University Medical Center. The PACK-CXL was performed as additional therapy in cases with no respond to appropriate topical and systemic antibiotic therapy. Before the procedure, corneal epithelium was removed and hypo-osmolaric 0.1% riboflavin drops were applied during 25 minutes. Then the corneas were irradiated with UV-A light (365 nm) with an irradiance of 30 mW/cm2 for 3 minutes.

The grade of ulcers, size of epithelial defects, and area of infiltrates were recorded on admission and during the follow up in our ophthalmology department and the outpatient clinic. Additional data (demographic and clinical) was collected from the patients' medical records. Analysis was performed using Excel software.

Results: In period of six months (May-November 2015) 11 eyes with moderate-severe infectious keratitis were treated with PACK-CXL in our department. Six patients were man and 5 women. The mean age of study population was 53.27 [15-90]. The follow-up after PACK-CXL ranged from 1 to 6 months. The etiology of the infected keratitis were: 5 patients after keratoplasty surgeries, 2 contact lens wearier, 2 after corneal trauma and other 2 after ocular surgeries. The bacterial cultures were positive in 7 patients (3 for Pseudomonas Aeruginosa, 2 for Staphylococcus Aureus, 2 for candida parapsilosis). The mean PACK-CXL day of treatment was 5.8 [range 1-16] days after admission. In 10 cases, the progression of corneal melting was halted after PACK-CXL and only in one case therapeutic keratoplasty was performed. The average day of re-epitalization was 10 [range 4-22] days and the mean hospitalization period was 9 [4-16] days.

Conclusions: In this study we found that PACK-CXL is a promising treatment option with beneficial effect for patients with therapy-refractory infectious keratitis that can help to avoid emergency keratoplasty.

CHST6 Gene Mutations and in-vivo Assessment of Two Families with Macular Corneal Dystrophy

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Purpose: To identify the molecular cause of Macular Corneal Dystrophy (MCD) in two families and characterize them phenotypically.

Methods: Five affected members, four of Family-A, and a sporadic Family-B patient were recruited. Patients underwent a comprehensive ophthalmic examination including modern in-vivo technologies (anterior segment optical coherence tomography (OCT), ultrasound bio-microscopy (UBM), and Scheimpflug camera (Pentacam)). Special attention was given to the assessment of posterior corneal changes which may have influence on the surgical outcome when Deep Lamellar Keratoplasty (DALK) or full thickness Penetrating Keratoplasty (PKP) are considered. Blood samples were obtained from participants for DNA extraction, and the coding exons of the CHST6 gene were screened for mutations by direct sequencing.

Results: Affected patients developed grey, punctuate epithelial stromal corneal opacities, which lead to progressive opacification, and loss of visual acuity. Photophobia, foreign body sensation and recurrent erosions occurred frequently. Corneal transplantation was required in two patients (four eyes); each patient underwent PKP in one eye, while in the other DALK was performed. Recurrence of MCD in the donor eye was documented in one of the DALK eyes. Pentacam assessment marked diffuse corneal thinning and anterior lamella depositions. OCT demonstrated clearly anterior lamellar deposits, however peripheral and posterior pathologies were much less obvious. With UBM we were able to demonstrate not only the superficial pathologies but also deeper stromal opacities and loss of continuity as well as protrusions of the posterior corneal lamella which were not evident by the other devices.

In Family-A, a novel homozygous bi-nucleotide CHST6 deletion was identified (c.1089-1090delTG; p.E364Gfs8*), while in Family B a recently described missense mutation, (c.191C>T;p.P64L) was found.

Conclusions: UBM had a better yield than OCT or Pentacam in demonstrating deep corneal pathologies which may have prognostic value on surgical outcome. We also report a yet unrecognized null mutation and a recently described missense mutation; reconfirming the genetic heterogeneity of CHST6 in various MCD populations.

Albinism in the Israeli Jewish population: Causative Mutations and Phenotypes

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Purpose: To study the causative mutations and phenotypic spectrum in the Israeli Jewish albino population

Methods: Phenotypic evaluation included description of hair, eye and skin color, presence of nevi and ability to tan. Eye examination included visual acuity, presence of nystagmus, transillumination, visibility of choroidal vessels and hypoplasia of the macula. Genetic investigation included origin of grandparents and detailed pedigree analysis. Mutation analysis was performed on extracted blood DNA by PCR followed by restriction enzyme digestion, haplotype analysis and sequencing.

Results: We have screened almost 500 Israeli Jewish albinos for mutations in *TYR, P, SLC45A2, GPR143* and *HPS3* genes, causing OCA1, OCA2, OCA4, OA1 and HPS3, respectively. At least one mutation was detected in about 90% of the tested albinos. *TYR* is the major gene causing albinism (70%), and *P* mutations were detected in about 28% of patients. While the two *TYR* mutations were identified in 98% of albinos, in only 61% the two *P* mutations were identified, though linkage to *P* was demonstrated in several large families. Sequencing of the *P* gene in albinos with one *P* mutation revealed many polymorphisms. Comparison of haplotypes of the allele with unidentified mutation indicated more than one missing *P* mutation. Detailed phenotypes were correlated with *TYR*, *P* and *SLC45A2* mutations. While the severe phenotype, OCA1A, was always caused by mutations in *TYR*, no correlation exists between OCA1B and OCA2 phenotypes and the causative genes / mutations; the identified mutations can be divided into "severe" (causing OCA1A) "mild" and "very mild" (OCA1B/2) – with overlapping spectrum of phenotypes. Combination of "severe" and "mild" mutations resulted in severe OCA1B/2 phenotype. Interestingly, the phenotype of albinos having two mutations in either *TYR* or *P* and one mutation in the other gene was within the phenotypic spectrum of the major gene, and was not influenced by the additional mutation.

Conclusions: *TYR* and *P* are the causative genes among Jewish albinos. High detection rate was demonstrated for *TYR* mutations, while several *P* mutations were not identified by exon sequencing. In groups of albinos sharing the same genotype the spectrum of clinical manifestations can be determined and used for prediction of the range of severity of clinical manifestations in albino newborns.

A Combination of Oculopharyngeal Muscular Dystrophy and Inherited Retinal Dystrophy in Bukharan Jews due to Linked Mutations in *PABPN1* and *NRL*

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Purpose: To investigate the basis for inherited retinal dystrophy (IRD) in Bukharan Jews with oculopharyngeal muscular dystrophy (OPMD) who are homozygotes for a mutation of *PABPN1*.

Methods: PCR amplification and direct sequencing were used to test for mutations. One homozygote and three heterozygotes underwent complete ophthalmic examination.

Results: A recessive mutation of the *NRL* gene, p.R31X, was linked to a dominant mutation of the *PABPN1* gene, (GCN)13, on chromosome 14q11.1. Of 15 chromosomes from unrelated Bukharan Jewish OPMD patients, 12 harbored the *NRL* mutation. While heterozygotes for the *NRL* mutation demonstrated normal ERG responses, homozygotes developed IRD, which is a variant of Enhanced S-Cone Syndrome.

Conclusions: Our findings provide an explanation for the occurrence of IRD in Bukharan Jewish OPMD homozygotes. Moreover, they indicate that Bukharan Jewish OPMD patients are at high-risk for carrying the *NRL* mutation, and should be offered appropriate genetic counseling and testing.

A Variant of Enhanced S-Cone Syndrome due to a Recessive *NRL* Mutation

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Purpose: To characterize the form of an inherited retinal dystrophy in a patient homozygous for an *NRL* mutation.

Methods: The patient underwent complete ophthalmic examination, including best-corrected visual acuity, biomicroscopic examination, optical coherence tomography (SD-OCT), and fundus autofluorescence. Detailed electroretinography (ERG) testing was conducted including expanded ISCEV protocol for light-adapted and dark-adapted conditions, measurements of S-cone function and ON-OFF light-adapted recording.

Results: A patient homozygous for both a recessive mutation of the *NRL* gene and a dominant mutation of the *PABPN1* gene was examined. Ocular complaints were of reduced central vision and nyctalopia. Funduscopy revealed yellow pigment clumps. SD-OCT demonstrated waviness of the PR-RPE and choroicapillaris layers, hyper-reflective foci above the RPE and hyper-reflectivity of the choroicapillaris layer. ERG responses were dominated by short-wavelength-sensitive mechanisms, with no detectable rod function, very similar to the ERG responses in enhanced S-cone syndrome (ESCS).

Conclusions: A recessive *NRL* mutation leads to dominant S-cone responses with no rod function, similar to ESCS caused by *NR2E3* mutations.

Variable Clinical Presentation of X-Linked Dominant Retinitis Pigmentosa Caused by a Nonsense Mutation in RPGR Gene in Two Unrelated Bedouin Israeli Families

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

Methods: Two large families of Bedouin origin affected with RP were identified in southern Israel. All affected individuals underwent a thorough ophthalmologic examination and most had electroretinography (ERG). Blood samples were collected, and genomic DNAs were extracted. Linkage analysis was completed, and two-point LOD scores were calculated. The coding regions and intron/exon boundaries of the Retinitis Pigmentosa GTPase Regulator (*RPGR*) and Retinitis Pigmentosa 2 *(RP2)* genes were amplified by PCR and then sequenced directly. RPGR mutation screen was performed in 100 ethnically-matched controls.

Results: In both families inheritance pattern was X-linked. Affected males exhibited severe early onset disease with extinguished ERGs. They had variable fundus findings, with bone spicule-like pigment clumping evident only in a few patients. Most had myopia, but several were hyperopic. Many obligate carrier females had disease manifestations, which varied from minor symptoms to severe visual disability. ERG amplitudes were reduced and delayed under photopic and scotopic conditions. Female findings were highly variable between families, within the same family and even between the two eyes. High myopia was common, and six females had anisometropia of 2 diopters or more. Linkage analysis yielded a lod score of 2.93 and 1.37 at $\theta = 0$ with DXS1068 on chromosome Xp21.1 for these two families, respectively. This region harbors the *RPGR* and *RP2* genes. Sequencing of these two genes identified a nonsense mutation (c.259G>T, p. Glu87X) in exon4 of *RPGR* in both families. This mutation predicted to cause premature termination of the protein was not present in any of 100 ethnically-matched controls.

Conclusions: Our results suggest that mutations in *RPGR* are responsible for RP in two unrelated Bedouin families. Heterozygous females exhibited disease manifestations, which is compatible with X-linked dominant inheritance. Highly variable phenotype was detected in affected individuals, especially in heterozygous females. This includes marked inter- and intrafamilial variability, and discordant presentation among the two eyes. Our findings broaden knowledge on inheritance pattern, molecular basis and spectrum of phenotypes of XLRP. They also facilitate early diagnosis, screening, and genetic counseling in the Bedouin population.

Single Nucleotide Polymorphisms in the rs1495965 Locus of IL23R-IL12RB2 Gene is Highly Associated with Behcet's Uveitis, and Vary between Populations, thus Accounting for Differences in Disease Prevalence

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Purpose: Single nucleotide polymorphisms (SNPs) in the *IL-10* gene (rs1518111, rs1800872, rs1800871) and the *IL23R-IL12RB2* locus (rs1495965) were found to be highly associated with Behcet's disease. We tested the frequency of these SNPs in Israeli and Turkish patients with Behcet's disease and their possible relationship with ocular inflammation.
Methods: Blood samples were collected from 99 Behcet's patients, 86 with uveitis (Israeli (25); Turkish (64)) and 13 without uveitis (Israeli), uveitis patients of other etiologies (n=38; Israeli) and 88 healthy subjects (Israeli (20); Turkish (68)). Genomic DNA was extracted from peripheral blood leukocytes and genotyped. Findings were compared among the groups.
Results: The mutant A allele, rs1800871 located in the *IL-10* gene was found highly prevalent in both Behcet's uveitis and healthy control samples alike; Turkish (88.2%, 95.3%, respectively) and less in the Israeli populations (60%, 64%, respectively). These allele frequencies differ substantially between the two populations for both the behcet's uveitis group ($p<0.001$) and the control group ($p=0.008$). The mutant G allele of rs1495965 located in the *IL-23R* gene is highly prevalent in the healthy Turkish population compared to the Israeli (77.9%, 27.8%, $p<0.001$), interestingly, no difference were found between Behcet's uveitis patients of both populations (79.4%, 66.7%, respectively). Both SNPs (rs1800871 and rs1495965) were significantly more prevalent in Behcet's patients (with and without uveitis) compared to uveitis of other etiologies ($p\leq0.001$).

Conclusions: Turkish and Israeli healthy populations differ in the prevalence of rs1800871 mutant allele, possibly, accounting for the differences in disease prevalence between these populations. The rs1495965 mutant variant is associated with the affected Behcet' uveitis patients, thus may have a role in the pathogenesis of this disease. Further studies are required to map other healthy populations, and to search for the "second hit".

Mild Phenotype of Aniridia: a Missed Diagnosis of a Genetic Blinding Disease

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Purpose: Aniridia is a rare pan-ocular disorder characterized by complete or partial absence of iris and other severe ophthalmic anomalies. Heterozygous mutations in the *paired box 6* (*PAX6*) gene are the major cause of the classic aniridia phenotype. This study presents four patients who were mis-diagnosed for years, all suffering from visual impairment/blindness with very mild ocular findings and an identified mutation in *PAX6.*

Methods: Four patients from three unrelated families were identified: one family involved a mother and her daughter and the other two families involved a single patient each. The third patient reported extended familial history of visual impairment (family was not available for examination). The fourth patient was a sporadic case. Full ocular examination was performed on all patients. Genomic DNA was isolated from peripheral blood of all participants for genetic analysis. Sanger sequencing was used to screen *PAX6* exons and adjacent intronic sequences for mutations. Exome sequencing was performed in one case.

Results: In all four studied patients, the phenotypical findings in the anterior segment were atypical for aniridia with only mild expression of pupillary abnormality and corectopia. Three from our patients did not show lack of iris tissue, but only a minimal pupillary decentration. The fourth patient had a small iris coloboma. Foveal hypoplasia and nystagmus were present in all subjects. Pre-senile cataract, corneal pannus, and optic nerve hypoplasia were seen in different combinations in our patients. None of the patients had glaucoma at the time of diagnosis. Mutation analysis of the *PAX6* gene in affected members of Family #1 revealed a previously described missense mutation, c.97G>Cp.(A33P). In family #2, we identified a novel deletion of 9bp, c.233_241del9bpp (V78_P81delinsA). In the sporadic case a novel missense mutation was identified by whole-exome sequencing analysis, c.197T>C p.(C66R).

Conclusions: The possibility of a mild phenotype of aniridia should be kept in mind, when diagnosing patients affected by nystagmus and foveal hypoplasia. Searching for minimal pupillary changes and/or peripheral corneal pannus, in order not to miss the hidden diagnosis of aniridia, is imperative. The importance of the recognition of these mild phenotypes lies in the fact that correct diagnosis will allow the family to obtain appropriate genetic testing and counseling, and offer the possibility of pre-natal diagnosis or pre-implantation genetic testing to stop the transmission of this severe disease to other family members.

Whole Exome Sequencing Reveals a Homozygous Splicing Mutation in CEP78 as the cause of Atypical Usher Syndrome in Eastern Jewish Patients

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Purpose: To identify the cause of disease in patients with inherited retinal diseases, and particularly in patients with atypical Usher syndrome, using whole exome sequencing (WES)

Methods: The tenets of Helsinki Declaration were followed for all human studies. Patients underwent a comprehensive ophthalmic evaluation, including ophthalmic ancillary tests as well as hearing tests. WES was performed using Nextera Rapid Capture Expanded Exome kit (Illumina, San Diego, CA, USA).

Results: Using WES on the DNA sample of the index case (MOL0679-1 of an Eastern Jewish origin) we identified a homozygous splice-site variant (c.893-1G>A) in the acceptor site of exon 7 of *CEP78*. The variant was verified by Sanger sequencing and is absent from public variant databases. The affected brother of the index case was also homozygous for the variant. Both patients suffer from a cone-rod dystrophy phenotype with minimal fundus findings accompanied by sensorineural hearing loss involving mainly high frequencies. Mutation analysis in a set of 245 index cases with inherited retinal degenerations revealed another patient of the same origin who had a similar phenotype and was homozygous for this mutation (p=0.0495 by chi square analysis). RT-PCR analysis of *CEP78* RNA in blood samples of the patients and controls revealed that the c.893-1G>A mutation causes skipping of exon 7 leading to deletion of 65bp that can lead to a frame shift mutation followed by a truncated protein (p.Asp298Valfs*17**)**. The mutation is likely to either be null or produce a short and mutated protein lacking most of the wt protein sequence. The expression level of the mutant transcript was lower than the wt allele, as is expected upon activation of the nonsense mediated mRNA decay mechanism. RT-PCR analysis of 15 human tissues revealed expression in a few tissues (mainly brain and spleen) with the retina showing the most intense PCR amplification.

Conclusions: CEP78 is a centrosomal protein that was reported previously to interact with c-nap2, encoded by the *CEP250* gene that we reported earlier to cause atypical Usher syndrome. Here we show that a mutated CEP78 protein can cause a different, yet another atypical Usher phenotype**.**

Heterozygous and Homozygous *BEST1* and *RDS* Mutations in Israeli and Palestinian Patients with Best Vitelliform Macular Dystrophy

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Purpose: To characterize the clinical phenotype and molecular genetic causes of Israeli and Palestinian patients with Best Vitelliform Macular Dystrophy (BVMD).

Methods: Thirty Israeli and Palestinian families with BVMD were recruited for clinical and genetic workup from six different medical centers in Israel and Palestinian territories. The patients underwent comprehensive ophthalmological examination, and ancillary tests were performed including: electro-oculography (EOG), full-field electroretinography (ffERG), optical coherence tomography (OCT), fundus autofluorescence photography (FAF) and wide field fundus photos. Blood samples were drawn, genomic DNA purified and *BEST1* was screened for mutations by direct Sanger sequencing.

Results: We recruited 82 patients of 30 families with BVMD while 22 families were genetically solved (~ 73%). All affected subjects have normal ERG and diminished EOG responses. Genetic analysis revealed 10 heterozygous *BEST1* missense mutations in 17 families, therefore confirming the more common autosomal dominant inheritance pattern of Best disease. Seven of the ten mutations were novel (p.Trp93Arg, p.Glu98Asp, p.Met107Arg, p.Ser108Arg, p.Gly135Asp, p.Asp303Val and p.Ser111Pro); three mutations (p.Arg218His, p.Asn296Ser and p.Ala10Val) were reported previously. We identified homozygous *BEST1* mutations in three Arab-Muslim families and one Ashkenazi Jewish. One mutation was novel (p.Arg596*) while other three mutations were reported previously (p.Leu472ProX10, p.Arg25Gln, p.Arg128His). One family with adult onset BVMD harbored a mutation in the *RDS* gene (p.Ser212Thr). One subject in family MOL0335 presented with mild Best disease while the other affected subjects in the same family had typical BVMD phenotype demonstrating the different expressivity of this AD disease. In addition, we present here a family (MOL1171) with severe BVMD, three siblings harbouring a heterozygous mutation (p.Asp303Val) who developed choroidal neovascularization at a very young age (mean age of 9 years old) and were treated by multiple intravitreal anti-VEGF injections with poor response.

Conclusions: We report here novel heterozygous and homozygous mutations in *Best1* gene among Israeli and Palestinian BVMD patients. To our knowledge, this is the largest cohort of BVMD patients reported up to date among these populations.

RS1 gene mutations and clinical assessment of four patients with X-linked Retinoschisis (XLRS)

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Purpose: To identify the molecular cause of X Linked Retinoschisis (XLRS) in four patients, characterize them phenotypically and document treatment effects.

Methods: Four non-related patients were recruited. They underwent a comprehensive ophthalmic examination including optical coherence tomography (OCT) and color retinal photographs. Blood samples were obtained from participants for DNA extraction, and the coding exons of the RS1 gene were screened for mutations by direct sequencing. Two patients were treated with Nepafenac and Acetazolamide.

Results: Affected patients developed impaired vision starting at childhood. Vitreous examination revealed vitreous veils and turbidity. Retinal changes included stellate spokelike maculopathy, and peripheral vitroe-retinal adhesions and strands. OCT demonstrated cystic spaces primarily in the inner nuclear and outer plexiform layers of the retina.
Three different RS1 gene mutations (p.G14OR; p.R141C; p.P193L) were identified in patients of Balkanise Jews, Bedouin and Ashkenazi Jews ethnicities, respectively. Mutation screening in the fourth patient is still underway. Our limited experience with Nepafenac and Acetazolamide treatments was not effective.

Conclusions: We report three different mutations in Israeli XLRS patients reconfirming the wide genetic heterogeneity of RS1 mutations. There was no favorable response for treatment either with Nepafenac or Acetazolamide.

Novel Method for Laser Suturelysis after Trabeculectomy

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Purpose: Trabeculectomy is the most common surgical procedure to reduce the intra ocular pressure (IOP) of eyes with uncontrolled glaucoma. The surgery includes the formation of a scleral "trap door" that is usually sutured with 10/0 nylon sutures. Laser suturelysis is often indicated to titrate the flow throughout the scleral flap. Suturelysis may be difficult to achieve, especially in patient with less than total cooperation. The purpose of this study is to describe a new method for laser suturelysis of scleral sutures after glaucoma surgery.

Methods: The Valon TT multispot laser is a new laser system, capable of delivering a series of multiple laser spots by one single shot. The system is a 532 nm (green) laser, originally designed for retinal treatments, with a user-defined, programmable, laser patterns. We configured the system to deliver a series of 5 consecutive laser spots, 50 micrometer each, to form a pattern of linear line, 250 micrometer long. This "laser line" was targeted perpendicular to the suture to be opened, and the laser was delivered using a standard suturelysis lens after good visualization.

Results: In all patients treated with this method, a fast and easy suturleysis was achieved by one single shot. Both in-vitro and in-vivo videos documented the method.

Conclusions: The new method enables to achieve a safe and quick laser suturelesis. The method is especially convenient for patients with low cooperation or uncontrolled head or eye movements.

Digoxin Derivatives with Selectivity for the α2β3 Isoform of Na,K-ATPase Potently Reduce Intraocular Pressure

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Purpose: Glaucoma is associated with increased pressure in the eye, which can be alleviated by increasing outflow or reducing inflow of aqueous humor.
The α2β3 isoform of Na,K-ATPase powers production of aqueous humor. We describe derivatives of a classical Na,K-ATPase inhibitor, digoxin, with selectivity for the α2β3 isoform, and show that topical application of α2β3-selective derivatives to rabbit eyes efficiently reduces pharmacologically-raised or basal IOP.

Methods: IOP measurements were made with a Pneumatonometer (Model 30, Reichert technologies) in New-Zealand white rabbits, after raising IOP with 4AP (40mg/ml), or on basal IOP after addition of one drop of 1mM digoxin derivatives to the right eye(RE) and one drop of PBS to the left eye(LE) as control. A local anesthetic, Oxybuprocaine HCl (0.4%, 25 µl) was applied to each cornea before IOP measurements. For comparison of DcB with Latanoprost, three groups of five rabbits were used. Rabbits treated with Latanoprost, received the medication daily for 5 days. On the day of the experiment rabbits were treated at 5 min interval with one drop of 1mM DcB, one drop of 0.005% Latanoprost(XalatanTM, Pfizer), one drop each(RE), or normal saline(LE, Control). IOP was measured every hour for 12 hours, and after 24 hours.
Corneal thickness (µm) was measured using an ultrasonic pachometer(Sonogage, Cleveland, USA). For histologic examination, animals were sacrificed, eyes were removed, fixed in 10% neutral buffered formalin, trimmed at 4µm, and stained with hematoxylin and eosin.

Results: Several new digoxin derivatives, the isobutyl, methylcyclopropyl and cyclobutyl derivatives, DiB, DMcP and DcB, have rather strong selectivity for α2β3:α1β1 reaching 16- 22- and >33-fold, respectively compared to digoxin.
≥10µM concentrations of DMcP or DcB prevented 4AP-induced rise in IOP. Both are considerably more effective than the optimal compound in our previous study, DMe. Higher concentrations (0.1-0.3mM) of either reduced IOP below the starting value. Both Derivatives reduced basal IOP by 20-25%.
Compared to Latanoprost, steady-state IOP was lower by 3.5±0.15, 2.6±0.11 and 3.44±0.39mmHg for DcB, Latanoprost and DcB plus Latanoprost, respectively.
Reduced IOP was maintained by DcB for about 8 hours. With DcB plus Latanoprost low IOP was maintained for 24 hours. There was no detectable effect of either drug on corneal thickness. Histologic examination did not reveal significant damage to the anterior chamber or retina

Conclusions: α2β3 plays a central role in production of aqueous humor. Digoxin derivatives, such as DcB, might become interesting candidates for development as drugs for treatment of glaucoma.

Safety and Efficacy of Sub-Conjunctival 5-Fluorouracil Injections after Trabeculectomy Surgery

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Purpose: Trabeculectomy is the most common surgical procedure to reduce the intra ocular pressure (IOP) of eyes with uncontrolled glaucoma. The surgery includes the formation of a scleral "trap door" and conjunctival pouch (Bleb). Scaring of the sclera and/or conjunctiva are the most common reasons for trabeculectomy failure, and anti-metabolic agents are usually used intra-operatively to prevent this scar formation. The purpose of this study was to evaluate the effect of postoperative sub-conjunctival 5-fluorouracil (5FU) injections on failure rates of trabeculectomy surgery.

Methods: The study is a retrospective cohort study from the Department of Ophthalmology database of Soroka Hospital. The study population consists of patients who underwent Trabeculectomy surgery in the years 2010-2015. Starting from 6/2012 patient began to be treated with subconjunctival 5FU after surgery in appropriate cases. The comparison was made between a group of patients who underwent surgery between the years 2010-6/2012 vs. a group of patients who underwent surgery between the years 6/2012-2015. The study examined the following parameters: intraocular pressure, visual acuity, number of pressure-lowering medications, complications and surgical interventions. The data was collected for all patients pre-operation, at 6 weeks, at 3 months and at 9 months after surgery.

Results: Forty four eyes were included in group 1 (without 5FU, till 6/2012) and 68 eyes were included in group 2 (with augmenting 5FU in appropriate cases, between 6/2012 and 2015). There was a trend towards higher success rates in group 2 (57% vs. 68%, in 3 months, and 52% vs. 63% in 9 months, respectively) but this trend did not reach statistical significance. There was no difference in safety issues between the two groups.

Conclusions: The use of postoperative sub-conjunctival 5FU injections after trabeculectomy is safe and effective. A larger study is needed to further prove our findings.

Diurnal Variation of Intraocular Pressure in EX-Press Valve Surgery

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Purpose: To compare IOP fluctuation in the diurnal tension curve (DTC) of glaucoma patients under ocular hypotensive therapy, with those under EX-Press Valve Surgery.

Methods: The study included open-angle glaucoma (OAG) patients using ocular hypotensive medication (medical group, N:17), and OAG patients previously submitted to one EX-Press Valve Surgery, without or with medication at the time of the study [surgical success (N: 12) and failed surgical groups (N:8)]. DTC was measured during a 24-H period in at 2-hour intervals.

Results: The IOP peak and fluctuation during DTC were significantly greater in the medical group than in the surgical success group. The surgical success group had lower IOP at 4 pm, 2 am and 4 am, as compared to the medical group. The DTC OF failed surgical group had was similar to the medical group.

Conclusions: DTC pattern of patients with EX-Press Valve Surgery could represent an additional benefit of surgery in controlling the intraocular pressure of glaucomatous patients.

Through Wnt Signaling Pathway, NPCE Derived Exosomes Modulate Pan-Cadherin Expression in Trabecular Meshwork Cells

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Purpose: Cross-talk between the PI3K/AKT and Wnt signaling has been shown to regulate cadherin-dependent cell adhesion and glaucoma pathogenesis. The purpose of this study is to extend the understanding of signaling transference between the non-pigmented ciliary epithelium (NPCE) and the trabecular meshwork (TM) by NPCE derived exosomes. We tested the hypothesis that exosomes isolated from NPCE cells would affect Wnt and PI3K/AKT signaling in TM cells.

Methods: Exosomes were isolated by differential ultracentrifugation from NPCE cells condition media. Using confocal microscopy we study the specific interaction of NPCE derived exosomes with TM cells along their ability to accumulate DiD-labled NPCE-derived exosomes along time vs. different other cell lines. In order to investigate the presence of the relevant signaling molecules, immunoblotting of exosomal proteins was performed. Confluent TM cells were treated with extracted NPCE exosomes and changes in the TM cells levels of the mRNA and Wnt, Akt/PI3K proteins were determined by real-time quantitative PCR and Western blot analysis, respectively. The effect of exosome exposure on pan-cadherins expression in TM cells was experienced by flow cytometry.

Results: Specific accumulation of NPCE exosomes in TM cells was found while, other cell lines hardly took up exosomes. Western blot analysis of exosomal proteins revealed the expression of a major Ser/Thr phosphatase, PP2A that is involved in AKT inactivation. We found a 3-fold AKT protein decrease in TM cells after 2 hr of exosome treatment. When exosomes were incubated with TM cells for 6 hr a significant decrease ($p<0.01$) in β-catenin, p-GSK and pan-cadherin proteins expression was found without a significant change in the corresponding mRNA expression. Furthermore, AXIN2 mRNA expression decreased significantly ($p<0.01$) in TM cells following exposure to NPCE derived exosomes.

Conclusions: Collectively, our data showed that NPCE derived exosomes decreased cell-cell adhesion proteins. Reduced cadherin expression may be mediated by exosomes through Wnt and PI3K/AKT signaling. Wnt pathway proteins were down-regulated in TM by exosomes. In contrast, the relative mRNA levels of target genes remained unchanged. Therefore, we suggest that suppression of Wnt signaling might involve exosomal miRNA.

Evaluation of EX-Press Valve Blebs in Glaucoma Patients by Anterior Segment Optical Coherence Tomography

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Purpose: To assess the qualitative (morphological) and quantitative characteristics of filtering blebs after EX-Press implantation surgeries using anterior segment optical coherence tomography and to compare between successful and unsuccessful surgery characteristics.

Methods: A Prospective Cross-sectional study, using Topcon anterior segment OCT to assess filtration bleb's features in glaucoma patients who had undergone Ex-Press Filtration device surgery, and a control group of non-glaucomatous diabetic patients examined during regular follow-up. This evaluation was done by measuring bleb thickness (including conjunctiva, episclera and sclera) and assessing its different morphological features. Complete successful blebs were defined as a 30% drop in baseline IOP without ocular hypotensive medication and partial success blebs reduce the IOP by 30% with the concomitant use of IOP-lowering medications.

Results: Thirty three eyes of 31 patients who underwent EX-Press filtration device surgery were imaged during an average follow-up of 7.9 months. Sixteen eyes had successful blebs which were thicker compared to partially successful blebs and failed blebs (844 µm vs. 710 µm, p=0.009, 883 µm vs. 713 µm, p=0.045, respectively). The qualitative bleb morphology features consisted of: hyper- or hypo-reflectivity areas, layered vs. diffuse bleb shape, filtration channels and the existence of microcysts in the filtration area. These characteristics were not unique to successful blebs.

Conclusions: Quantitative features of bleb filtration area following Ex-Press surgery can be readily measured using anterior segment OCT. Successful Ex-Press blebs are accompanied by a thicker filtration area. Anterior segment OCT is a promising tool for imaging and evaluating bleb morphological features post EX-Press surgery.

A New Zebrafish Model for Studying Molecular Genetic Mechanisms Underlying Fibrotic Cataract

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Purpose: To identify molecular genetic mechanisms underlying cataract that forms as a result of a fibrotic reaction**.**

Methods: We used a forward genetic screen to identify mutations that interfere with eye and lens development in zebrafish. We cloned the mutant gene using whole-genome sequencing and RNA-Seq. We analyzed the phenotype using tissue-labeling techniques, e.g. immunohistochemistry, *in situ* hybridization and histological stainings and used small molecule inhibitors to assess the contribution of TGF-beta signaling.

Results: One identified mutation led to the formation of a cellular mass arising from the lens epithelium, thereby generating cataract. Additionally, lenses in the mutants showed a dislocated phenotype (ectopia lentis). We identified the mutant gene as *plod3*, which encodes Lysyl hydroxylase 3 (Lh3). Molecular analyses show that mutant lens epithelial cells and the cellular masses exhibit hallmarks of fibrotic reaction. Inhibition of TGF-beta signaling blocks the fibrotic reaction but not the lens dislocation phenotype.

Conclusions: Loss of Lh3 activity results in a fibrotic reaction in the lens epithelium, leading to the formation of cataract and to ectopia lentis. This novel *in vivo* model of fibrotic cataract should enable the search of pharmacological treatment to inhibit fibrosis in the lens, a complication of cataract surgeries.

Predicting Cataract Surgery Time Based on Preoperative Risk Assessment

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Purpose: Operation room (OR) time is an expensive resource that should be optimized to reduce costs. Individual pre-operative risks parameters (PORS) assessment may aid in predicting cataract surgery time.
Our aim was to examine the feasibility of predicting surgery time based on a patient's PORS score and designated surgeon.

Methods: Dedicated software was developed and known risk factors for cataract surgery were integrated into it. PORS were assigned to each patient in the preoperative meeting and the risk score was calculated.
150 Patients were divided according to a standard classification into low risk group (PORS≤ 2) and high risk group (PORS>5).
Main outcome measures were duration of surgery was retrospectively analyzed in each group and regression analysis of OR time was conducted for each surgeon

Results: Patients in the high PORS group had longer surgery times when compared with patients in the low PORS group (37.6 vs. 20.9, $p<0.001$). Risk scores positively correlated with surgery time ($r=0.28$, $p=0.01$).
Prediction equations for the OR time demonstrated for two surgeons that every increase in 1 risk point added 2.2 or 3.5 minutes to the OR time. Outliers (more than one standard deviation (SD) from each surgeon's surgery mean time) had more than twice the risk score of cases within one SD from the mean

Conclusions: The PORS system may be a useful tool for predicting OR time based on individual patients risk group and may improve OR scheduling.

Post Cataract Surgery Administration of oral Acetazolamide

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Purpose: Intra ocular pressure (IOP) elevation in the early post-operative period after cataract surgery is not rare. Since severe IOP spikes are potentially sigh threatening, many surgeons routinely give one to four tablets of acetazolamide after the surgery in order to reduce the risk of IOP spike development. The purpose of this study was to evaluate the efficacy and safety of this routine after an uneventful cataract surgery in patients without other risk factors for IOP elevation.

Methods: In this retrospective comparative study, the files of patient who underwent an uneventful cataract surgery were reviewed. One group was consisted of patients that received 4 tablets of acetazolamide after the surgery and the second group was consisted of patients that did not receive any IOP lowering treatment. Patients with any other condition that may have effect on IOP or vision, were excluded from this study. IOP and best corrected visual acuity (BCVA) were recorded in 1 day, 1 week and 1 month post operatively.

Results: One hundred and thirty one patients were included in the study, 50.4% of them routinely received 4 tablets of acetazolamide after the surgery. There was no statistically significant change in IOP or BCVA between both study groups in all three points of time.

Conclusions: In an uneventful cataract surgery, in patients without risk factors for IOP elevation, routine administration of oral acetazolamide may be unjustified.

Wound Temperature Profiles of Coaxial Mini-Incision versus Sleeveless Micro-Incision Phacoemulsification

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Purpose: To compare corneal temperature profiles at the surgical wound of coaxial mini-incision (2.4 mm) cataract surgery and sleeveless micro-incision (1.1mm) cataract surgery

Methods: Twenty patients underwent bilateral cataract surgery within a one month period. One eye was operated on by conventional coaxial mini-incision (2.4 mm) phacoemulsification. The second eye underwent microincision surgery using a naked phacoemulsification tip and a specialized 19G anterior chamber maintainer as the sole fluid source (Tri-MICS technique). Patients had moderate bilateral cataracts with no other anterior segment pathology. Temperature at the corneal wound was constantly recorded using infrared thermal imaging.

Results: Mean temperatures at the corneal surgical wound were not significantly different between the coaxial and sleeveless groups (31.1^{o}C ± 2.3 vs. 31.0^{o}C ± 2. 0 P= 0.89). There was also no difference in maximum temperatures reached during phacoemulsification. Temperatures did not rise above 40^{o}C during any surgery and there were no corneal burns. Final visual acuity and intra- and post-operative complication rates were similar between the two groups.

Conclusions: The temperature profile at the surgical wound using a micro-incisional sleeveless phacoemulsification technique is comparable to that of the conventional coaxial mini-incision method. Phacoemulsification using a sleeveless tip is at least as safe as the conventional mini-incision coaxial technique

Laser Capsulotomy Rates Following Implantation of Hydrophilic versus Hydrophobic Acrylic Intraocular Lenses

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Purpose: To compare laser capsulotomy rates after uneventful cataract surgery with implantation of a hydrophilic versus hydrophobic single-piece acrylic posterior chamber intraocular lenses.

Methods: Retrospective case series of 222 patients (255 eyes), who have undergone neodymium: yttrium-aluminum-garnet laser capsulotomy in 2011-2014, following uneventful phacoemulsification surgery with implantation of either hydrophilic (SeeLens AF, Hanita Lenses, Kibbutz Hanita, Israel) or hydrophobic (AcrySof SA60AT, Alcon Laboratories Inc., Fort Worth, Texas, USA) single-piece acrylic posterior chamber intraocular lenses.

Results: The mean duration between date of cataract surgery and laser capsulotomy procedure was 24 months. Time elapsed between cataract surgery and laser capsulotomy treatment was significantly shorter in the hydrophilic group ($P < 0.05$). Laser capsulotomy rates were significantly higher in the hydrophilic group in comparison to the hydrophobic group ($P < 0.05$). No significant difference was noted regarding laser capsulotomy rates in cataract surgery performed by junior surgeons compared to senior surgeons.

Conclusions: The acrylic hydrophilic intraocular lens was associated with almost twice the number of Nd: YAG-laser capsulotomy rate and a shorter time to laser capsulotomy treatment in comparison to the hydrophobic acrylic intraocular lens. Surgeon's experience did not play a statistically significant role between the two lenses.

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

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Purpose: To describe a novel ex vivo assay for examining the efficacy of various compounds for the reversal of human crystalline lens opacification in the search for pharmacological treatment for cataract.

Methods: After obtaining informed consent, fragments of cataractous lenses were collected from patients undergoing routine clear corneal incision phacoemulsification cataract surgery. Following quantification of total protein concentration in each cataract sample using the standard Bradford assay, the concentration was adjusted to obtain an optimal absorbance value. Ex vivo cataract samples were then incubated with several concentrations of various compounds being screened for cataract disintegration effect. Reversal of protein aggregates was monitored several times a day up to 48 h using the common turbidity assay. In between measurements samples were kept at 37 °C with constant shaking.

Results: Each compound selected for screening was tested on cataract samples obtained from 5-10 different patients, in triplicates. Initial total protein concentrations ranged between 1-10 mg/mL and after adjustment for optimal absorbance final concentrations ranged between 0.5-3 mg/mL. Of the 15 compounds screened, five showed no effect on protein turbidity measurement over time, while five other showed inconsistent results. Treatment with five compounds resulted in significant reduction in the optical density of the solution, reflecting restoration of transparency of the cataractous samples, two of which showed a dose-dependent effect. Among them each agent demonstrated different efficacy and unique kinetics.

Conclusions: This simple yet innovative experimental approach implements spectrophotometric principles to enable direct testing of the impact of potential compounds on disintegration of actual human crystalline lens material ex vivo. Further biophysical studies, currently conducted by our group, will provide mechanistic insight on the cataract reversal effect.

Pharmacogenetic Analysis of Patients with Neovascular Age-Related Macular Degeneration

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Purpose: Treatment for neovascular age-related macular degeneration (nvAMD) involves injection of anti-vascular endothelial growth factor (anti-VEGF) agents. Patient response to anti-VEGF varies, where some enjoy substantial improvement in visual acuity (VA) and some major visual loss. We aim to discover genetic variants that may underlie outcome of anti-VEGF therapy in nvAMD.

Methods: DNA was collected from nvAMD patients (n=187) who underwent anti-VEGF injections at Hadassah-Hebrew University Medical Center. Demographics, clinical, imaging parameters, and treatment details were retrospectively collected. Genome-wide association analysis was performed using the international AMD gene consortium (IAMDGC) exome chip platform and bioinformatics with the software PLINK, EPACTS, and R, according to standardized methods. Association analysis with treatment outcome (delta VA) was performed using LASSO or other mixed linear model (MLM) analysis or statistical testing. Variants with minor allele frequencies <0.01 were not included. Principle component analysis (PCA) was applied as a covariate to account for population stratification.

Results: Via statistical analysis testing in EPACTS, several variants reach a genome-wide significance level of P<1E-6, via MLM testing and other statistical tests. Several variants (>3, P<1E-4) were present in intronic and exonic variants in the same gene, including one gene on chromosome 12 and one on chromosome 13. Several other variants were found via LASSO analysis with a slight correlation with VA after 3 months (R^2:0.28079). Of 65 patients who underwent treatment in both eyes, and had similar baseline VA (±3 ETDRS line difference between fellow eyes) there was no correlation between the change in VA in the eyes (R^2:0.02).

Conclusions: The variable treatment outcome following anti-VEGF remains poorly explained. Conceivably, complex genetic and environmental interactions can underlie such a response. We show that genetic variants that may associate with treatment outcome (defined as deltaVA) can be found in patients with nvAMD. Yet, a significant portion of the variable response is not explained by genetics alone. This variance may be explained by environmental factors, their interaction with genetics, and chance. This is the first time that a genetic variant that may influence AMD treatment has been found in the Israeli population.

Functional Aspects of Polarized Macrophages From Patients with Age-Related Macular Degeneration

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Purpose: Macrophages were implicated in the pathogenesis of both atrophic AMD (aAMD) and neovascular AMD (nvAMD). The main activated phenotypes of macrophages are M1 and M2. While these phenotypes have proposed functions, their specific role in AMD is unclear. We aim to assess the function of these cells in the context of AMD.

Methods: Monocytes were cultured from patients with AMD, differentiated to macrophages, and polarized to the M1 and M2 phenotypes. Gene expression of specific anti-oxidative, inflammatory, and pro-angiogenic genes (VEGF, SOD1, TNFα, MRC1, IL-12, HMOX1, GPX1, and CAT) were evaluated using QPCR. ELISA was performed for specific proteins in these pathways, including TNFα, SDF1, VEGF, ICAM, IL-8, IL-6 and MCP1. Angiogenic potential was assessed via addition of culture media from polarized macrophages to a choroidal sprouting assay. Sprouting was assessed by measurement of sprout vessel area.

Results: QPCR demonstrated increased expression of VEGF (P=0.00016, Fold Change (FC)=4.97) and SOD1 (P=0.002, FC=22.28) in M1 vs. M2 macrophages. ELISA demonstrated increased expression of IL-6 (P=0.0001, FC=47.3) and TNFα (P=0.0047, FC=3.08) in M1 macrophage supernatant as compared to M2. Addition of media from M1 macrophages (P=0.0001, FC=3.47) and M2 macrophages (P=0.052, FC=2.83) was associated with increased area of choroidal sprouting as compared to control medium alone.

Conclusions: These data suggest that both M1 and M2 macrophages may be implicated in the pathogenesis of AMD via proangiogenic and potentially cytotoxic effects. Interestingly, M1 cells demonstrate a marked pro-angiogenic effect, suggesting that traditional polarization paradigms should be reevaluated.

Identification of High-Penetrance Rare Genetic Variations Among Israeli Patients Manifesting Early Severe Age-related Macular Degeneration

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Purpose: To identify rare genetic variations in Israeli patients with severe, early-onset Age-related Macular Degeneration (AMD).

Methods: We performed Whole Exome Sequencing (WES) on eight patients (four sib pairs from four families – two from Tunisian ancestry and two from Ashkenazi ancestry) manifesting early-onset AMD, and searched for disease-causing genetic variants in previously identified macular degeneration related genes. Validation studies of the variants included bioinformatics tools, segregation analysis of mutations within the families, and an estimate on variant prevalence in an ethnically matched cohort of AMD patients.

Results: All index patients were in their 6^{th} to early 7^{th} decade when diagnosed, with severe visual impairment due to extensive geographic atrophy and/or choroidal-neovascularisation common by the age of 75 years. Approximately, 400,000 genomic variants for each DNA sample were included in the downstream bioinformatics analysis, which ended in the discovery of four rare variants: a single base-pair deletion (c.4162delC) in the Hemicentin (HMCN1) gene; a missense variant (p.V412M) in the Complement Factor-I (CFI) gene; a missense variant (R735W) in Complement Factor 3 (C3) gene; and a missense variant (R1210C) in Complement Factor-H (CFH) gene. Screening for these variants in ethnically matched cohorts confirmed their rarity (<0.05%), and identified another family with the CFI variant.

Conclusions: Our study identified four rare genetic variants including two novel ones (*CFI* p.V412M; and *HMCN1* c.4162delC) in a cohort of aggressive AMD patients. These results further support the significance of rare pathogenic variants in the complement system components in AMD pathogenesis.

Characterizing the Phenotype of Differentiated Macrophages from Patients with Age Related Macular Degeneration

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Purpose: Monocytes/macrophages have been implicated in the pathogenesis of age-related macular degeneration (AMD). We previously showed the pro-angiogenic phenotype of activated and polarized human macrophages which contribute to growth of laser-induced choroidal neovascularization (CNV) in a rat. We aim to further investigate the role of macrophages in neovascular AMD (nvAMD).

Methods: Monocytes were isolated from 13 nvAMD patients and 12 age-matched controls. Cells were matured to macrophages and polarized to M1 and M2 phenotypes using LPS+IFN-γ for M1 and IL-13+IL-4 for M2. Cells or PBS were injected intravitreally to rat eyes following generation of laser–induced CNV. CNV area was measured via ImageJ using isolectin staining of the choroid-RPE flat mounts. Flow cytometry (FACS) analysis of CD45+, human HLA+, CD206+, and INOS2+ cells was performed to assess for the potential inflammatory rat reaction for the human xenograft.

Results: Increased mean CNV area was associated with injection of M2 polarized macrophages from unaffected controls and from nvAMD patients, as compared with the PBS-injected contra-lateral eye (1.78-fold, p=0.005; fold-1.37, p=0.04, respectively). M1 polarized macrophages from nvAMD patients also showed higher CNV area as compared to their control PBS injected eye (2.29-fold, p=0.005). A comparison between the ratio of M1 or M2 injected eyes and PBS-injected eye, and the ratio of M0 injected eye and PBS-injected eyes showed that M2 of both nvAMD and controls induced higher CNV area than M0 (1.6-fold, p=0.008; 2.23-fold, p=0.005, respectively). nvAMD M1 macrophages induced larger CNV area than nvAMD M0 (2.72-fold, p=0.001) and even higher than nvAMD M2 macrophages (1.67-fold, p=0.04). FACS results showed no correlation between HLA-DR-CD45+ cells (rat leukocytes) and CNV area (R2=0.0017) or HLA-DR+CD45+ cells (human leukocytes).

Conclusions: Our previous research demonstrated that monocytes driven from nvAMD patients have an inflammatory phenotype. The current study extends these findings suggesting that the macrophage descendent of monocytes also show a pro-angiogenic phenotype. Furthermore, our data imply that the proangiogenic effect is derived from the macrophage function rather than from the rat's own inflammatory response. Combined with our previous findings from the macrophages gene and protein expression profile, it is conceivable that activated macrophages have an important role in the pathogenesis of nvAMD, and that they may serve as therapeutic targets for the disease.

Focal ERG and Focal VEP for Evaluating Localized Retinal Function

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Purpose: Chronic and long term measurements of focal retinal function is of high importance in assessing treatment efficiency in various research models where only a localized area of the retina is treated (e.g. retinal prosthesis). This work characterized the focal Electroretinogram (fERG) and Visual Evoked Potentials (fVEP) in response to a localized visual stimulus projected on the retina.

Methods: fERGs and fVEPs signals were recorded in both albino Wistar and pigmented Long-Evans anesthetized rats. The visual stimulus consisted of led flashes relayed through circular apertures which are incorporated into a fundus camera (Micron IV) optical path, thus enabling the projection of circular spots with diameters ranging from 0.5 to 3.0 mm at any desired location on the retina. The Micron IV imaging objective served for imaging of the retina for stimulus localization and projection and as the ERG recording electrode as it comes in contact with the cornea. VEP was recorded using intracranially implanted screws over the primary visual cortex (V1). The electrophysiological signals were recorded using either the amplifier available with the Micron IV system or the AlphaSNR recording system (Alpha Omega). To measure focality of stimulation responses we induced localized photobleaching by projecting a bright spot of light for 5 minutes and calculated the ratio between the ERG recorded from the bleached area to that from the non bleached areas

Results: fERG and fVEP amplitude increased with both light intensity and pulse duration, and also increased with stimuli spot size. Amplitude decreased with increasing stimuli repetition rate and when background illumination was applied. More interestingly, focality of the response was enhanced when background illumination was applied.

Conclusions: We demonstrated the ability to record fERG and fVEP in rats in responses to localized retinal stimulation of various sizes. fVEP and fERG are affected by several stimuli parameters, such as spot size, illumination, repetition rate and background illumination. Focality of the response can be enhanced by introducing background illumination, probably because of decreased sensitivity to scattered light resulting from background illumination.

Chromatic Multifocal Pupillometer for Objective Early Diagnosis of Mild Cognitive Impairment

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Purpose: To evaluate the use of chromatic multifocal pupillometry (CMP) for objective diagnosis of neurodegeneration in the brain.

Methods: A CMP device (Accutome, Inc.) was used to record pupillary responses to red and blue light presented at 76 different locations of a 16.2-degree visual field (VF). Maximal percentage of pupil constriction (PPC), maximal constriction velocity (MCV) and the latency of MCV (LMCV) were determined. Twelve cognitively normal subjects (ages 60-74) with no detected ophthalmic pathology were included. CMP results were associated with cognitive (Montreal Cognitive Assessment, MoCA) testing.

Results: Low MoCA (<26) was associated with reduced PPC in response to red light in the nasal region compared to normal MoCA (≥26) (3.3% [SE=0.3] vs 10.1% [SE=0.8]; p=0.018). Subjects with MoCA<26 compared to MoCA ≥26 showed reduced PPC in response to blue light in all regions except the inferior (nasal 5.8% vs 15.1% p=0.032; temporal 4.6% vs 13.9% p=0.028; superior 4.8% vs 13.8% p=0.033).

Conclusions: This study demonstrated the feasibility of using the CMP for identification of functional focal defects associated with cognitive impairment. Specific parameters of pupil response to chromatic multifocal stimuli may indicate specific pathophysiology of different neurodegeneration diseases.

Contrast Sensitivity Revealed by Spontaneous Eye-Blinks

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Purpose: Spontaneous eye-blinks are known to serve important physiological functions, but recent evidence shows that they are also linked to cognitive processes. It is yet unclear whether this link reflects a crude rate modulation to avoid the loss of valuable information, or alternatively, an automatic and precise process, tightly linked to the low-level properties of sensory stimuli and perceptual saliency. Here we provide evidence for the latter, by showing that spontaneous eye-blinks like microsaccades can be used to derive a contrast sensitivity function in passive viewing.

Methods: During fixation observers (n=18) viewed and silently counted sequences of 100 randomly-ordered Gabor patches with varied contrast and spatial frequency briefly flashed at 1 Hz repetition rate in different runs. Only observers with sufficient blinking (>10% of trials, 18-of-23 observers tested) were included in the analysis.

Results: Spontaneous eye-blinks, although less frequent, were very similar to microsaccades in their modulation pattern in response to transient stimuli, demonstrating inhibition and rebound, which were dependent on the contrast and spatial-frequency of the stimuli. The average blink-RT, measured as the latency of the first blink, following its release from inhibition, was longer for lower contrast and higher spatial-frequency, and was highly correlated with psychophysical measures of contrast sensitivity.

Conclusions: Eyeblinks, like microsaccades, are linked to an inhibitory mechanism that presumably turns-off oculomotor events while processing previous events, thus providing an indirect but precise measure for internal processing speed, which can be used to uncover contrast sensitivity.

The Role of Angiotensin Converting Enzyme in the Diagnosis of Sarcoidosis Related Uveitis

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Purpose: Angiotensin converting enzyme (ACE) serum levels may be elevated in patients with sarcoidosis and are typically used in its diagnosis. However other conditions, such as tuberculosis, hyperthyroidism, amyloidosis and histoplasmosis, can also present with elevated serum ACE, and the value of performing this test on all patients with uveitis is uncertain. In this study we aimed to evaluate the efficacy of blood angiotensin converting enzyme levels for the diagnosis of sarcoidosis related uveitis.

Methods: Retrospective data analysis performed at Moorfields Eye Hospital in 2015. The study included adult patients diagnosed with uveitis treated by our uveitis clinic. We collected patient demographic and clinical data, as well as blood ACE levels. For patients found to have an elevated ACE (determined as above 52µg/L), clinical notes were reviewed to determine their ultimate diagnosis.
Sensitivity and specificity, as well as receiver operating characteristic (ROC) curves, were calculated.

Results: Results were obtained from 1,035 patients with uveitis. Average age at diagnosis was 41.7 ± 17.2 years and 56.1% were female. Of these patients 110 (10.6%) had a final diagnosis of sarcoidosis. For the entire population the median ACE level was 32µg/L [IQR 21-47], for sarcoidosis patients this was 97µg/L [61.3 – 116.5] and for non-sarcoidosis patients 30µg/L [20 – 41.8]. The sensitivity and specificity of ACE for the diagnosis of sarcoidosis in these patients was 77.3% and 88.0%, respectively. The positive predictive was 43.4% and the negative predictive value was 97%. A ROC demonstrated an area under the curve of 0.9 ($p<0.0005$, 95% CI 0.85-0.94).
Among patients with elevated ACE but no diagnosis of sarcoidosis the ultimate diagnosis was most frequently idiopathic (52.3%), HLA-B27 related (5.4%) or tuberculosis-related (3.6%).

Conclusions: Serum ACE levels offer a good method for excluding sarcoidosis in uveitis patients. However among those with elevated ACE levels, clinical presentation as well as other investigations, such as chest roentgenograms and high resolution chest computerized tomography scans may be needed to confirm the diagnosis.

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