

PROGRAM & ABSTRACTS

33rd Annual Meeting

Avenue Congress Center, Airport City

14-15th March, 2013

תכנית ותקצירים

הכינוס השנתי ה-33

מרכז הכנסים Avenue, קרית שדה התעופה

14-15 מרץ, 2013

עריכת התוכנית:

פרופ' אבי סולומון, פרופ' איתי חוברס ופרופ' רות אשרי פדן

עיצוב והבאה לדפוס: יעקב אלבו - דפוס הדסה, ודבורה מרקס אוחנה

ISRAELI SOCIETY FOR VISION AND EYE RESEARCH**The 33rd Annual Meeting, March 14-15, 2013****Program at a glance****Thursday, March 14, 2013**

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יושבי-ראש של האגודה הישראלית לחקר העין והראיה
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האגודה הישראלית לחקר העין והראיה
Israeli Society for Vision & Eye Research

**מרצים המקבלים פרס על עבודות שהוצגו בכינוס השנתי ה-32,
מרץ 2012**

**AWARD RECIPIENTS FOR THE BEST PRESENTATIONS AT
THE 32nd MEETING, MARCH 2012**

Nir Erdinest: ANTI-INFLAMMATORY EFFECTS OF ALPHA LINOLENIC ACID ON HUMAN CORNEAL EPITHELIAL CELLS VIA NUCLEAR FACTOR-kB.

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

Gil Ben-Shlomo: A NOVEL CORNEAL ANATOMY OBSERVED IN THE FLORIDA MANATEE.

Department of Veterinary Clinical Sciences, College of Veterinary Medicine - Iowa State University, Ames, Iowa

Shira Hagbi-Levi: MODULATION OF LASER-INDUCED CHOROIDAL NEOVASCULARIZATION BY DIFFERENTIATED MACROPHAGES FROM PATIENTS WITH AGE RELATED MACULAR DEGENERATION.

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

Anat London: MONOCYTE-DERIVED MACROPHAGES ARE HEALING CELLS ESSENTIAL FOR NEUROPROTECTION AND PROGENITOR CELL RENEWAL IN THE INJURED MAMMALIAN RETINA.

Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Alexey Obolensky: PHASE I GENE THERAPY TRIAL IN ISRAELI PATIENTS WITH LEBER CONGENITAL AMAUROSIS CAUSED BY A FOUNDER RPE65 MUTATION: AN UPDATE WITH UP TO TWO YEARS OF FOLLOW-UP.

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

Michelle Grunin: GENE EXPRESSION SIGNATURE IN THE MONOCYTE POPULATION OF PATIENTS WITH NEOVASCULAR AGERELATED MACULAR DEGENERATION.

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

**מלגות נסיעה ל- ARVO מטעם עמותת "לראות" - העמותה לחקר בריאות העין
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תודה לעמותת "לראות"



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צמל 28 טכנולוגיות רפואיות בע"מ



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

מטרות עמותת "לראות" (העמותה לחקר בריאות העין ומניעת עיוורון בישראל)

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

המועצה המדעית של "לראות"

מורכבת מהשורה הראשונה של רופאים וחוקרי עיניים בישראל, וכן מגורמים בכירים מתחומי הבריאות, האקדמיה והתעשייה; כולם מתנדבים בעמותה.

משרד הבריאות בחר בעמותה כגוף מייעץ בתחום תרופות וטכנולוגיות חדשות. המועצה מרכזת פרויקטים מחקריים הקיימים בישראל בתחום רפואת העיניים, בוחנת ומתקצבת אותם במסגרת המשאבים העומדים לרשותה ועל פי סדר עדיפות מוגדר. המועצה פועלת לגיוס מיטב החוקרים מתחומים רלוונטיים, וכן להקמת רשות מחקרית בינלאומית.

בין יוזמות עמותת "לראות" בשנת 2012

"לילה של בריאות בפארק הרצליה" - קיום בדיקות סקר לילדים.

"יום בריאות העין – רפואת עיניים בקרב האוכלוסייה הערבית בצפון הארץ" - כנס שני ותערוכה לאוכלוסייה הערבית בישראל שהתקיים בנצרת בשפת הערבית לקהל של רופאים ואופטומטריסטים. הפקה והפצת מוסף מיוחד על בריאות העין בשפה הערבית.

"נבדקים היום כדי לראות את המחר" - חודש מודעות לבריאות העין הרביעי, שכלל בדיקות ראייה ללא עלות בכל רחבי הארץ, הפצת מוסף בריאות העין לכל המשפחה, המופץ בתפוצה ארצית עם עיתון סוף שבוע, בדיקות סקר לילדים ברחובות ובירושלים וקמפיין בתקשורת.

Evening honoring Israeli vision researchers – New York 03.05.2012 - יוזמה של אגודת ידידי עמותת "לראות" בארה"ב עם "לראות" בישראל - מפגש חוקרים ישראליים ואמריקאים והצגת הפעילות המחקרית לקהל האמריקאי במטרה להגביר את שיתוף הפעולה המחקרי.

תכנית פעילות לשנת 2013

פעילויות שוטפות

1. תכנית למימון מחקרים במוסדות מחקר רפואיים בישראל ובארה"ב
2. מתן יעוץ רפואי על ידי פורומים של רופאים מומחים ומנהלי מחלקות עיניים
3. ארגון חודש המודעות לבריאות העין החמישי
4. יום בריאות העין – רפואת עיניים בקרב האוכלוסייה הערבית בנצרת

פרויקטים מתוכננים

1. ניידת עיניים לבדיקות קשישים מזקנים
2. קידום פעילות סקר ראייה לילדים באמצעות הפוטו סקרינר
3. המשך גיוס משאבים למחקר רפואי בארץ ובחו"ל

לזכרו של פרופ' שאול מרין

הכרתי את פרופסור מרין במהלך הקמת עמותת "לראות", במטרה לקדם מחקרים בתחום מחלות העיניים.

פרופסור מרין נרתם ברצון ובמלא המרץ לסייע ולמנף את מטרות העמותה למען החולים. דרכו העידה על ליבו הרחב והנדיב. אישיותו יוצאת הדופן ומקצועיותו תרמו רבות לטובת הכלל.

למדתי ממנו רבות והוא יחסר לי ולכולם.

יהי זכרו ברוך

אוהד להב, יו"ר עמותת "לראות"

המחקרים הממומנים ע"י עמותת "לראות" ב- 2012

שישה מחקרים מצטיינים זכו למענק כולל של מיליון שקל השנה, ומצטרפים ל- 13 המחקרים הממומנים החל משנת 2007, כתוצאה מהפעילות של עמותת "לראות".

1. **ד"ר סאמר ח'טיב** – ביה"ח הדסה.
זיהוי גנים חדשים לתסמונת אשר באוכלוסיה הישראלית תוך שילוב מיפוי הומוזיגוטי וריצוף אקסומי.
2. **פרופ' איתי חוברס** – ביה"ח הדסה.
מודולציה של מעורבות מונוציטים באמצעות איתות כמוקינים בנוון מקולרי גילי (נמ"ג)
3. **ד"ר חיים כהן** – אוניברסיטת בר אילן.
מעורבות SIRT6 בתהליכי הזדקנות וניוון של הרשתית.
4. **ד"ר יוסף מנדל** – אוניברסיטת ת"א.
שיקום ראייה באמצעות השתלת רשתית מלאכותית מבוססת תאים פוטוולטאים, אימון ופלטיות נאורנלי.
5. **ד"ר עדי ענבל** – האוניברסיטה העברית.
מנגנונים מולקולריים של פגמים בעצב הראייה המתווכים ע"י SIX3.
6. **ד"ר אברהם קציר** – אוניברסיטת ת"א.
שימוש במערכת חדשנית המבוססת על לייזר וסיב אופטי יחיד, לאיחוי חתכים בקרנית ללא תפרים.

PROGRAM

Thursday, March 14, 2013

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Session I - Rapid Fire Presentations 1 08:35-10:00

Moderators: Prof. Itay Chowers and Prof. Ron Ofri

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2	Functional and morphological changes in the retinas of CCR2, CX3CR1 and CCR2-CX3CR1 knockout mice carrying RD8 mutation <i>(1) Ezra-Elia Raaya (1) Shpigel Y Nahum (1) Barishak Robert (1) Ofri Ron</i> <i>(1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel</i>	34
3	Computer Aided Diagnosis of Diabetic Retinopathy <i>Yonatan Serlin (1)#; Geva Tal (2)#; Yoash Chassidim (1); Yisrael Parmet (3); Oren Tomkins (4),(5); Boris Knyazer (6); Alon Friedman (1),(7); Jaime Levy(6)</i> <i>(1) Departments of Physiology and Neurobiology, (2) Biomedical Engineering and (3) Industrial Engineering and Management, Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva, Israel; (4) Moorfields Eye Hospital, London, UK; (5) Royal Surrey County Hospital, Guildford, UK; (6) Department of Ophthalmology, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel; (7) Institute of Neurophysiology, Neurocure Research Center, CharitéUniversitätsmedizin, Berlin, Germany</i>	35

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¹Department of Ophthalmology, Rabin Medical Center, Petach Tikva, ²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
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(1)Ophthalmology Department, Rabin Medical Center (2)Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv Israel.(3)The Krieger Eye Research Laboratory, Felsenstein Medical Research Center; (4)Pediatric Unit, Ophthalmology Department, Schneider Children's Medical Center of Israel, Petach Tikva, Israel.
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2. Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel 3. Laboratory of Eye Research, Felsenstein Medical Research Center, (FMRC) Petach Tikva, Israel 4. OTM Technologies*

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1The Goldschleger Eye Research Institute, Sheba Medical Center, 2Department of Neurobiology, George S. Wise Faculty of Life Science, Tel Aviv University 3Department of Neurology, Felsenstein Medical Research Center, Rabin Medical Center, Beilinson Campus, 4Cancer and Vascular Biology Research Center, The Bruce Rappaport Faculty of Medicine, Technion.
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1 The Maurice and Gabriela Goldschleger Eye Research Institute, Sheba Medical Center, Tel-Hashomer 2 The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv
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1 Xceed Imaging Ltd, 20 Ha-Magshimim st., Petach-Tikva, Israel 2 Goldshleger Eye Research Institute, Tel-Aviv University, Tel-Hashomer, Israel 3 Faculty of Engineering, Bar-Ilan University, Ramat-Gan 52900, Israel.
- 27 **Gene expression patterns in monocytes isolated from patients with neovascular age-related macular degeneration** 59
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(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center (2) Institute of Dental Sciences, Hadassah-Hebrew University Medical Center

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- 28 **Bevacizumab Treatment for Choroidal Neovascularization Associated with Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD)** 60
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Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
- 29 **Sequence variants in HTRA1, CFH and C3 and response to Anti-VEGF treatment in neovascular age-related macular degeneration in the Israeli population** 61
Gala Beykin, Michelle Grunin, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Coffee break & Exhibition 10:00-10:30

Session II - Retina 1 10:30-11:40

Moderators: Dr. Nitza Goldenberg-Cohen and Dr. Ygal Rotenstreich

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10:30-10:37	<p>The eye - A window to the brain - The effect of apoE genotype on retinal neurons and function</p> <p><i>1Ran Antes, 2Raaya Ezra-Elia, 3Arieh Solomon, 4Dov Weinberger, 2Ron Ofri and 1Daniel Michaelson</i> <i>1Department of Neurobiology, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Israel. 2 Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel. 3 Goldschleger Eye Research Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel. 4 Department of Ophthalmology, Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel.</i></p>	62
10:37-10:44	<p>Visual evoked potentials, electroretinography and sodium channel expression in contactin associated protein knockout mice</p> <p><i>S. Sandalon¹, V. Bar², E. Peles², R. Ofri¹.</i> <i>1 Koret School of Veterinary Medicine, The R.H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem. 2 Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel.</i></p>	63
10:44-10:51	<p>Sip1 in Retinal Development</p> <p><i>Menuchin, Yotam¹; Oren-Giladi, Pazit¹; Xie, Qing²; Cvekl, Ales²; Ashery-Padan, Ruth¹.</i> <i>1. Tel-Aviv University, Tel Aviv, Israel. 2. Albert Einstein College of Medicine, Bronx, NY, United States.</i></p>	64

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- 10:51- **Intravitreal Injection Of Bevacizumab May Be** 65
10:58 **Neuroprotective In A Mouse Model Of Optic Nerve Crush**
Daniel Rappoport, 1 Dana Morzaev, 2,4 Shirel Weiss,2,4 Mark Vieyra, 4 Hana Leiba 1 and Nitza Goldenberg-Cohen 2,3,4
1Ophthalmology Department, Kaplan Medical Center, Rehovot, Israel 2The Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Tel Aviv University, Petah-Tiqwa,Israel;; 3Pediatric Unit, Ophthalmology Department, Schneider Children's Medical Center of Israel, Petah- Tiqwa, Israel; 4Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. 5Hadassah and Hebrew University Medical School, Jerusalem, Israel.
- 10:58- **Curcumin as Adjunctive Therapy for Proliferative** 66
11:05 **Vitreoretinopathy**
Yoreh Barak (1,2), Kazuhiko Umazume(2), LanHsin Liu(2), Kevin L. McDonald(2), Henry J. Kaplan(2), Shigeo Tamiya (2),.
1- Rambam Medical Center. 2- University of Louisville vphthalmology and Visual Sciences
- 11:05- **Quantitative reduction of vascular injury after optic** 67
11:12 **nerve stroke with a single 15d-PGJ2 treatment**
James D. Nicholson(1), Yan Guo(2), Adam C. Puche(2), Steven L. Bernstein(2)
(1)The Krieger Eye Research Labratory, Felsenstein Medical Research Center; (2)Ophthalmology Research Department, University of Maryland Baltimore, USA
- 11:12- **Functional characterization of the PRCD gene, involved** 68
11:19 **in hereditary retinal degeneration**
Lital Remez, Ben Cohen, Tamar Ben-Yosef
Department of Genetics, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
- 11:19- **In-vivo Performance of Photovoltaic Subretinal** 69
11:26 **Prosthesis**
Yossi Mandel(1,2), Georges Goetz(1,3), Daniel Lavinsky(2), Phil Huie(1,2), Keith Mathieson(4), Lele Wang(3), Theodore Kamins(3), Richard Manivanh(2), James Harris(3), Daniel Palanker(1,2)
(1)Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA, 94305, USA (2)Department of Ophthalmology, Stanford University, Stanford, CA, 94305, USA (3)Department of Electrical Engineering, Stanford University, Stanford, CA, 94305, USA (4)Institute of Photonics, University of Strathclyde, Glasgow, Scotland, G4 0NW
- 11:26- **Exposure of RPE to thrombin induces long lasting** 70
11:33 **proangiogenic signals and barrier disruption**
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1. Laboratory of Eye Research ,Felsenstein Medical Research Center, PetachTikva, Israel. 2. Department of Ophthalmology, Rabin Medical Center, Petah Tiqwa, Israel. 3. The Israeli National Hemophilia Center and Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer, Israel. 4. Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.

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11:33- **A novel technique for subretinal transplantation of cells** 71
11:40 **covering most of the subretina in Rat and Rabbit models**
Ygal Rotenstreich, Adi Tzameret, Ifat Sher, Michael Belkin
Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer, Israel.

Awards and ISVER update 11:40-12:00

Prof. Jacob Pe'er - Remembering Prof. Saul Merin
The Prof. Saul Merin Awards
The Prof. Ahuva Dovrat Award
The Lirot Society Awards

Session III - Keynote Guest Lecture 1 12:00-12:30

Prof. Amir Amedi, PhD

Department of Medical Neurobiology, Faculty of Medicine (IMRIC); The Edmond and Lily Safra Center for Brain Sciences (ELSC); The Hebrew University of Jerusalem.

Lecture title: Seeing with the ears, hands and bionic eyes: from basic research to visual rehabilitation.

Lunch break 12:30-13:30

Session IV - Visual Perception 13:30-15:00

Moderators: Prof. Amir Amedi and Prof. Dov Sagi

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13:30- 13:35	Above chance identification of missed targets is predicted by signal detection theory <i>Ron Dekel (1), Andrei Gorea (2), Dov Sagi (1)</i> <i>(1) Weizmann Institute of Science, (2) Centre National de la Recherche Scientifique</i>	72
13:35- 13:40	Human perception of order-disorder transition <i>Mikhail Katkov, Dov Sagi</i> <i>Weizmann Institute of Science, Neurobiology department</i>	73

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- 13:40- **Crowding modulations by spatial attention, stimuli** 74
 13:45 **contrast, and object formation**
Yaffa Yeshurun (1) Einat Rashal (1) Branka Spehar (2)
(1) University of Haifa, Haifa Israel (2) University of New South Wales, Sydney
Australia
- 13:45- **The development of visual crowding, collinear** 75
 13:50 **facilitation and contour detection in young children**
Doron R, Spierer A and Polat U.
Tel-Aviv University, Faculty of Medicine, Goldschleger Eye Research Institute, Sheba
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- 13:50- **Visual disappearance in a case of simultanagnosia -** 76
 13:55 **Insights on PPC contribution to conscious perception**
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(1) Dept. of Human Biology, University of Haifa (2) Loewenstein Rehabilitation
Hospital, Raanana (3) Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv (4)
Life Sciences Institute, Hebrew University, Jerusalem
- 13:55- **Training-induced recovery of low-level vision followed** 77
 14:00 **by high-level perceptual improvements in an adult with**
developmental object and face agnosia
Sharon Gilaie-Dotan, Maria Lev, Dana Gotthilf-Nezri, Oren Yehezkel,
Anat Perry, Shlomo Bentin, Yoram Bonne, and Uri Polat
Faculty of Medicine, Goldschleger Eye Research Institute, Tel Aviv University, Tel
Hashomer, Israel; Institute of Cognitive Neuroscience, University College London,
London, UK, Department of Psychology&Center for Neural Computation, Hebrew
University of Jerusalem, Jerusalem, Israel; Department of Human Biology, University
of Haifa, Haifa, Israel
- 14:00- **Perceptual training on mobile devices restores normal** 78
 14:05 **processing of blurred images to overcome the optical**
deficits in presbyopia
Anna Sterkin, Oren Yehezkel, Maria Lev, Uri Polat
Ucansi Inc. New York, NY 10170
- 14:05- **Cross-modal functional specialization in the ventral** 79
 14:10 **visual cortex of the congenitally blind**
Ella Striem-Amit¹, Laurent Cohen^{2,3,4}, Stanislas Dehaene^{5,6,7,8} and
Amir Amedi^{1,9,10}
1. Department of Medical Neurobiology, The Institute for Medical Research Israel-
Canada, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem,
Israel.; 2. Université Pierre et Marie Curie-Paris 6, Faculté de Médecine Pitié-
Salpêtrière, IFR 70, Paris, France.; 3. INSERM, ICM Research Center, UMR5 975,
Paris, France.; 4. AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of
Neurology, Paris, France.; 5. Collège de France, 11 Place Marcelin Berthelot, 75005
Paris, France 6. Institut National de la Santé et de la Recherche Médicale, Cognitive
Neuroimaging Unit, Gif sur Yvette, 91191 France.; 7. Commissariat à l'Energie
Atomique, Division of Life Sciences, Institute of Bioimaging, Neurospin, Gif sur
Yvette, 91191 France. ; 8. Université Paris 11, Orsay, France. 9. The Edmond and
Lily Safra Center for Brain Sciences (ELSC), The Hebrew University of Jerusalem,
Jerusalem, Israel.10. The Cognitive Science Program, The Hebrew University of
Jerusalem, Jerusalem, Israel.

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- 14:10- **Interactions between perceptual learning and adaptation** 80
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Pinchuk-Yacobi N and Sagi D
Dept. of Neurobiology, Brain Research, The Weizmann Institute of Science, Rehovot, Israel
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14:20 *Shaul Hochstein¹&Keren Haroush²*
¹ELSC, ICNC, Neurobiology, Life Sciences, Hebrew University, Jerusalem ² Current Address: Harvard Medical School, Brookline, MA
- 14:20- **How Can We Assist Forgetting?** 82
14:25 *Volodya Yakovlev and Shaul Hochstein*
Edmond&Lily Safra Center for Brain Research, Hebrew University, Jerusalem, Israel
- 14:25- **Visual parsing using visual-to-auditory sensory-** 83
14:30 **substitution vs. medically restored sight in early blind individuals**
Lior Reich (1) and Amir Amedi (1,2)
1. Department of Medical Neurobiology, The Institute for Medical Research Israel-Canada, Faculty of Medicine, The Hebrew University of Jerusalem. 2. The Edmond and Lily Safra Center for Brain Sciences (ELSC), The Hebrew University of Jerusalem.
- 14:30- **Returning part of the sensory substitution spotlight from** 84
14:35 **research to visual rehabilitation**
Shachar Maidenbaum, Sami Abboud, Amir Amedi
Hebrew university Jerusalem
- 14:35- **Blind in a virtual world - using distance information to** 85
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Shachar Maidenbaum, Amir Amedi
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- 14:40- **Precise dynamic near visual acuity evaluation using** 86
14:45 **mobile and PC screens**
Yehezkel Oren; Sterkin Anna¹; Lev Maria¹; Polat Uri¹
Ucansi Inc., New York, NY, United States
- 14:45- **Elimination of sensory adaptation during visual training** 87
14:50 **allows for generalization of learning**
Harris H and Sagi D.
Dept. of Neurobiology, Brain Research, The Weizmann Institute of Science, Rehovot, Israel

Coffee & Exhibition

15:00-15:30

Session V - Cornea and Anterior Segment

15:30-17:00

Moderators: Dr. Tamar Kadar and Dr. Arie Marcovich

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15:30- 15:38	Efficacy of primary collagen cross-linking treatment on Staphylococcus aureus induced corneal ulcer <i>Kfir Tal (1), Orly Gal-Or (1), Shani Goldshtein (1), Alon Zahavi (1) Oded Rock (1), Igor Kaiserman (2), Irit Bahar (1) (1) Ophthalmology Department, Rabin Medical Center, Petach Tiqva (2) Ophthalmology Department, Barzilai Medical Center, Ashkelon</i>	88
15:38- 15:46	The Role of lukSF-PV in Staphylococcus aureus Keratitis Henri Sueke (1), Stephen Kaye (1), Tim Neal (2), Jayendra Shankar (1), Stephen Tuft (3) and Mal Horsburgh (4) <i>(1) St Pauls Eye Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom (2) Department of Medical Microbiology, Royal Liverpool University Hospital, Liverpool, United Kingdom (3) Ophthalmology Department, Moorfields' Eye Hospital, London, United Kingdom (4) Institute of Integrative Biology, University of Liverpool, Liverpool, UK</i>	89
15:46- 15:54	The Anti-inflammatory Effects of Resolvin-D1 on Human Corneal Epithelial Cells <i>Nir Erdinest, Haim Ovadia, Abraham Solomon</i> <i>Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel</i>	90
15:54- 16:02	Transplantation of Limbal Stem Cells Cultured on Contact Lenses for treatment of LSCD <i>Gore A., Horwitz V., Gutman H., Cohen M., Cohen L., Fishbine E., Turetz J., Dachir S. and Kadar T.</i> <i>Israel Institute for Biological Research</i>	91
16:02- 16:10	Study of corneal pathophysiology and therapy by induced pluripotent stem cells <i>Laura Serror, Daria Putin and Ruby Shalom-Feuerstein</i> <i>Faculty of Medicine of the Technion, Haifa, Israel</i>	92
16:10- 16:18	Open-Capsule Device for PCO Prevention <i>Roy Alon, Ehud I. Assia, Guy Kleinmann</i> <i>Meir Hospital, Kaplan Hospital</i>	93

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- 16:18- **The inhibitory effects of bevacizumab (Avastin) on** 94
16:26 **corneal neovascularization depends on timing of**
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Israeli Institute for Biological Research
- 16:26- **Cross-linking of rabbit sclera using riboflavin and UVA** 95
16:34 **for the prevention of progressive myopia**
Assaf Dotan¹, Israel Kremer^{1,2}, Tami Livnat³, Arie Zigler⁴, Dov Weinberger^{1,2} Dan Bourla¹
¹Department of Ophthalmology, Rabin Medical Center, Petach Tikva, ²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel ³Laboratory of eye research Felsenstein Research Center, Rabin Medical Center, ⁴Racah Institute of Physics, The Hebrew University, Jerusalem, Israel
- 16:34- **Collagen cross-linking as an adjunct to trabeculectomy** 96
16:42 **surgery in a rabbit model.**
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Carmel Medical Center
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Departments of ¹Plant Sciences, ²Biological Regulation, ³Veterinary Resources,, ⁴Materials and Interfaces, The Weizmann Institute of Science, ⁵Department of Ophthalmology, Kaplan Medical Center, Rehovot, Israel
- 16:50- **Characteristics of 244 patients with keratoconus seen in** 98
16:58 **an optometric contact lens practice**
Einat Shneur, Michel Millodot+, Sharon Blumberg*, Ilya Ortenberg*§, Shmuel Behrman§ and Ariela Gordon-Shaag*
Dept. of Optometry, Hadassah Academic College, Jerusalem +School of Optometry, Cardiff University, Cardiff, Wales§Microlens, Tel Aviv

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Friday, March 15, 2013

Coffee & Exhibition 08:00-08:30

Session VI - Rapid Fire Presentations 2 08:30-10:00

Moderators: Prof. Jacob Pe'er and Dr. Tamar Ben-Yosef

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1	The long-term outcome of the refractive error in hypermetropic children <i>Eedy Mezer^{1,2}, Tamara Wygnansi-Jaffe^{3,4}, Yaacov Sahuly¹, Wolfgang Haase⁵, Albert W. Biglan⁶, Ewy Meyer^{1,2}</i> <i>1Department of ophthalmology, Rambam health care campus, Haifa, Israel, 2Ruth and Baruch Rappaport faculty of medicine, Technion– Israel institute of technology, Haifa, Israel; 3Goldschleger eye Institute, Haim Sheba medical center, Tel-Hashomer, Ramat-Gan, Israel, 4Sackler faculty of medicine, Tel-Aviv university, Tel-Aviv, Israel; 5Hamburg University, Germany; 6 University of Pittsburgh School of Medicine, USA</i>	99
2	The effect of accommodation on Maddox Rod phoria testing at distance <i>Rachel Eichler, Shlomo Abramson, Raizel Davidowitz and Einat Shneor</i> <i>Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem, Israel.</i>	100
3	Intracameral Tissue Plasminogen Activator (TPA) in the management of severe fibrinous anterior chamber reactions in Toxic anterior segment syndrome (TASS) <i>Itay Lavy, MD, Perach Osaadon, MD, Tova Lifshitz, MD, Eyal Walter, MD, Nadav Belfair, MD, Boris Knyazer, MD, Jaime Levy, MD.</i> <i>Ophthalmology Department, Soroka University Medical Center</i>	101
4	Comparison Between Manual and Automated Interpupillary Distance Measurements in the Israeli Population <i>Liat Gantz, Einat Shneor, Simon Barnard, Vanessa Elbaz, Ruth Wolff, Gabrielle Chiche, Rasha Ghantous, Medicha Duchi, Ariela Gordon-Shaag</i> <i>Department of Optometry and Vision Science, Hadassah Academic College</i>	102
5	Identification of miR-450b-5p as a new repressor of Pax6 <i>Laura Serror and Ruby Shalom-Feuerstein</i> <i>Faculty of Medicine of the Technion, Haifa, Israel</i>	103

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- 6 **Contralateral lateral rectus muscle recession in patients with Duane retraction syndrome type 3** 104
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1Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petach Tikva; 2Department of Ophthalmology, and 3Neuro-Ophthalmology Unit, Rabin Medical Center, Petach Tikva; both affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Israel
- 7 **Wavefront Aberrations in RGP vs. Soft Toric Contact Lenses for Corneal Astigmatism** 105
Philip Fine, Noga Basan, Talya Gutenberg, Ariela Gordon-Shaag, Liat Gantz
Department of Optometry and Vision Science, Hadassah Academic College, Jerusalem, Israel
- 8 **Single Nucleotide Polymorphism Signature in Behcet's Uveitis** 106
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1 Department of Ophthalmology, Rabin Medical Center, Petah-Tikva 2 Krieger Eye Research Laboratory, Felsenstein Research Center 3 Rheumatology Unit, Rabin Medical Center, Petah-Tikva 4 Gynecological Research Unit, Sheba Medical Center 5 Sackler School of Medicine, Tel Aviv university, Tel Aviv
- 9 **Black and white and in-between** 107
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(1) Meir Medical Centre, Kfar Saba, Israel (2) Sir Charles Gairdner Hospital, Perth, Western Australia
- 10 **The protective effect of TLR4 KO knock out mice against corneal chemical burn.** 108
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(1)The Krieger Eye Research Laboratory, and (2)Laboratory of Cardiac Research, Felsenstein Medical Research Center, Petah Tikva; (3)Department of Ophthalmology, Pediatric Unit, Schneider Children's Medical Center, Petah Tikva; (4)Sackler School of Medicine, Tel Aviv University, Tel Aviv; Israel
- 11 **Signaling between macrophages and trabecular meshwork cells in-vitro and their potential contribution to glaucoma.** 109
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Clinical Biochemistry and Pharmacology Department; Ben-Gurion University of the Negev
- 12 **Do signaling between the ciliary epithelium and the trabecular meshwork has a role in intraocular pressure maintenance?** 110
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Clinical Biochemistry and Pharmacology Department; Ben-Gurion University of the Negev

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1 Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel 2 Goldshleger Eye Research Institute, Tel Aviv University, Tel Hashomer, Israel
- 14 **Chromatic components in underwater targets do not affect Great cormorants (*Phalacrocorax carbo*) visual resolution** 112
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(1) Department of Evolutionary and Environmental Biology, University of Haifa, Haifa 31905, Israel. (2) Department of Marine Biology, University of Haifa, Haifa 31905, Israel.
- 15 **Air-pulse corneal applanation signal curve parameters for the characterization of astigmatic corneas** 113
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- 16 **Ocular anterior segment changes during pregnancy** 114
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- 17 **Functional Macrophage Heterogeneity in Experimental Autoimmune Uveitis** 115
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(1) Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel. (2) Laboratory of Immunology, National Eye Institute/NIH, Bethesda, MD. (3) Department of Internal Medicine, University of Regensburg, Regensburg, Germany
- 18 **Specular microscopy findings in early well controlled diabetes** 116
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1 Ophthalmology Department, Soroka University Medical Center 2 Epidemiology department, Ben Gurion University of Negev
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- 20 **The role of PPM1A in early corneal wound healing response** 118
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1Goldschleger Eye institute, Sackler Faculty of Medicine, Tel Aviv University, Sheba Medical Center, Tel Hashomer. 2The Department Of Cell Research and Immunology, George Wise Faculty of Life Sciences, Tel Aviv University. 3Department of Clinical Microbiology and Immunology, Sackler Faculty of Medicine, Tel-Aviv University.
- 21 **Endothelial survival after DSAEK in eyes with retained anterior chamber intraocular lenses** 119
Irit Bahar, MD, Sagi Spitzer, Gilli Tessler, MD, Ayelet Dreznik, MD
Rabin Medical Center
- 22 **Sodium Iodate-Induced Model for Retinal Degeneration Secondary to RPE Injury** 120
Matan Cohen, Eyal Banin and Alexey Obolensky
Center for Retinal and Macular Degenerations, Department of Ophthalmology, Hadassah-Hebrew University Medical Center
- 23 **Human CNGA3 Gene Therapy Rescues Cone Function in a Sheep Model of Achromatopsia** 121
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(1) Center for Retinal and Macular Degenerations, Department of Ophthalmology, Hadassah-Hebrew University Medical Center; (2) Agricultural Research Organization, The Volcani Center, Israel; (3) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Israel; (4) Department of Ophthalmology, University of Florida, Gainesville, USA
- 24 **Incidence of Demodex parasites in Chronic Blepharitis and Controls** 122
Eitan Livny, Zahi Abu Ghosh, Igor Kaiserman, Iftach Yassur, Irit Bahar
1. Ophthalmology department, Rabin Medical Center, Petach Tiqva, Israel 2. Ophthalmology department, Barzilai Medical Center, Ashkelon, Israel
- 25 **Higher levels of IL-8 in tear fluid preceded the clinical manifestation of corneal neovascularization following chemical ocular injury in rabbits.** 123
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1 Department of Electric Engineering, Technion-IIT, Haifa 32000, Israel 2 Ophthalmology Department, HaEmek Medical Center, Afula, Israel
- 27 **Parafoveal processing of semantic information** 125
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- 28 **Incidence and Causes of Blindness in Israel between 1999 and 2010** 126
*Michael Belkin*¹, *Angela Chetrit*², *Michael Kinori*³, *Ofra Kalter-Leibovici*², *Alon Skaat*³
¹ Goldschleger Eye Research Institute, Tel Aviv University, Tel Hashomer, Israel ² Gertner Institute for Epidemiology&Health Policy Research, Tel Hashomer, Israel ³ Goldshleger Eye Institute, Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel
- 29 **The Correlation between Visual Acuity, Refraction and Cognitive Function in the Elderly** 127
Oriel Spierer⁽¹⁾, *Naomi Fischer*⁽¹⁾, *Adiel Barak*⁽¹⁾, *Michael Belkin*⁽²⁾
¹. Department of Ophthalmology, Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel ². Ophthalmic Technologies Laboratory, Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Israel

Session VII - Keynote Guest Lecture 2 10:00-10:30

Prof. Hagai Bergman, MD, PhD

Department of Medical Neurobiology, Faculty of Medicine (IMRIC); The Interdisciplinary Center for Neural Computation (ICNC) and the Edmond and Lily Safra Center (ELSC) for Brain Sciences, The Hebrew University of Jerusalem.

Lecture title: Exploiting basal ganglia tricks to treat their disorders.

Brunch break and Exhibition 10:30-11:00

Session VIII - Retina 2 11:00-12:00

Moderators: Prof. Eyal Banin and Prof. Dov Weinberger

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1) *Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, 2) Department of Biochemistry and Molecular Biology, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, 3) The Western Galilee Hospital in Nahariya, Israel*
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1) *Department of Biochemistry and Molecular Biology, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, 2)Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*
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(1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Israel; (2) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Israel; (3) Agricultural Research Organization, The Volcani Center, Israel; (4) Department of Ophthalmology, University of Florida, USA
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(1) Faculty of Bio-Medical Engineering, Technion (2) Edmund and Lily Safra Center for Brain Sciences, Hebrew University in Jerusalem (3) Department of Ophthalmology and Visual Science, University of Nebraska Medical Center, Omaha, NE, USA
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(1) The Maurice and Gabriela Goldschleger Eye Research Institute, Sheba Medical Center, Tel-Hashomer (2) The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv (3) Department of Life Sciences, Ben-Gurion University of the Negev

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(1) The Maurice and Gabriela Goldschleger Eye Research Institute, Sheba Medical Center, Tel-Hashomer (2) The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv (3) The Cancer and Radiation Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel-Hashomer (4) The Bert W Strassburger Lipid Center, Sheba Medical Center, Tel-Hashomer

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Dedicated to Prof. Shaul Merin

Moderators: Prof. Dror Sharon and Dr. Eran Pras

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(1) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel. (2) Department of Ophthalmology, Scheie Eye Institute, Philadelphia, PA, United States.
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(1) Department of Ophthalmology, Soroka Medical Center and Clalit Health Services, Faculty of Health Sciences, Ben Gurion University, Beer Sheva; (2) The Morris Kahn Laboratory of Human Genetics, Ben Gurion University, Beer Sheva; (3) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem; (4) Genetic Institute, Soroka Medical Center, Beer Sheva
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(1) Department of Ophthalmology, Assaf Harofeh Medical Center. (2) Danek-Gartner institute of human genetics, Sheba
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(1) Department of Ophthalmology, Hadassah—Hebrew University Medical Center, Jerusalem, Israel. (2) Molecular Genetics Laboratory, Institute for Ophthalmic Research, Centre for Ophthalmology, Tübingen University, Germany.
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Eran Pras (1), Eva Eting (1), Nadav Shoshany(1), Dina Volodarsky(2), Inna Vulih(2), Ofer Isakov(3), Noam Shomron(3)
1-Department of Ophthalmology, Assaf-Harofeh Medical Center, Tel Aviv University.; 2- Dyn Diagnostic Laboratories, Assaf-Harofeh Medical Center; 3-Functional Genomics Laboratory at Tel Aviv University.

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Session X - Glaucoma

13:20-14:00

Moderators: Dr. Miriam Zalish and Dr. Ronit Neshet

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Concluding Remarks: Prof. Avi Solomon

14:00

ABSTRACTS

תקצירים

Developmental fate of neonatal mouse eyes isografted in the peritoneal cavity. Metaplastic modulation by cyclosporine

(1) Ezra-Elia Raaya (1) Shpigel Y Nahum (1) Barishak Robert (1) Ofri Ron (1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel

Purpose: In 2003 Angio et al transplanted embryonic human eyes into the peritoneal cavities of mice with the aim of developing a new source of retina for tissue transplantation studies. We modified the technique to isograft neonatal eyes between mice, with the aim of maintaining normal eye development in this new anatomical environment, for eventual use in a retinal degeneration study. To suppress possible rejection response, half the recipients were treated with cyclosporine.

Methods: Ten eyes were removed from 9-day-old C57BL/6 mouse pups. Eight eyes were transplanted in the peritoneal cavity of eight adult C57BL/6 mice recipients. The remaining two eyes were studied as non-implanted controls. Four recipients were treated with daily intraperitoneal cyclosporine (20mg/kg) injections for 21 days. Three weeks after surgery the implanted eye were removed, processed, and stained with H&E and PAS stainings.

Results: In the two control eyes we found a normally-developing retina with all retinal layers present except photoreceptors. Eyes implanted in untreated recipients demonstrated loss of normal retinal lamination and dedifferentiation of its cell populations. The retina became a mass of proliferating primordial cells. The extremely thickened retina caused obliteration of the vitreal and anterior chamber cavities. However, primordial cells proliferation was not observed in eyes implanted in cyclosporine-treated recipients. Instead, we observed fibrous and osseous metaplasia which may have originated from developing retinal pigmented epithelium cells.

Conclusions: We did not achieve normal tissue preservation of implanted eyes, as reported by Angio et al. On the contrary, in untreated recipients we observed tissue dedifferentiation and suspected primordial cells proliferation. Treatment with cyclosporine, originally intended to prevent tissue rejection, unexpectedly resulted in reduction of cell proliferation and led to stimulation of fibrous and osseous metaplastic reaction. Future immunohistochemical studies are needed to determine the origins of the proliferating and metaplastic cells, and to understand the role of cyclosporine in this new metaplastic model.

Acknowledgement: This study was funded by The Joseph Alexander Foundation

Functional and morphological changes in the retinas of CCR2, CX3CR1 and CCR2-CX3CR1 knockout mice carrying RD8 mutation

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Purpose: Recently it has been shown that a leading model for age-related macular degeneration (AMD), the Ccl2-Cx3cr1 double knockout (DKO) mouse, is carrying another mutation at Crb1 gene; the rd8 mutation, and this mutation, rather than the knockout genes, is responsible for the AMD-like signs observed in the model. Our aim was to evaluate the functional and morphological changes in the retinas of Ccr2-Cx3cr1 DKO, Ccr2 knockout (KO), Cx3cr1 KO and controls mice, all carrying the rd8 mutation.

Methods: Scotopic and photopic electroretinograms (ERGs) were recorded from seven Ccr2 KO, five Cx3cr1 KO, five Cx3cr1-Ccr2 DKO and nine age-matched control (C57BL) mice. Retinas were studied histologically, and DNA samples were analyzed to confirm rd8 mutation.

Results: Scotopic a-wave amplitudes of Cx3cr1-Ccr2 DKO were significantly lower at the two highest intensities. A-wave implicit times of Ccr2 KO and Cx3cr1 KO were significantly longer at the highest intensity. B-wave amplitudes of Cx3cr1 KO were significantly lower and b-wave implicit times were significantly longer in both Ccr2 and Cx3cr1 KOs. No differences were found in response to photopic flash stimuli between KOs, DKOs and controls. In all Ccr2 KO retinas (n=7) and in 2/5 of the Cx3cr1 KO retinas no abnormalities were found. In one Cx3cr1 KO retina an area devoid of retinal pigment epithelium (RPE) cells was evident. In two other Cx3cr1 KO retinas an area of double layered RPE was noticed. In 4/5 of the DKO retinas, no abnormalities were found. In one DKO retina an area lacking the outer plexiform, outer nuclear and photoreceptor layers was evident, allowing the inner nuclear layer to come in contact with the RPE.

Conclusions: Although we identified rd8 mutations in addition to the genes knockouts in all specimens, the ERG deficits and morphological changes we observed are not typical of the extensive retinal degeneration known to be caused by the rd8 mutation. We conclude that not all of the reported retinal changes in this model can be attributed to the rd8 mutation. Our findings could be considered as another confusing aspect in the investigation of the role of Ccl2-Ccr2/Cx3cl1-Cx3cr1 axes in the DKO murine model of AMD.

Acknowledgement: This study was funded by The Joseph Alexander Foundation.

Computer Aided Diagnosis of Diabetic Retinopathy

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These authors contributed equally to this work.

Purpose: To present a novel method for quantitative assessment of retinal vessel permeability using a fluorescein angiography-based computer algorithm.

Methods: Twenty-one subjects (13 with diabetic retinopathy, 8 healthy volunteers) underwent fluorescein angiography (FA). Image pre-processing included removal of non-retinal and noisy images and registration to achieve spatial and temporal pixel-based analysis. Permeability was assessed for each pixel by computing intensity kinetics normalized to arterial values. A linear curve was fitted and the slope value was assigned, color-coded and displayed. The initial FA studies and the computed permeability maps were interpreted in a masked and randomized manner by three experienced ophthalmologists for statistical validation of diagnosis accuracy and efficacy.

Results: Permeability maps were successfully generated for all subjects. For healthy volunteers permeability values showed a normal distribution with a comparable range between subjects. Based on the mean cumulative histogram for the healthy population a threshold (99.5%) for pathological permeability was determined. Clear differences were found between patients and healthy subjects in the number and spatial distribution of pixels with pathological vascular leakage. The computed maps improved the discrimination between patients and healthy subjects, achieved sensitivity and specificity of 0.974 and 0.833 respectively, and significantly improved the consensus among raters for the localization of pathological regions.

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

Retinal and peripapillary nerve fiber layer thickness in eyes with thyroid-associated ophthalmopathy

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Purpose: Extraocular muscle enlargement and orbital fat expansion in thyroid-associated ophthalmopathy (TAO) may result in proptosis, diplopia, compressive optic neuropathy and visual acuity impairment. Although the orbital and histopathological structural changes associated with TAO are well documented, no significant change in retinal and/or nerve fiber layer (RNFL) thickness has been demonstrated. Optical coherence tomography (OCT) is a noninvasive imaging technology that accurately assesses RNFL thickness. The purpose of this study was to compare retinal and peripapillary RNFL thickness values in TAO patients with those of normal subjects and to assess the correlation between the severity of the orbital disease and the changes observed in macular and RNFL thickness.

Methods: Twenty-one patients with TAO (mean age 44.1 years) and 41 healthy controls (mean age 42.9 years) were evaluated. The participants underwent complete ophthalmological and OCT examinations (including measurements of macular and peripapillary RNFL thicknesses).

Results: The inner macula was significantly thinner ($270.4 \pm 17.27 \mu$) in 40 eyes of 21 patients compared to $281.79 \pm 15.2 \mu$ in 63 eyes of the 41 controls ($p=0.001$). The average RNFL thickness was significantly greater in the TAO group ($n=42$, $110.06 \pm 33.3 \mu$) compared to the controls ($n=73$, $96.25 \pm 9.42 \mu$) ($p=0.013$). The superior, inferior and nasal quadrant RNFL thicknesses were significantly greater in the TAO group (136.7 ± 45.73 , 137.95 ± 35.03 , and 99.38 ± 65.85 , respectively) compared to controls (118.47 ± 14.25 , 125.52 ± 13.55 , and 71.91 ± 13.95 , respectively). There was also a correlation between the above-mentioned changes in RNFL thickness and the clinical severity of the orbital disease.

Conclusions: Eyes of patients with TAO have a thinner macula and a thicker peripapillary RNFL compared to healthy controls, as demonstrated by OCT. There is also a correlation between the clinical severity of the disease and these changes on imaging. Retinal thinning may be secondary to mechanical compression on the retina by orbital contents. OCT may serve as a noninvasive tool for the diagnosis and follow-up of TAO.

Evaluation of Anticholinergic and Oxime Treatments Against Miosis and Visual Impairment Following Ocular Exposure to the Nerve Agent Sarin

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Purpose: Eye exposure to the organophosphorus irreversible acetylcholinesterase inhibitor sarin results in long-term miosis (a reduction of at least 50% of pupil width) and reduction in visual function. Anti-cholinergic drugs, such as atropine, are used topically in order to counter these effects and obtain symptomatic relief. Unfortunately, such compounds attenuate ocular discomfort at the expense of producing mydriasis and partial cycloplegia symptoms, which may worsen visual performance. This study was aimed to test beneficial drugs in contradicting the sarin-induced miosis and visual impairment, which will minimally affect vision.

Methods: Male Pigmented Long-Evans rats were topically exposed to sarin (0.2-1 μ), and 20 min later were topically treated. Pupils were illuminated with an infrared spotlight and images were digitally recorded with a computerized infrared-capable video camera, thus measuring pupil width. Pupil width was determined 15 min -8 h following exposure and treatment. Visual function assessment was performed using the Cued Morris Water Maze task, 15-35 min following sarin exposure and treatment. In this version, cued navigation involves finding a goal location by approaching a single cue that marks the visible goal.

Results: Rats exposed topically to various sarin doses showed a dose-dependent miosis, which partially recovered within 4-8 h. Oxime treatments with or without the anti-cholinergic drug tropicamide differentially improved the sarin induced miosis and the resulting impairment in visual performance.

Conclusions: The miotic as well as the visual defects observed, following topical sarin exposure are contradicted to various extent by the treatments used.

Oral Rifampin for the Treatment of Chronic Central Serous Chorioretinopathy

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Purpose: To evaluate the efficacy of oral rifampin for the treatment of chronic central serous chorioretinopathy (CSCR). In a previous publication, rifampin was suggested as an off-label treatment after observing incidental improvement of chronic CSCR in a patient on rifampin therapy for tuberculosis.

Methods: A retrospective study of eight patients treated with rifampin for chronic CSCR was performed. Patients were given rifampin 600 mg daily and then re-examined periodically. Additional visits were scheduled at 1, 5, and 13 weeks after the end of treatment. Snellen visual acuity, complete ophthalmic examination, fluorescein angiography, and optical coherence tomography were performed at baseline. Optical coherence tomography was repeated at all visits. All patients had a normal baseline laboratory panel (including liver enzymes, which were reevaluated during rifampin use).

Results: Mean patient age was 50 years (range 35-66). Mean duration of disease was 53+56 months (8-156 months). All patients were male. Six patients were treated with rifampin >6 weeks (6-20 weeks). One patient had two courses of rifampin therapy, which lasted 20 and 8 weeks, respectively. Two patients discontinued treatment due to nausea, rash and headache 3-4 weeks after initiation of treatment.

Mean log MAR visual acuity was 0.12±0.12 (Snellen 20/26) before treatment, and 0.09±0.13 (Snellen 20/24), 0.04±0.09 (Snellen 20/21), and 0.04±0.07 (Snellen 20/21) at 1, 5, and 13 weeks after the end of treatment, respectively.

Mean initial central macular thickness was 329+76 microns, and 293+107, 299+102 microns, and 277+82 microns at 1, 5, and 13 weeks after treatment, respectively. The difference between the initial and final central macular thickness was -52 microns.

Conclusions: Rifampin should be considered as treatment in patients with chronic CSCR after conventional treatment has failed. Subretinal fluid and visual acuity may improve with treatment. Larger, prospective studies are needed to further evaluate this treatment.

A Decrease in VEGF and Inflammatory Markers is Associated with Diabetic Proliferative Retinopathy

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Pade medical center– Poria ISRAEL

Purpose: Measuring inflammatory and angiogenic markers levels in diabetic patients in relation to the level of diabetic retinopathy.

Methods: Seventy three type II diabetic patients were randomly assigned to three groups (A– 25 patients [12 males], no diabetic retinopathy; B – 25 patients [19 males], non-proliferative retinopathy; and C – 23 patients [13 males], proliferative retinopathy), when they came for a routine follow-up visit in the ophthalmologic outpatient clinic. Twenty-three healthy subjects (14 males) served as controls. High-sensitivity C reactive protein (hs-CRP), soluble vascular cell adhesion molecule 1 (sVCAM-1) and vascular endothelial growth factor (VEGF) were studied.

Results: A difference in hemoglobin A1C (HBgA1C) levels was detected between groups A ($7.1\pm 2.7\%$) and B ($8.5\pm 1.5\%$) ($p=0.02$), but none was found between groups B and C ($8.5\pm 1.6\%$) ($p=0.98$). Only six patients (out of 23) used insulin treatment in group A, compared with 16 in group B (out of 25) and 17 in group C (out of 25) ($p=0.004$). All three groups of diabetic patients were older (62.8 ± 10.8 , 61.9 ± 9.4 , 59.2 ± 10.3 years, respectively) than the controls (44.3 ± 11.6 years) ($p\leq 0.001$).

Hs-CRP levels were higher in diabetic patients (4391 ± 4175 , 4109 ± 4533 , 3005 ± 3842 ng/ml, respectively) than in controls (1659 ± 1866 ng/ml); however, only the levels in patients of groups A ($p=0.01$) and B ($p=0.03$) were significantly different from those of the controls, in contrast to group C, which did not differ ($p=0.180$). Similar findings were observed for sVCAM-1 (706 ± 347 , 746 ± 328 , 638 ± 208 ng/ml, respectively, vs. controls [552 ± 143 ng/ml]); sVCAM-1 levels of groups A and B, but not C, differed from the controls ($p=0.05$, $p=0.01$ and $p=0.125$, respectively).

With the exception of group B ($p=0.03$), soluble VEGF DM type II levels (493 ± 353 , 625 ± 342 , 368 ± 223 , respectively) did not vary from those of the controls (392 ± 355 ng/ml, $p\geq 0.05$). However, as the disease progressed, there was a significant decrease in VEGF levels, accompanied by a significant difference between groups B and C ($p=0.006$).

Conclusions: Patients with type II diabetes with no-retinopathy and with non-proliferative retinopathy had high levels of inflammatory and angiogenic markers, which decreased in patients with diabetic proliferative retinopathy.

Prevalence and Risk factors for CHRPE using Optos Scanning Laser Ophthalmoscope

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Purpose: Congenital hypertrophy of the retinal pigment epithelium (CHRPE) consists of a single flat, round lesion, with sharply demarcated smooth or scalloped margins, which may vary in color, and is unilateral in almost 100% of cases (e.g. Cohen et al., 1993).

CHRPE is primarily of optometric and ophthalmological interest when considering a differential diagnosis of choroidal melanoma, and is almost always completely benign.

To the best of our knowledge, only one study looked at prevalence of CHRPE and found a prevalence of 1.20% (Coleman and Barnard, 2007). This study aims to determine the prevalence and risk factors associated with CHRPE in a healthy population, using the Panoramic 200 Scanning Laser Ophthalmoscope (Optos plc, Dunfermline, UK), which can capture up to 200° view of the retina, without pupil dilation.

Methods: A large cohort of healthy students were recruited from the student body of Hadassah Academic College. Images from each eye were obtained using the Optos SLO along with a visual assessment. Each Optomap image was analyzed by 3 independent examiners. Subjects were asked to complete a self administered questionnaire covering socio-economic status, ethnicity, medical and eye health history. Hair, eye and skin pigmentation was assessed using previously reported methodology (Blue Mountain Eye Study). Prevalence was calculated, and control and nevi cohorts were compared using chi-square analysis.

Results: Preliminary analysis was carried out on the first 340 subjects (88 men, 252 women, average ages 23.71 ± 4.54). 19 subjects (5.6%) had one or more CHRPE. All subjects had monocular CHRPE (10 in the Right eye). Multiple CHRPE were observed in five subjects (16.7%). The average maximum diameter of the CHRPE was 553.4 ± 426.7 , and they were located mostly in the inferior temporal quadrant (52.6%).

We found no statistically significant risk factors for CHRPE. This includes gender, Ethnicity, consanguinity, sun exposure and eye and hair color.

Conclusions: The prevalence CHRPE using the Optos was 5.6%. No significant risk factors for CHRPE were found, supporting the congenital etiology. This is in contrast to our analysis of the same cohort for choroidal nevi, where gender and sun exposure were found to be risk factors (Gordon-Shaag, in preparation).

Visual Acuity and Contrast Sensitivity Improvement in Cases of Congenital Nystagmus Using NeuroVision™ Technology

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Purpose: To evaluate the effectiveness of NeuroVision™ (RevitalVision, LLC) perceptual learning program, in improving contrast sensitivity and visual acuity in Congenital Nystagmus (CN) patients.

Methods: Twenty eight patients with CN (18 males and 10 females) were enrolled, and treated with NeuroVision™ treatment (RevitalVision LLC, KS).

Data was collected from 16 clinics in 5 countries. Baseline Best Corrected Visual Acuity (BCVA) was 6/9 to 6/60 (20/30-20/200). Within the group, 5 patients had albinism, one patient was diagnosed with Punctata Albescens and rest had motor nystagmus. Only two patients received medication during treatment period. The patients age range was 11 to 51 (mean 24.8).

Results: 23 of the 28 patients treated showed improvement in BCVA. The average improvement was 2 Snellen lines (range 0-5) (figure 3). Contrast sensitivity improved in 9 out of 10 patients tested, mostly in low spatial frequencies. Eight patients obtained at least 6/12 (20/40) vision in their better eye, allowing them to meet the driving license criteria for the first time in their lives.

Conclusions: NeuroVision™ (RevitalVision, LLC) perceptual learning program may be an effective technique to improve vision in patients with CN. Further controlled studies should be performed in order to confirm these encouraging findings.

Effects of Ranibizumab in patients who failed on previous treatment with Bevacizumab

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Purpose: The use of anti-vascular endothelial growth factor (anti-VEGF) agents in the treatment of neovascular age-related macular degeneration (AMD) has revolutionized the field and has given hope to many patients suffering from this debilitating disease. Although Ranibizumab (trade name Lucentis) is a drug that has been researched extensively and its effectiveness has been proven for the treatment of neovascular, its use was not approved by Clalit HMO till recently, and patients who required anti VEGF intravitreal injections received Bevacizumab (trade name Avastin). As of April 2012- patients afflicted by neovascular AMD who are insured by Clalit Mushlam, and who are unresponsive to treatment with Bevacizumab (Avastin) can be offered treatment with Lucentis (Ranibizumab).

The purpose of this study is to investigate whether the switch to Ranibizumab does in fact improve the Best Corrected Visual Acuity (BCVA) and/or Central Foveal Thickness (CFT) of treated patients.

Methods: Patients who fail to improve on treatment with Bevacizumab, as determined by their treating ophthalmologist, can apply for a series of Ranibizumab intravitreal injections. Outpatients of the SUMC ophthalmology clinic have their BCVA taken at every encounter, and undergo Ocular Coherence Tomography (OCT) of the macula before and after being treated with a course of intravitreal Ranibizumab. Records of patients that have received Ranibizumab were reviewed and BCVA before and after treatment were analyzed and compared. CFT from OCTs before and after the Ranibizumab were in a masked fashion by a retina specialist.

Results: Eighty-four eyes were included. Mean pre-ranibizumab visual acuity was 0.23 decimal (6/26). Mean duration of bevacizumab treatment was 31.1 ± 16.4 months. Mean number bevacizumab injections was 14.9 ± 9.9 injections. Mean post-ranibizumab visual acuity was 0.22 decimal (6/27). There was no statistically significant difference in visual acuity before or after ranibizumab injections ($p=0.25$). There was no statistically significant difference in CFT before or after ranibizumab injections

Conclusions: In our subset of patients with neovascular AMD switched from bevacizumab to ranibizumab therapy, there were no apparent differences in visual acuity outcomes or central retinal thickness.

Characterization of Diabetic Retinopathy (DR) in NOD Mouse Model Reveals Molecular Mechanisms involved

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Purpose: The pathogenesis of DR has been investigated using several animal models of diabetes. Nonobese diabetic (NOD/LtJ) mice exhibit susceptibility to spontaneous development of autoimmune (type 1) insulin dependent diabetes mellitus (IDDM), followed by DR.

To study the vascular, neural, and glial abnormalities in retinae of a NOD/LtJ mice.

Methods: 2 months following diabetes onset diagnosed by high glucose levels, mice were euthanized and the retinae were harvested (n=15). Histological and immunohistochemical analysis for retinal structure, vasculature and thickness was conducted. Fluorescein angiography and flat mount analysis were performed for vasculature imaging. Molecular analysis for various gene expression was carried out following RNA extraction and cDNA conversion using Real Time PCR. Levels of oxidative-stress, apoptosis-, ischemic- and angiogenic- related genes were analyzed. Mice that did not develop diabetes from the same colony served as controls (n=15).

Results: DR changes showed thickening of the vasculature basement membrane, as stained by H&E and PAS staining. Increased permeability of the vasculature was detected on FA, but no leakage could be demonstrated on flat mount retina following perfusion with Indian ink. No neovascularization was demonstrated. Immunohistochemistry revealed loss of pericyte and endothelial cells. Molecular analysis revealed increased in apoptosis, oxidative stress, ischemic and angiogenic related genes expression as compared to the non diabetic retina.

Conclusions: NOD/LtJ mice can serve to evaluate early and late DR complication, although in this preliminary study we did not demonstrate neovascularization. The vascular changes, in the basement membrane and cell loss underlie shown by histology and apoptotic staining, followed by the leakage shown on FA, contributes for the edema and retinal thickening. Oxidative stress might exacerbate the damage. Having this model at hand, further studies could measure the effect of various treatments to prevent DR.

Intraocular injection of Brimonidine did not show any protective or toxic effect on mouse injured retina

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Purpose: Brimonidine tartrate (BRM; Alphagan P, 0.15%; Allergan Inc. Irvine, CA, USA) is an alpha2 adrenergic agonist, used in eye drops for glaucoma. Previous studies have reported a neuroprotective effect on retinal cells. Our group previously described a protective effect when given by drops or intraperitoneally in ischemic optic neuropathy model. In this study we aim to investigate the effect of intravitreal (IVT) injection on RGCs in a mouse model of optic nerve crush (ONC).

Methods: ONC was induced in the right eye of 50 C57BL6 wild type mice simultaneously with IVT BMN injection to the right eye (n=25) or saline (n=25). The left eye served as an internal control. Evaluation included: quantitative real-time PCR for gene expression on day 3 of apoptosis related genes (BAX, BCL-2), ischemia and oxidative stress associated genes (HO-1, SOD). Histological and immunohistochemistry analysis of optic nerves and retina was performed on day 21.

Results: 3 days following ONC, the IVT BMN injection revealed increased BAX levels (1.38 ± 0.7) and baseline BCL-2; IVT saline group showed reduced levels of both. In the IVT BRM group, HO-1 levels increased (1.63 ± 1.3) and SOD did not change, while both increased (1.33 ± 0.6 , 1.33 ± 0.9) in the saline group.

In the control group of IVT BMN without ONC, no RGC loss on day 21 was observed. Following ONC, both IVT BMN or IVT saline had 53% RGC loss.

Conclusions: We did not find a protective effect of intravitreal injection of brimonidine. IVT injection of BMN alone was not found to be toxic. Although on day 3 increased levels of apoptosis related genes were detected in the IVT BMN ONC group and not the saline (NS), similar levels of SOD and HO-1 were measured, and same RGC loss was calculated on day 21. We speculate that the induced vasoconstriction of retinal blood vessels by this drug might prevent its known neuroprotective effect when injected intravitreally in the model of mouse ONC.

The effect of intraocular or systemic injection of Revatio (Sildenafil) on mouse ocular blood vessels and neurons

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Purpose: Revatio (Sildenafil) relaxes muscles and increases the blood flow to particular areas of the body. The purpose of this study was to measure the effect of Revatio on mouse ocular blood vessels and neuronal tissue.

Methods: Transgenic Thy-1-CFP and C57Bl6 mice underwent Revatio injection intravitreally to the right eye (IVT, n=12) or intraperitoneally (IP, n=20). The left eye with or without saline injection served as a control. Another control group (n=6) was with no intervention. Evaluation included: 1. Retinal fluorescence angiography; 2. Flat mount retinae analysis; 3. TUNEL staining for apoptosis; 4. TTC staining of the nerves for stroke detection; 5. Molecular analysis for the expression of apoptosis and ischemic related genes: SOD, HO-1, GFAP, MBP, Bcl-2 and BAX.

Results: Retinal vessels dilatation and increased choroidal effusion were detected by FA and flat mount retinae immediately following IVT and 30 minutes after IP Revatio injection. No RGC loss was detected in the retina 21 days following IVT injection (n=5) and IP (n=10). None of the 5 optic nerves following direct IVT injection revealed stroke. TTC staining revealed one (out of 20) stroke suspected area in the anterior segment of the nerve following Revatio IP. In the IVT group, gene expression analysis showed an increase in Bcl-2 on day 1 which reverted to baseline at day 3; no significant change was detected in the other gene levels. All genes measured in the IP group, increased (2-3 fold) on both days 1 and 3 and every 10th optic nerve tested showed a significant increase in all genes examined, higher than those of other samples.

Conclusions: Revatio increased choroidal perfusion and mildly dilated retinal vessels. Following IP injection, we detected, histological and molecularly, clues towards an optic nerve stroke in a few samples, with an increase in apoptotic and ischemic related gene expression. These marginal examinations should be further investigated in a large number of mice, to validate the possible association of Revatio and stroke.

The relationship between diabetic retinopathy and diabetic nephropathy in patients with diabetes mellitus type 2

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Purpose: To evaluate correlation between the severity of diabetic nephropathy and diabetic retinopathy in patients with diabetes mellitus type 2.

Methods: A retrospective study including 917 patients with diabetes type 2. Diabetic retinopathy (DR) was diagnosed based on fundus photographs taken with a non-mydriatic camera. Diabetic nephropathy (DN) was diagnosed based on urinary albumin concentration in a morning urine sample. All the patients' data were extracted from the corresponding medical records. Statistical analysis was performed using the seemingly unrelated regression (SUR) model, which provides more efficient estimates than regular separately run regression models do.

Results: Our SUR analysis is statistically significant: the test for "model versus saturated" is 2.20 and its significance level is 0.8205. The model revealed that creatinine and glomerular filtration rate (GFR) have strong influence on albuminuria, while body mass index (BMI) and HbA1c have less significant impact. DR is affected positively by diabetes duration, insulin treatment, glucose levels, HbA1c, and affiliation with the Arabic community, and it is affected negatively by GFR, triglyceride levels, and BMI. The association between DR and DN was statistically significant and had a unidirectional correlation (coefficient 0.22 at significance $p < 0.001$), which can be explained by chronological order; that is, DN precedes DR.

Conclusions: The present study indicates that a more serious renal impairment (DN) is associated with more serious damage to the eye (DR). Furthermore, this correlation has a chronological aspect— the renal injury precedes retinal damage. To our knowledge, no previous research either looked at or established such a finding.

A simple model for creation of chorioretinal neovascularization (CNV) in pigmented mice using indirect diode laser

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Purpose: Chorioretinal neovascularization (CNV) formation in animal models is essential for the investigation of the pathophysiology and treatment modalities of human neovascular chorioretinal diseases. Models are designed in order to be efficient, reproducible and repetitive over-time. The current and most popular animal model for CNV is based on disruption of the Bruch's membrane of mice retina by immobile direct-laser. This setup is inconvenient for laboratory use, difficult to conduct and expensive. Our aim was to establish a novel laser-induced model for CNV creation in pigmented mice, using a mobile indirect-diode laser and to establish the parameters of the lens, laser beam and working modality that will ensure consistent and repeatable model.

Methods: Indirect diode laser ophthalmoscope (Iris Medical Oculight SLX System) was used. Large scale of laser power (200-800 mW) and duration (100-200 msec) was applied around the optic disc of pigmented male mice (CD57BL/6J strand), in order to achieve white bubble formation. CNV presence was searched with Hematoxylin&Eosin (H&E) and CD31 immunohistochemical staining of thin sections, and by fluorescein angiography (FA). CNV total area was determined by using CD31 staining of a flattened choroid performed at 5 and 14 days after laser. Correlations between lesion number and area of CNV were performed.

Results: The 90D treating lens was chosen, because of the smallest depth of focus and highest accuracy in its focal point. Formation of acute vapor white bubbles was demonstrated in the laser range of 200-400 mW and 100-200 msec. CNV existence was proved at 5 and 14 days after laser by H&E and CD31 staining, and by FA. Quantitative measurements of CNV area revealed a linear correlation between CNV area and number of laser lesions performed.

Conclusions: We described for the first time a repeatable laboratory model of CNV induction by indirect diode-laser in pigmented mice. Since indirect diode-laser is an easy-to-use, inexpensive, mobile and convenient form we suggest that it can serve as an alternative for the current immobile laser systems used for creation of CNV.

Identification of the rd8 mutation in commonly used mouse models for retinal degeneration and diseases.

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Purpose: Mouse models have been commonly used for the study of retinal degeneration, including the highly published chemokine receptor/ligand knockouts (KOs) used for the study of age-related macular degeneration (AMD). Recent publications have brought to light the possible prevalence of the naturally occurring rd8 mutation which is associated with retinal degeneration in the C57/Bl6-N background, upon which many of the KO mice have been created. We report here how to identify the Rd8 mutation in mice, as well as the identification of the Rd8 mutation on CCR2 KO mice, but the lack of such mutation in the CCR2/CX3CL1 double KOs (dKO).

Methods: PCR with specific primers was performed on the CRB1 gene in WT, CCR2^{-/-} KOs, and CCR2/CX3CR1 dKO mice. Sequencing was performed to identify the single base pair deletion of C at nt3481, which causes a frameshift and premature stop codon, known as the recessive rd8 mutation. The chemokine deficient mice were evaluated for characteristics of the rd8 associated phenotype.

Results: All WT mice tested were negative for the mutation, while all CCR2 single KOs were positive for the single nucleotide deletion. When CCR2/CX3CL1 dKO mice were tested, all were negative for the rd8 mutation, possibly due to breeding out the mutation by crossing the single KOs with each other. Microarray performed on the CCR2 single KO confirmed the low gene expression for the CRB1 gene due to the deletion (fold change=-1.82, P=1.92E-05). ERG and histology in CCR2 deficient mice were not affected by the rd8 mutation.

Conclusions: Mouse models or embryonic stem cells on the C57/Bl6-N background may have the rd8 mutation, which can induce an ocular phenotype with or without other knocked-out genes, thereby, potentially confounding analysis on such models. Therefore, researchers using mouse models for retinal diseases should screen their mice for the rd8 mutation.

Modulation of Laser-Induced Choroidal Neovascularization by Macrophages from Patients with Age-Related Macular Degeneration and Unaffected Controls

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Purpose: Monocytes/macrophages have been implicated in the pathogenesis of age-related macular degeneration (AMD), and it has been speculated that macrophages can modulate the formation of choroidal neovascularization (CNV). Our previous work showed that activated macrophages from AMD patients have pro-angiogenic capabilities in a model of laser-induced CNV. Therefore, our aim is to compare the effect of activated macrophages derived from AMD patients with those derived from age-matched controls.

Methods: Monocytes were isolated from peripheral blood of individuals older than 60 years unaffected by AMD (n=3). Monocytes were cultured and matured to M0 phenotype and then polarized to M1 or M2 phenotypes using LPS and IFN-g for M1, and IL-13 and IL-4 for M2. Generation of polarized macrophages was validated by QPCR for CCL22, CCL17, TNF- α and IL-12. Fluorescently-labeled polarized M1 or M2 macrophages, M0 macrophages, or PBS were injected into the vitreous of rat eyes following the formation of laser-induced CNV. Measurement of CNV size was performed according to isolectin staining of retinal pigment epithelium (RPE)-choroid flatmounts. Macrophage survival and migration pattern was assessed in retinal and RPE flat mounts. CD11b and CD45 staining was performed to identify endogenous macrophages and white blood cells, respectively.

Results: Intravitreal delivery of polarized human macrophages did not cause inflammation, and survived up to 7 days following the injection to rat eye. Injected macrophages were detected throughout the retinal layers and in the vicinity of CNV lesions. According to isolectin staining of RPE-choroid flat mounts, increased CNV size was observed following injection of M1 derived from control patients ($X1.26 \pm 0.008$, $P=0.02$, Student's t-test), and M2 ($X1.68 \pm 0.005$, $P<0.0001$) macrophages, but not following M0 macrophage injection ($X0.95 \pm 0.01$, $P=0.62$). Similarly, increased CNV size was observed following injection of M1 macrophages ($X1.46 \pm 0.13$, $P=0.006$), and M2 ($X1.38 \pm 0.13$, $P=0.022$) macrophages from AMD patients (n=12), but not M0 macrophage injection ($X1.23 \pm 0.16$, $P=0.22$).

Conclusions: Intravitreal delivery of differentiated human macrophages is associated with a pro-angiogenic effect in the rat model of laser-induced CNV regardless of the individual's AMD status. Accelerated monocytes' recruitment to the eye may account for support of CNV growth. Further work has to be done to evaluate the monocytes' recruitment.

Semaphorin-3A: a leading factor in apoptotic programmed death of neuronal cells

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Purpose: To analyze the expression of semaphorin-3A (sema3A) and its effect on degenerative processes following trauma to the optic nerve (ON) and retina. Understanding sema3A role may lead to neuroprotective treatments for diseases and trauma that end in blindness.

Methods: Using Western blot and immunohistochemical analysis, the expression levels of sema3A were studied in glaucomatous rabbits, a mouse model of genomic instability syndrome, rhegmatogenous retinal detachment (RRD) in rats and ON injury in rat (vision abolition) and goldfish (capable of vision restoration).

In two parallel experiments, Function-blocking antibodies against sema3A were injected into the vitreous of rats following ON axotomy while sema3A molecules were injected into the vitreous of goldfish eyes after ON injury. At a given time after injury, the retrograde neurotracer 4-Di-10-Asp was applied to the transected nerve 0.5 mm from the proximal border of the transection site. This dye serves as a marker for living retinal ganglion cells (RGC) because it is transmitted through the axonal network and stains the cell bodies of live neurons only.

Results: Sema3A levels were elevated in all rodent models, i.e glaucomatous rabbits, transgenic mice, RRD and ON axotomy in rats. In contrast, sema3A levels were temporarily down-regulated following injury to the ON of goldfish.

Intravitreal injection of sema3A to goldfish eye, shortly after ON injury, led to destructive effects on several pathways of the regenerative processes, including the survival of RGC. On the other hand, Intravitreal injection of Function-blocking antibodies against sema3A to rat eye, shortly after optic nerve injury, led to a significant increase in RGC survival.

Conclusions: These data indicate that sema3A plays a pivotal role as a mediator of neuronal fate and may participate in a crucial step of the apoptotic cascade. It is necessary to down-regulate sema3A in order to enable functional regeneration. Thus, inhibitors of sema3A signaling will most likely be good candidates for neuroprotective therapy.

The A481T Change in the P Gene Causing Oculocutaneous Albinism type 2: A Pathogenic Mutation or a Polymorphism?

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Introduction: Mild phenotypes of Oculocutaneous Albinism type 2 (OCA2) or hypopigmentation with normal vision were described for the P change A481T in Northeastern Asian populations. However, A481T was not detected as a polymorphisms in Caucasian populations, but was detected in compound heterozygotes Caucasian albinos. Our accumulated data indicate that the phenotype of albinos with two different mutations in the same gene is determined by the “mild mutation”.

Purpose: To determine the phenotypic range of albinism caused by A481T in Jewish albinos.

Methods: Phenotypic evaluation included hair, eye and skin color, presence of nevi and ability to tan. Eye examination included visual acuity, photophobia, presence of nystagmus, transillumination, visibility of choroidal vessels and hypoplasia of the macula. Blood DNA was PCR amplified followed by restriction digest or sequencing.

Results: Compound heterozygotes for A481T and an additional P mutation– G27R were detected in two extended families. However, upon clinical examination of compound heterozygotes, all were hypopigmented but only part of the members of Family 1 had visual handicap. To determine if A481T was involved in the OCA2 phenotype in Family 1, we sequenced TYR, P, TYRP1, SLC45A2 and GPR143, causing OCA1-4 and X-linked Ocular albinism (OA), in one of the albinos in Family 1, but no additional mutation was identified. Hence, G27R and A481T are presumably the only mutations in this family. We further screened the cohort of Israeli Jewish albinos and identified one homozygote and 14 additional heterozygotes for A481T, all exhibiting mild phenotypes with the differential diagnosis of OCA, OA congenital nystagmus or normal. The second P mutation was identified in part of these 14 albinos. None of 130 unrelated, normally pigmented Israeli Jewish individuals carried the A481T mutation. We also detected normal to very mild phenotypes of albinism in compound heterozygotes for “severe” TYR mutations and the TYR common polymorphism R402Q.

Conclusions: The P mutation A481T causes normal phenotypes of hypopigmentation to very mild phenotypes of albinism with inter- and intra-familial variability in compound heterozygotes. The same phenomenon was detected in compound heterozygotes for “severe” TYR mutations and the change R402Q in TYR. What is the relevance of two identified TYR or P mutations in normal individuals?

Filed-Induced motion of magnetic-hydrogel sealant to patch retinal breaks

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Purpose: Retinal Detachment is a serious condition in which the retina is detached from its underlying layer due to a tear, and if left untreated, it can lead to vision loss and blindness. While several approaches are available to seal retinal breaks; These means are laser applications, cryo, scleral buckle, gas and silicon oil, each one of them have disadvantages and is not compatible for every case or patient. Aims: This important medical need to find alternatives, led us to develop a new method of inserting a magnetic implant to the retina and remotely control its location towards the retinal tear using a magnetic field. A novel design which combines the advantages of both biological hydrogel sealants and ferrofluids in the presence of magnetic field will give us better control over manipulating the “magnetic-hydrogel sealant” towards the retinal tear

Methods: Isolated porcine eyes were used in this study as ex vivo model. Retinal detachment was created by removal of the eye cap followed by gentle injection of 0.5ml of saline between the retina and choroid using 30-gauge needle, thus forming a subretinal space and retinal detachment. The magnetic sealant was composed of a hydrogel known as DuraSeal and ferrofluids composed of magnetic nanoparticles. Ferro-DuraSeal (F-DS) was prepared in a 1:1 ratio and 0.1ml was immediately injected to the subretinal space. An external NdFeB magnet (35N) was placed on the other wall (the sclera) and field-induced motion of the magnetic-sealant was evaluated and recorded.

Results: Ferro-DuraSeal sealant was easy to prepare and inject into the subretinal space. Retraction of the magnetic-sealant was feasible in the sub-retinal space with the ability to maneuver its movement in different directions using an external magnetic field.

Conclusions: Field-induced movement of magnetic-hydrogel sealant is feasible and enables us to retract the magnetic-sealant to a desired location such as a potential retinal tear. Further in vivo studies are set to evaluate this model and its potential as patching retinal breaks for clinical application.

Single- and multi-photon fluorescence retinal imaging in the intact rodent eye

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Purpose: Non-invasive fluorescence fundus imaging could prove to be an important tool for in-vivo small animal retinal imaging in a wide array of translational vision applications, including the tracking of fluorescently tagged cells and the expression of gene-therapy and optogenetic vectors. Recently, we demonstrated the ability to achieve cellular resolved images by means of 1P fluorescence micro-endoscopy in a retina transduced with fluorescent proteins and the GCaMP-family of optogenetic calcium indicators (Schejter et al., 2012, TVST). Here we demonstrate two-photon imaging in the same animal models.

Methods: A custom endoscope-based fundus system and a two-photon microscope were used to acquire fluorescence images from head-fixed animals expressing optogenetic probes in-vivo.

Results: Two-photon imaging yielded well-resolved fluorescence images of retinal fine structure which were axially sectioned to individual retinal layers. Interestingly, both two-photon imaging (without adaptive optics) and the endoscope-based images appeared to be robust to PSF distortions that completely smeared out cellular details in a conventional 1P fluorescence microscopic image of the same retina. The two methods have major differences in their sectioning ability, field of view, resolution, and the practicality of extending them to functional imaging.

Conclusions: This study demonstrates the ability to acquire fluorescent fundus images in-vivo by implementing two different imaging modalities. We will discuss the advantages and disadvantages of both methods and possible methods for improvement.

Subretinal transplantation of human adult mesenchymal stem cells ameliorate retinal structure and function in a rat model of retinal dystrophies

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Purpose: To examine the effect of subretinal transplantation of human-derived bone marrow mesenchymal stromal cell population (hBM-MSCs) on retinal structure and function in RCS rats.

Methods: A quarter million hBM-MSC cells (CD73+, CD90+, CD105+, CD45-) from healthy human donors were transplanted subretinally into one eye of 69 RCS rats at p28 using a novel transplantation system that was recently developed in our laboratory. Ten RCS rats were similarly injected with medium as control. Retinal functions were tested electroretinographically before and following transplantation for 22 weeks. Histological analysis and immunofluorescence staining with anti-rhodopsin antibody were used to assess photoreceptor rescue following cells transplantation

Results: Transplanted cells were identified shortly after transplantation as a uniform sheet of cells distributed under most of the retina and the choroid in RCS rats. One week after transplantation, cells were confined to the subretinal area. A prolonged (up to p168) and statistically significant enhancement of retinal function following hBM-SC transplantation was demonstrated by electroretinographically. These results correlated with histological analysis that revealed a significant preservation of retinal structure with increased number of photoreceptors in the outer nuclear layer along most of the retina. In spite of using no immunosuppressant utilization, long-term safety analysis demonstrated no gross or microscopic adverse effects of cell transplantation.

Conclusions: Subretinal transplantation of hBM-MSCs preserves retinal structure and function in RCS rats. Our findings suggest that hBM-SCs may possibly be an effective and safe treatment for retinal dystrophies.

Chromatic pupillometer-based perimetry in patients with retinal dystrophies

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Purpose: To objectively assess visual field defects and retinal functions in patients with retinitis pigmentosa and cone-rod dystrophy using a novel objective chromatic pupillometer.

Methods: Twenty seven participants were recruited (11 healthy individuals and 16 retinitis pigmentosa or cone-rod dystrophy patients). A computerized infrared video pupillometer was used to record changes in pupil diameter in response to short- and long-wavelength stimuli (peak 485 nm and 620 nm, respectively) size V, at light intensities of 40 cd-s/m² and duration of 1000 ms at 13 different points in the visual field. Percentage changes of pupil diameter were calculated. The pupillary responses of patients were compared with their findings on dark-adapted chromatic Goldmann perimetry and with the pupillary responses obtained from normal control subjects.

Results: Significantly reduced pupillary responses were obtained in retinitis pigmentosa patients under testing conditions that emphasized rod contribution (short-wavelength stimuli) in nearly all perimetric locations ($P < 0.05$). By contrast, under conditions that emphasized cone contribution (long-wavelength stimuli), RP patients demonstrated significantly reduced pupillary responses only in superior and nasal locations ($P < 0.05$). In a cone-rod dystrophy patient, the pupillary response to both long- and short-stimuli was

significantly lower in the scotoma area identified by the dark-adapted chromatic Goldmann perimetry.

Conclusions: This study demonstrates the potential feasibility of using pupillometer-based chromatic perimetry for objectively assessing visual field defects in patients with retinal dystrophies. This method may enable the identification of the damaged photoreceptor cells underlying the visual field defects.

Clinical and Genetic Characteristics of Primary Acquired Vitelliform Lesions (AVL)

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Purpose: Adult-onset foveomacular vitelliform dystrophy (AOFVD) was described as an autosomal dominant maculopathy which is usually diagnosed in the 3-5 decades of life. We aim to characterize AOFVD in comparison with typical age related macular degeneration (AMD).

Methods: Eighty two eyes of forty three consecutive patients AOFVD which were not accompanied by additional retinal pathology other than drusen were retrospectively evaluated. Data collected included demographics, ophthalmic findings, genetic analysis for the peripherin/RDS and BEST1 genes, and CFH and HTRA1 SNPs and review of imaging. Data was compared with 327 consecutive neovascular AMD (NVAMD) patients.

Results: Mean age (SD) of AOFVD patients (77.3 ± 9.9 years) and NVAMD patients (78.36 ± 12.4), and the female/male ratio (AVL: 23/21, AMD: 36/44) were similar. AOFVD patients were negative for peripherin/RDS and BEST1 gene mutations. Nine (11%) of the AOFVD patients eyes had typical drusen while two (2.5%) had cuticular drusen and ten (12%) had sub retinal drusen in addition to the vitelliform lesion. Thirty nine patients had bilateral lesions. Per OCT, twenty three (28%) of the eyes had vitelliform lesions while five (6%) had showed the pseudohypopyon stage, thirty nine (47.6%) had vitelliruptive stage and eleven (13.4%) had atrophy. The mean visual acuity (LogMAR) (\pm SD) was 0.38 in patients with vitelliform lesion and 0.51 in patients who developed atrophy ($P=0.1$).

Conclusions: These data, combined with our previous report on the association of the HTRA1 risk SNP for AMD with AOFVD, suggest that AMD and AOFVD overlap in terms of genetics, demographics, and some of the clinical characteristics. Individuals with AOFVD may have either the autosomal dominant form, or alternatively, a multifactorial form associated with HTRA1 SNP and an older age of onset.

Reduction in the incidence of autosomal recessive Retinitis Pigmentosa in Israel: probably due to lowered consanguinity rates

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Purpose: To evaluate trends in the incidence of retinitis pigmentosa according to mendelian heritage and consanguinity rates in Israel between 1931 and 2011.

Methods: A retrospective cohort study was performed on 202 patients with retinitis pigmentosa (RP) registered at the Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer (2010-2012). Patients were analyzed for year of birth, mendelian pattern of inheritance and for parental consanguineous marriage.

Results: Percentage of autosomal recessive RP (AR-RP) patients were 71%, 73%, 75% in patients born between 1931-1950, 1951-1970 and 1971-1990, respectively. The percent of AR-RP patients declined to 63% in patients born between 1991-2011. The percent of autosomal dominant RP (AD-RP) remained nearly constant (around 9% of RP patients) in the last 60 years. Percentage of parental consanguinity declined from 59.2% of patients born between 1951-1970 to 47.5% in those born between 1971 and 1990, and to 21.4% in patients born during the last 2 decades ($p=0.04$).

Conclusions: A decline in parental consanguinity in recent years in Israel may have reduced incidence of AR-RP, an observation which may explain the recently described decline in RP blindness rates in Israel.

Multifocal RGP Contact Lenses with Reduced Halo

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Purpose: To present extended depth of focus and multi focal RGP contact lenses having reduced halo and simpler procedure for their adaptation to the patients' eyes.

Methods: Laterally large (tens of wavelengths) concentric scratches with depth of less than one micron are added to the base curve of a regular RGP contact lens in such a way that via the effect of interference, at the focal spot of the lens, axially extended point spread function is generated. By avoiding discontinuity in the scratches the halo effect are significantly suppressed. The proposed RGP contact lenses were fabricated and tested both on an optical bench constructed according to the Arizona eye model as well as in clinical trials. The performance of the proposed lens was compared to existing aspheric RGP multifocal lens.

Results: The obtained results show significantly better image quality in resolution and significantly smaller halo effects in respect to what is obtainable with aspheric RGP lenses. In resolution we obtained contrast of 65% and 30% for the distance and near vision respectively for spatial frequency of 100 cy/mm. In aspheric RGP lenses the obtainable contrast for spatial frequency of 100 cy/mm is below 20% for both distances. The halo ring of the point spread function (PSF) existing in the aspheric lenses was completely eliminated.

Conclusions: The proposed interference based concept for designing extended depth of focus RGP contact lenses proposes a significantly better performance (in sense of obtainable contrast and halo) in respect to the currently existing alternatives. The proposed concept is based on adding special concentric scratches on the posterior surface of regular monofocal RGP lens and thus they exhibit much simpler and faster process of adapting the lenses to the patients.

Gene expression patterns in monocytes isolated from patients with neovascular age-related macular degeneration

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Purpose: The role of monocytes/macrophages in the pathogenesis of age-related macular degeneration (AMD) is still unclear. Our previous work has shown that there is an inflammatory signature from peripheral blood monocytes from patients with NVAMD as compared with age-matched controls. We then speculated for possible mechanisms correlated with the signature using bioinformatics methods on the gene expression profile of monocytes from NVAMD patients.

Methods: Affymetrix Human Gene 1.0 ST microarrays were previously performed on total blood monocytes, including the CD14+CD16+ subset, taken from treatment-naïve NVAMD patients (n=14) and age-matched controls (n=15). RMA normalization and inclusion of batch effect was performed using bioinformatics software, and transcription factor (TF) motif analysis was performed with open sourceware programs ISMARA (Swiss Institute) and GSEA (Broad Institute). QPCR was performed to validate expression patterns identified by the microarray analysis.

Results: Using RMA normalized data, 2,342 genes were found to be significantly differentially expressed between NVAMD patients and controls ($P < 0.05$, ANOVA and Student's T-test). Many of the genes were connected to inflammation or the inflammasome including NLRP3 ($P = 0.025$). Validation of the most significant genes TMEM176A/B ($P = 0.01$), part of dendritic cell maturation, on AMD (n=6) and control (n=6) mRNA not previously used for microarray, using QPCR confirmed the analysis. GSEA overlap analysis was performed to view specific TFs that regulated a significant number of genes found to be differentially expressed. Of lists scanned in the Molecular Signatures Database (MSigDB), the highest TF that correlated with a motif found in 274 of significant genes was the TF TCF3, also known as E2A, an immunoglobulin-enhancer TF ($P < 0.0001$). ISMARA analysis found several upregulated TF motifs in differentially expressed genes, the highest of which upregulated in AMD patients was the AHR TF family (Z-value=0.58, considered significant), which controls, among others, the gene encoding for vascular endothelial growth factor alpha (VEGFA) (Z-value=3.74).

Conclusions: Microarray analysis of gene expression in monocytes from patients with NV-AMD reveals not only an inflammatory gene signature, but a possible transcription factor network underlying the inflammatory profile. Further research is needed to examine the control of the immune system's response in the pathogenesis of AMD.

Bevacizumab Treatment for Choroidal Neovascularization Associated with Adult-Onset Foveomacular Vitelliform Dystrophy (AOFVD)

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Purpose: Adult-onset foveomacular vitelliform dystrophy (AOFVD) may be complicated by choroidal neovascularization (CNV). We aim to evaluate the response to anti-vascular endothelial growth factor (VEGF) therapy in AOFVD -associated CNV.

Methods: A retrospective consecutive group of 10 eyes of 10 patients with AOFVD associated CNV was included. Demographics, clinical characteristics, and response to anti-VEGF therapy were evaluated. Results were compared to 80 consecutive neovascular age related macular degeneration (AMD) patients treated at the same clinic and time period using the same bevacizumab loading dose-PRN treatment algorithm

Results: Mean \pm SD AOFVD and AMD patients age at time of presentation with CNV was 78.4 \pm 12.36 and 77.15 \pm 8.17, respectively ($p=0.66$). Mean LogMAR visual acuity at presentation in AOFVD and AMD was 0.62 \pm 0.61 and 0.92 \pm 0.83, respectively, while mean final visual acuity was 0.90 \pm 0.60 vs. 0.84 \pm 0.77 in AOFVD and AMD, respectively ($p<0.05$). Mean follow-up time was 20.5 \pm 11.6 months in AOFVD and 25.6 \pm 19 months in AMD ($p=0.37$), and mean number of bevacizumab injection administered was 12.8 \pm 8.9 and 8.61 \pm 9.04 in AOFVD and AMD, respectively ($p=0.98$). At the end of follow-up, visual acuity stabilized in 4 eyes and decreased in 5 of the AOFVD eyes.

Two of the AOFVD patients had typical drusen, 2 had cuticular drusen and 1 had sub retinal drusen in addition to the vitelliform lesion. Nine patients had bilateral lesions. Per OCT, 5 of the eyes had vitelliform lesions while 4 had showed the vitellirruptive stage and 1 had atrophy

Conclusions: In this small group of AOFVD patients the final visual acuity outcome didn't improved comparing to the AMD patients at the same treatment algorithm.

Sequence variants in HTRA1, CFH and C3 and response to Anti-VEGF treatment in neovascular age-related macular degeneration in the Israeli population

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Purpose: Single nucleotide polymorphism(SNP) in the CFH, HTRA1 and C3 genes are associated with age-related macular degeneration (AMD) in the Israeli population. Our aim was to evaluate the association of those SNPs with anti-VEGF treatment response of neovascular age-related macular degeneration (NVAMD) eyes in the Israeli population.

Methods: Genotyping for the rs1061170 SNP of CFH gene, the rs11200638 SNP in HTRA1 and the rs2230199 SNP of C3 gene was performed in 140 NVAMD patients (160 NVAMD eyes) who were treated with anti-VEGF therapy. Clinical information and demographics were extracted from patient's charts. Statistical analysis was performed to identify associations between SNPs and anti-VEGF treatment response (using Fisher's Exact test).

Results: The rs1061170 SNP of CFH gene, the rs11200638 SNP in HTRA1 and the rs2230199 SNP of C3 gene are not associated with anti-VEGF treatment response of NVAMD patients in the Israeli population, evaluated by visual acuity (VA) change. The CFH ($p=0.636$), HTRA1 ($p=0.221$) and C3 ($p=0.794$) risk SNPs did not differ between patients whose eyes demonstrated improvement or preservation of VA during follow-up and patients whose eyes demonstrated worsening of VA during follow-up.

Conclusions: Though the rs1061170 SNP of CFH gene, the rs11200638 SNP in HTRA1 and the rs2230199 SNP of C3 gene are associated with NVAMD in the Israeli population; These variants do not have a major contribution to the response to anti-VEGF treatment of NVAMD in the Israeli population.

The eye - A window to the brain - The effect of apoE genotype on retinal neurons and function

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Purpose: The vertebrate retina, which is part of the central nervous system, is the window into the brain. The present study investigated the extent to which the retina can be used as a model for studying the brain pathological effects of apolipoprotein E4 (apoE4), the most prevalent genetic risk factor of Alzheimer's disease (AD).

Methods: We examined these questions by investigating the retinas of young naïve ApoE3 and ApoE4 targeted replacement mouse, utilizing immunohistochemistry, western blots and electroretinography (ERG).

Results: ApoE4 had no effect on either the width of the different retinal layers, nor the density of the perikarya and glia of the different classes of retinal neurons. In contrast, ApoE4 had isoform specific effect on retinal synapses. Accordingly, the synaptic density (monitored by synaptophysin) was lower in both the inner and outer plexiform layers in ApoE4 retinas. This was associated with decreased levels of the presynaptic vesicular glutamatergic transporter Vglut but not of the corresponding GABAergic vesicular transporter Vgat, suggesting that the glutamatergic synapses are specifically affected by apoE4. ERG recordings revealed significant attenuation of mixed rod-cone responses in dark adapted eyes of apoE4 mice. These findings suggest that the reduced ERG response in the apoE4 mice may be related to the observed decrease in retinal nerve terminals. Measurements of the ApoE levels showed lower levels in ApoE4 retinas compared to ApoE3, correlative with the observation in the brain.

Conclusions: The present findings show that retinal synapses are affected by apoE4 in young mice. The finding that the effects of apoE4 on the retina and the brain are similar and the unique advantages of the eye for imaging studies suggest that the retina is an excellent system for non invasive monitoring the effects of apoE4 and of potential anti apoE4 treatments.

Visual evoked potentials, electroretinography and sodium channel expression in contactin associated protein knockout mice

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Purpose: Contactin associated protein (CASPR) is an axonal structural protein involved in axon-oligodendrocyte interactions at the nodes of Ranvier (NOR) in the central nervous system. CASPR knockout (KO) mice show reduced concentration of sodium voltage gated channels (Na⁺v) in the NOR together with altered distribution pattern of Na⁺v subtypes. Positive immunohistochemistry (IHC) staining for CASPR was found in the retina, even though it is unmyelinated. Previously we reported mild attenuation of mixed rod-cone a-wave electroretinogram (ERG) amplitudes, normal light adapted responses and substantial pattern ERG (PERG) attenuation in CASPR KO mice. The purpose of this study was to further evaluate retinal and optic nerve function, along with retinal Na⁺v expression, in CASPR KO mice.

Methods: Three month old CASPR KO and wildtype (WT) mice were studied. A 40 minute ERG dark adaptation curve was recorded in response to low intensity flash, after controlled rod bleach. Dark adapted visual evoked potentials (VEP) were recorded. IHC and real-time PCR for Na⁺v subtypes were performed on cryo-sections and whole retinas, respectively.

Results: ERG dark adaptation kinetics were similar in most time points ($p > 0.40$). VEP signals in KO mice were virtually abolished. In WT mice, VEP N1 implicit times decreased with flash intensity from 98.5 to 61.25 milliseconds, while N1-P1 amplitude increased with flash intensity from 19.82 to 39.38 microvolts. IHC showed similar distribution and intensity staining patterns of Na⁺v1.2 in KO and WT mice. In 5 out of 12 IHC sections, Na⁺v1.6 expression in KO RGC was mildly attenuated. Preliminary real-time PCR results revealed insignificant fold changes of 2.3 and 0.71 for Na⁺v1.2 and 1.6, respectively, in KO mice.

Conclusions: Abolished VEP, which may be partially explained by the previously-reported attenuated PERGs, indicate optic nerve and/or optic tract dysfunction, most likely as a result of NOR distortion. As the ERG dark adaptation curve was unchanged in KO mice, we are unable to explain the previously-reported mild attenuation of mixed rod-cone responses. The moderate changes in retinal Na⁺v expression and distribution does not fully explain the severity of the PERG attenuation. Therefore further evaluation of retinal ganglion cell viability and axonal loss are indicated.

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Sip1 in Retinal Development

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Purpose: Smad-interacting protein 1 (Sip1,Zeb2) is a zinc finger homeobox transcription factor (ZFHX) known to play multiple roles during nervous system development. Sip1 is required for neural induction during early embryogenesis, while at later stages it is essential for the development of the hippocampus and for the differentiation of cortical neurons. In the developing eye, Sip1 has been documented to play a role in lens development, while its functions in retinogenesis are currently unknown. The aim of the study was to determine the functions of Sip1 during retinal development in mammals.

Methods: To study the functions of Sip1 in the developing retina we employed Cre/loxP mutagenesis for tissue-specific deletion of Sip1 in the retina. We determined changes in morphology, cell fate, cell-cycle dynamics, differentiation dynamics and cell survival by detection of gene and protein expression in situ.

Results: The expression of Sip1 is initially detected in retinal progenitor cells (RPCs) and is later restricted to horizontal and subtypes of amacrine cells. Somatic loss of Sip1 was evident by E12.5. Sip1 deletion from RPCs resulted in retinal hypoplasia due to a reduction in the number of interneurons and in a reduction in the thickness of the plexiform layers. In addition to their reduced number, the timing of mature interneurons appearance was postponed in the Sip1 deficient retina, indicating a delay in their differentiation.

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

Intravitreal Injection Of Bevacizumab May Be Neuroprotective In A Mouse Model Of Optic Nerve Crush

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Purpose: Disk edema may exacerbate axonal damage in acute optic neuropathy. Bevacizumab (Avastin®) inhibits the signaling of Vascular Endothelial Growth Factor (VEGF), thereby potentially reducing the vasogenic edema of the disk.

The aim of this study was to evaluate the effect of an intravitreal injection of bevacizumab on optic nerve edema and RGC loss in a mouse model of optic nerve crush (ONC).

Methods: ONC was induced in the right eye of 50 C57BL6 wild type mice. Bevacizumab was injected intravitreally to 25 of them immediately afterwards. A control group (n=25) had a single intravitreal Bevacizumab injection without crush. The left eye of each mouse was used as a healthy control. Evaluation included: quantitative real-time PCR for gene expression of Heme-oxegenase-1 (Ho-1), Superoxide-Dismutase (SOD) and VEGF on days 1,3. Histological and immunohistochemistry analysis of optic nerves and retina on days 1,3 and 21. Fluorescein angiography (FA) was taken on days 0, 1 and 3 following ONC induction with and without intravitreal injection of bevacizumab.

Results: FA following ONC showed disk leakage and vascular dilatation. When ONC was followed by intravitreal Bevacizumab injection there was no disk leakage nor vascular dilatation.

Following intravitreal Bevacizumab injection or ONC, gene expression of HO-1 and SOD increased. HO-1 and SOD levels further increased when ONC was followed by Bevacizumab injection. VEGF expression decreased following intravitreal Bevacizumab injection, remained at baseline after ONC, and was slightly elevated after ONC and Bevacizumab injection. This was confirmed by immunohistochemistry. 52% of the RGCs were lost 21 days following ONC. Bevacizumab injection reduced this loss to 14% ,a level similar to Bevacizumab injection alone (15%).

Conclusions: Bevacizumab has a protective effect following ONC damage demonstrated by reduced optic nerve head edema, reduced RGC loss, and reduced upregulation of antioxidative and ischemic genes.

Curcumin as Adjunctive Therapy for Proliferative Vitreoretinopathy

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Purpose: Proliferative vitreoretinopathy (PVR) is the major complication of retinal detachment surgery and a frequent complication of posterior segment ocular trauma. Retinal pigment epithelial (RPE) cells are believed to play an important role in the fibrosis associated with PVR. Recent studies have shown that curcumin, a polyphenol which is the main ingredient of the spice turmeric (*Curcuma longa*), can prevent the development of fibrosis. We investigated the ability of curcumin to prevent RPE cell growth in vitro, as well as the development of PVR in vivo in a large animal model, the pig.

Methods: Porcine RPE sheets were isolated using dispase, and cultured with 10%FBS supplemented DMEM in the presence or absence of curcumin for 6 days. The effect of curcumin on cell growth and proliferation was assessed by measuring RPE sheet enlargement and BrdU uptake, respectively. A three-step procedure consisting of: (1) pars plana vitrectomy, (2) retinal detachment created by the subretinal injection of BSS, and (3) intravitreal injection of RPE cells (80,000 cells), was used to induce PVR in pig eyes. Curcumin (in the experimental eye, n=9) or the solvent DMSO (in the control eye, n=9) was injected intravitreally on days 0, 3, 7 and 10, with indirect ophthalmoscopy performed on days 3, 7 and 14.

Results: Curcumin (up to 20 μ) inhibited RPE cell growth and proliferation in vitro, in a dose dependent manner, and significantly prevented PVR in vivo. Retinal folding and/or detachment were observed in all control eyes (n=9) within 14-days post-surgery. In contrast, only one eye out of 9 injected with curcumin developed aretinal fold and no animal developed a retinal detachment.

Conclusions: Curcumin significantly inhibited RPE cell growth in vitro, and the development of PVR in a large animal model, the pig. Curcumin may be useful as adjunctive therapy for the prevention of PVR

Quantitative reduction of vascular injury after optic nerve stroke with a single 15d-PGJ2 treatment

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Purpose: Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) is an idiopathic, painless ischemia of the anterior segment of the optic nerve (ON) affecting the capillary network in the proximal ON with no effective treatment. This study examines whether an anti-inflammatory drug preserves the ON microvasculature after rodent Anterior Ischemic Optic Neuropathy (rAION), a rodent injury model simulating NAION.

Methods: ON ischemia was induced in Sprague-Dawley rats using i.v. Rose Bengal and laser illumination (rodent anterior ischemic optic neuropathy, or rAION) of the right optic disc, with the left eye serving as an internal control. 100 μ /kg 15-deoxy- Δ 12,14 prostaglandin J2 (15d-PGJ2) or vehicle was administered intravenously immediately post-injury. Retinal ganglion cells (RGCs) were counted using Brn3a immunofluorescence and stereology. Vascular quantitation was accomplished by transcardial perfusion with fluorescent gelatin, cryosectioning of the proximal ON, confocal microscopy, and digital microvascular reconstruction. Edema was examined using quantitative IgG leakage and transmission electron microscopy (TEM).

Results: 15d-PGJ2 reduced RGC loss 30 days after injury (55 \pm 12% vehicle vs. 38 \pm 14% 15d-PGJ2). Microvascular volume loss in the proximal ON at 4 h was not significantly different between treatment groups, but was significantly restored with 15d-PGJ2 treatment compared to vehicle (OD vs. OS, 0.66 \pm 0.15 vs. 0.25 \pm 0.14, n=6, p<0.05). Serum protein leakage due to rAION was significantly reduced by 15d-PGJ2. (2-factor ANOVA, p<0.05). Microvascular luminal restriction was observed via confocal microscopy. TEM showed endothelial cell swelling in ON areas that had restricted microvascular lumens, suggesting that endothelial cell swelling is responsible for the infarct and the site of action for 15d-PGJ2.

Conclusions: Intravenous 15d-PGJ2 is an effective treatment that preserves RGC cells after rAION, reduces ON microvascular edema, and preserves anterior ON microvascular perfusion, possibly by acting on endothelial cells.

Functional characterization of the PRCD gene, involved in hereditary retinal degeneration

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Purpose: PRCD mutations are associated with retinitis pigmentosa (RP) in both dogs and humans. PRCD encodes for a 54 aa amino acids long protein of unknown function. The first 20 amino acids of PRCD appear to encode for a signal peptide, suggesting that PRCD is a secreted protein. The purpose of this work is to characterize PRCD's retinal function.

Methods: To test the secretion ability of PRCD we expressed myc-tagged PRCD in cultured cells and used western blot analysis to test for the presence of the protein in both cell extracts and conditioned media. To identify PRCD-binding proteins we used the Ras-Recruitment system. The identified interacting protein was TULP1, which is also involved in retinal degeneration. The interaction between PRCD and TULP1 was confirmed by co-immunoprecipitation (co-IP). To map the interacting region we performed pull down experiments, using truncated TULP1_HA and PRCD_GST. Samples were analyzed by Western blot with anti-HA and anti-GST antibodies.

Results: PRCD was found both in cell extracts and conditioned media. Moreover, the p.C2Y mutation eliminated the secretion of PRCD from cells. The interaction between PRCD and TULP1 was confirmed by co-IP. Within TULP1, the interacting region was mapped to the C-terminal part of the protein (aa 289-543), the region which includes the conserved "tubby domain".

Conclusions: Our data suggest that PRCD functions in the retina as a secreted protein. The identified interaction between PRCD and TULP1 indicates that both proteins may act in a common pathway. These findings shed a new light on PRCD function and the etiology of RP.

In-vivo Performance of Photovoltaic Subretinal Prosthesis

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Purpose: Patterned electrical stimulation of the inner retinal neurons was recently demonstrated to restore some vision in patients blinded by retinitis pigmentosa (RP). The purpose of this work is to evaluate the anatomical and physiological performance of a novel wireless photovoltaic subretinal prosthesis.

Methods: We have developed a photovoltaic retinal prosthesis, in which camera-captured images are projected onto the retina using pulsed near-IR light. Each pixel in the subretinal implant directly converts pulsed light into local electric current to stimulate the nearby inner retinal neurons. 30 μ -thick implants with pixel sizes of 280, 140 and 70 μ m were successfully implanted in the subretinal space of wild type (WT, Long-Evans) and degenerate (Royal College of Surgeons, RCS) rats. Optical Coherence Tomography and fluorescein angiography were used for anatomical evaluation of the implant post implantation. For visual evoked potentials (VEP) recordings, skull screw electrodes were implanted over the visual cortex.

Results: Follow-up with OCT imaging revealed close proximity of the implant to the inner nuclear layer (INL), where the target neurons for electrical stimulation (bipolar cells) reside. Fluorescein angiography revealed normal vasculature and good perfusion of the retina overlying the implants. Stimulation with NIR pulses over the implant elicited robust VEP at safe irradiance levels. Stimulation thresholds varied by pixel size and animal type. The lowest threshold in this series was 0.25mW/mm² at 10ms observed in a WT animal implanted with 140 μ pixel array. Implants with small pixel sizes had significantly higher thresholds, compared to large pixels. Thresholds decreased with longer pulses: on average, from 3.1 mW/mm² at 4ms to 1.4 mW/mm² at 10 ms. Latency of the implant-evoked VEP was at least 30 ms shorter than response evoked by the visible light, due to lack of phototransduction. Amplitude of the implant-induced VEP increased logarithmically with peak irradiance and pulse duration. It decreased with increasing frequency similar to the visible light response in the range of 2 – 10 Hz, but decreased slower than the visible light response at 20 – 40 Hz.

Conclusions: Modular design of the photovoltaic arrays allows scalability to a large number of pixels, and combined with the ease of implantation, offers a promising approach to restoration of sight in patients blinded by retinal degenerative diseases

Exposure of RPE to thrombin induces long lasting proangiogenic signals and barrier disruption

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Purpose: Thrombin is a multifunctional protease playing a central role in coagulation. Apart from its major function in vein and artery occlusion, thrombin was found to play a significant role in inflammatory diseases. Thrombin exerts cellular effects through its membrane receptor (PAR). In vivo testing of thrombin is difficult since its existence in plasma is short-term and transient. The retinal pigment epithelium (RPE) forms the outer blood retina barrier (BRB) and its integrity is essential for normal function of the retina. Retinal pathologies involving BRB disruption, such as diabetic retinopathy, inflammation, vascular occlusions and tumors may be accompanied by elevation in thrombin levels.

In the present work, we aimed to explore the impact of thrombin on the integrity and function of the RPE blood barrier. We induced in-vitro a short-term exposure of RPE to pathological levels of thrombin and studied the immediate and long lasting changes in the RPE permeability and angiogenic balance.

Methods: ARPE-19 cells were grown for a month to achieve definite polarity properties. Following a short (10 minutes) exposure to thrombin, the cells were washed and covered with new medium until measurements were performed. Permeability was evaluated based on spectrophotometric monitoring of the leakage of labeled dextran molecules. The expression of pro- and anti- angiogenic genes was evaluated using real time PCR. Protein levels were measured by ELISA or by FlowCytomix™. MMPs activity was examined by zymography.

Results: Short-term exposure to thrombin induced a long lasting (for hours) increase in RPE permeability to 10, 40 and 70 KD dextran. Decrease in PEDF mRNA and increase in VEGF and HGF mRNA expression and protein levels were detected even 24 hours after the 10 minute exposure to thrombin. MMPs 2 and 9 activities were also increased hours after the short-term exposure to thrombin.

Conclusions: Short-term exposure to thrombin induces proangiogenic signals in RPE and disruption of barrier properties. The data indicate that changes in permeability, gene expression, proteins levels and activity persisted for hours after short-term exposure to thrombin. Based on our findings, we suggest that accumulation of short-term exposures to thrombin over years contributes to the pathological processes involved in CNV development in the elderly.

A novel technique for subretinal transplantation of cells covering most of the subretina in Rat and Rabbit models

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Purpose: To develop an improved subretinal transplantation system for cell therapy.

Methods: The novel microsurgical system was developed included seven steps: peritomy; measurement of scleral and corenal depth by pachymetry; incision perpendicular to the corneal surface with an AK diamond knife; placing a specially fabricated ring on the eyeball; dissecting a scleral tunnel; insertion of a blunt needle with a movable pin with a micromanipulator into into the tunnel through the ring; creating an additional penetration of 1.0 mm with the pin to perforate the choroid and the retinal pigment epithelium. To test this system, stem cells were injected subretinally from an additional channel connected to the needle. The system was tested on 69 rats and 5 rabbits which were subretinally transplanted with 5 million cells/eye. Spectral Domain Optical Coherence Tomography (SD-OCT, Heidelberg) was used for eye imaging and detection of transplanted cells. The eyes were enucleated for histological analysis.

Results: Transplanted cells were identified shortly after transplantation as a uniform sheet of cells covering most of the subretinal surface and in the choroid in the rats. The retinal detachment produced by the injection was shallower and less traumatic using this method. Experiments in rabbits demonstrated similarly efficient subretinal transplantation using this method.

Conclusions: An efficient subretinal cell transplantation method which resulted in a thin layer of cells covering a large area of the eye. Implementation of this new transplantation technique may improve host to donor interaction and enhance the therapeutic effect of other cell-based and pharmaceutical therapies.

Above chance identification of missed targets is predicted by signal detection theory

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Purpose: Signal Detection Theory (SDT) assumes that a stimulus with fixed parameters evokes different internal responses on different presentations (internal noise). Low visibility is predicted when the stimulus evoked internal response is low relative to the internal noise. Observers are assumed to set an internal-response criterion above which a positive detection is reported, below which the stimulus is reported as absent. SDT hence posits the existence of neuronal responses even when presented stimuli are reported to be absent (missed targets). As a consequence, SDT predicts that information on the identity of a missed target is still available so that identification performance should be above chance. Here we experimentally tested this prediction.

Methods: Observers were presented randomly (50%) with a blank screen or with a target Gabor-patch whose contrast was set so as to be barely detectable. Targets assumed one of two orientations ($\pm 45^\circ$) or, in different experiments, one of two locations (left/right from fixation). There were two types of experiments: (1) Obs required to (a) rate on a 1-6 scale their confidence in the presence of the Gabor-patch (detection task), and (b) identify the target; (2) Obs required to (a) report the presence/absence of the target (Yes/No) and (b) identify the target. Under SDT, identification performances can be predicted from the area under the Receiver Operating Characteristic (ROC) function relating the proportions of False-Alarms and Hits ('detect' responses in the absence and presence of the target, respectively) for each confidence level used by the subject.

Results: ROC shapes varied across observers ($N=10$), but complied within experimental error with SDT assuming a normally distributed internal response with response dependent noise. Median identification performances for missed and detected targets were, respectively, 55% (significantly above chance; $p < 0.05$) and 90% in accord with SDT predictions. SDT also provided good predictions of identification performance for each detection confidence level given decision noise.

Conclusions: Above chance identification of missed targets is predicted by SDT.

Human perception of order-disorder transition

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Purpose: Local low-level mechanisms of human visual processing are reasonably well characterized using both physiological and psychophysical tools, but this is not the case with integrative functions combining local evidence into global percepts. In particular, the mechanisms governing perception of visual textures, requiring integration over a large visual field, are poorly understood. A popular theory suggests that the human visual system is tuned to represent statistical regularities of the external world. Using methods of statistical physics, we ask here whether the human visual system is sensitive to the presence of order in visual textures.

Methods: Sets of textures were generated. Each set was parameterized by a one-dimensional value analogous to thermodynamic temperature in statistical physics. Increasing this parameter, made textures to vary from ordered (gratings of different orientations, blobs of different sizes or uniform intensity) to random. For each set, using methods of statistical physics, a critical value of the parameter corresponding to the order-disorder transition was computed. More specifically, the critical value was computed as the parameter value for which the generated textures had maximal correlation length. Perceptual thresholds (characterized using this parameter) were psychophysically measured employing a 4AFC detection task (target texture embedded in one of the quadrants of a random texture), and compared with the critical value of order-disorder transition. The performances of human and ideal observers were compared.

Results: Linear regression between human detection thresholds and the critical values for different sets of visual textures produced a slope not significantly different from one, with an additional observer-dependent ($n=5$) constant shift toward noisy images. The ideal observer was perfect in the region of parameters corresponding to human thresholds.

Conclusion: Our results suggest that human observers are substantially suboptimal compared to ideal observer having complete knowledge of the statistical regularities in our artificial stimuli. Nevertheless, human perceptual thresholds showed sensitivity to the order-disorder parameter. This parameter was derived using standard tools of statistical physics, and characterizes the transition between different kinds of order, or order-disorder transition. This result shows that the sensitivity of the human vision to qualitative image properties can be quantified

Crowding modulations by spatial attention, stimuli contrast, and object formation

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Purpose: To test how performance under conditions of crowding, both in terms of accuracy and critical distance, is affected by three related factors: spatial attention, stimuli contrast, and object formation. Previous studies have shown that crowding increases when the target is more similar to its flankers, particularly when the target and the flankers form an object; but decreases when attention is directed to the target location. Because crowding is also reduced when the stimuli contrast is increased, and attention increases the apparent contrast, we tested in one study whether the effects of attention and contrast enhancement on crowding interact. Additionally, because contrast polarity alternations within an object weaken its “goodness”, we tested in another study whether the addition of contrast polarity alternations will reduce the effect of object formation on the extent of crowding.

Methods: In both studies the observers had to indicate the orientation of a target presented with flankers. In the first study we systematically varied the target and flankers contrast and added a manipulation of spatial attention: On the cued trials, a small dot appeared adjacent to the target location prior to its onset, attracting attention to the target location; on the neutral trials a small circle appeared in the center. In the second study the stimuli orientation varied so that on some of the trials colinearity encouraged the organization of the target and flankers into an object. The strength of this organization was further manipulated by including contrast polarity alternations.

Results: Both attending target location and increasing target contrast improved accuracy and reduced the critical distance. Interestingly, when both the target and flankers had high contrast, accuracy was higher than when both had low contrast, yet attention further improved performance in both cases. Moreover, there was no interaction between the effects of contrast and attention. In the second study, a significant interaction between object and contrast polarity emerged: Crowding was strongest when the target and flankers formed an object, but this effect was significantly smaller when contrast polarity was involved.

Conclusions: Crowding alleviation can be established by either spatial attention or contrast increment. These two factors seem to operate independently. Crowding also depends on the organization of the display into objects and the “goodness” of these objects.

The development of visual crowding, collinear facilitation and contour detection in young children

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Purpose: Visual crowding, lateral interactions, and contour detection are critical functions for visual perception, context effect, and recognition, but their underlying neural basis is still unclear. The existing models include low-level processing such as receptive field size and the masking effect, but top-down processing such as attention is also considered. It was shown that contour detection developed after six years of age, but the developmental states of crowding and lateral interactions are not known yet. We consider a model in which we assumed that the development of lateral interactions (collinear facilitation), crowding and contour integration in children are correlated. The aim of this study was to explore the development of these visual functions during the early age of 3-6 years in order to better understand the developmental process of these functions and to enable us to probe the critical age when maturation is reached.

Methods: The measurements are based on psychophysical tests that measure the human performance based on physical properties of the stimulus. Each test will provide different information such as contrast sensitivity, lateral interactions, the crowding effect, and contour threshold.

Results: We found a high degree of crowding, a higher threshold for contour detection, and no collinear facilitation at the age of 3. The thresholds improve with age and approach the adult level by the age of 8 years. The rate of development is correlated among the three phenomena: crowding, collinear facilitation, and contour detection all gradually improve with age.

Conclusions: Contrary to visual acuity, which mostly improved within the first year, reaching the adult level at 3 years, crowding is very significant: lateral interaction is suppressive and contour detection is poor. According to our hypothesis, the development of collinear facilitation enables the development of contour detection and the reduction of the crowding effect. These results may support the idea that in young children with a normal visual system there is a common developmental neuronal basis for the mechanisms underlying context processing.

Visual disappearance in a case of simultanagnosia - Insights on PPC contribution to conscious perception

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Purpose: Patients with Balint syndrome following bilateral parietal damage are typically described as being unable to perceive multiple objects simultaneously, a fact preventing them from understanding the visual scene despite correct identification of individual visual objects (simultanagnosia). Here we investigated DP, a patient with a rare stroke-related pattern of damage affecting the right and left posterior parietal cortex (PPC), with the purpose of characterizing the syndrome and the role of PPC in conscious perception.

Methods: we applied a set of psychophysical tests, attempting to quantify both function and dysfunction, including the observed visual disappearance.

Results: The observed deficits included (1) Visual disappearance or fading of salient objects or object parts such as face parts or even a single patch on a blank screen whose alternating onsets and offsets every few seconds could be reported, as well as anti-correlated disappearance of two competing objects such as orthogonal bars (2) Spatial crowding in which a surprisingly intact ability to identify very small digits or color patches was dramatically degraded with flanking patterns. (3) A severe deficit in reporting the relative position of objects or point to marked locations on a touch screen. In contrast DP showed a preserved ability for perceptual grouping of dot arrays even when partially invisible, in a size averaging task. These findings of an explicit and measurable disappearance of even an isolated small patch coupled with severe deficits in space perception is novel, and is not consistent with common single-object perception descriptions and theorizing of this syndrome stressing global/focal imbalance.

Conclusions: We propose that the PPC serves as a short-term data holding mechanism for spatially coded information by which internal and external context factors can modulate perception-action and perception-declaration links. Bilateral PPC damage causes simultanagnosia because of failed maintenance of visual information in spatio-temporal working memory.

Training-induced recovery of low-level vision followed by high-level perceptual improvements in an adult with developmental object and face agnosia

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Purpose: Long-term deprivation of normal visual inputs can cause perceptual impairments at various levels of visual function, from basic visual acuity deficits, to high-level face and object agnosia. Yet it is unclear whether training during adulthood, at a post-developmental stage of the adult visual system can overcome such developmental impairments.

Methods: Here, we visually trained LG, a 20-year-old individual with a developmental object and face agnosia. Prior to training, LG's basic visual functions such as visual acuity, crowding effects, and contour integration were at the level of a 5-6 year old. Intensive visual training, based on lateral interactions, was applied for a period of nine months.

Results: LG's directly trained but also untrained visual functions such as visual acuity, crowding, and contour integration improved significantly and reached near-age-level performance, with long-term (over 2 years) persistence. Moreover, the training facilitated additional binocular functions, and some improvement was observed in LG's higher order visual functions such as object recognition and part integration. LG's face perception skills have not improved thus far.

Conclusions: These results suggest that corrective training at a post-developmental stage, even in the adult visual system, can prove effective, and its enduring effects are the basis for a revival of a developmental cascade that can lead to reduced perceptual impairments.

Perceptual training on mobile devices restores normal processing of blurred images to overcome the optical deficits in presbyopia

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Purpose: Visual perception relies on streams of feedforward and feedback information between visual areas of the brain. In presbyopia (aging eye), the visual input to the brain is limited by the degraded optics of the eye, creating a bottleneck in the primary visual cortex. Consequently, there are multiple negative effects on near vision. Specifically, near visual acuity (VA) deteriorates, as well as other perceptual functions, such as contrast sensitivity (CS), reaction time (RT) and processing speed are reduced. It was shown that excitation (E) between neurons promotes neural plasticity, whereas higher levels of inhibition (I) arrests plasticity. Earlier we showed that training on a task targeted on increasing neural facilitation and decreasing suppression resulted in changes of the E/I balance, enabling plasticity and thereby inducing visual improvement. Our recent studies showed that perceptual learning (PL) in young subjects led to shortening of processing latency and, consequently, to suppression reduction, and that PL in presbyopia leads to remarkable improvement in VA ($\approx 1\%$), CS and contrast discrimination, without changes in the optical functions of the eye. These results show that cortical plasticity is retained in older adults. Here we report results from a study that adapted our PL method for presbyopia to mobile iOS-operated devices (iPhone, iPad, iPod).

Methods: Presbyopes were trained on contrast detection of Gabor targets under collinear facilitation (CF) and backward masking (BM) conditions, posing spatial and temporal constraints on the visual processing in order to induce changes in the E/I balance. Training (15 minutes / session, 3 times / week) covered a range of spatial frequencies and orientations.

Results: We show that CF increased and suppression decreased, resulting in changes of the E/I balance and improvement of VA, CS, RT and BM. Consequently, after training, near visual functions reached the level of young subjects, reducing the effective eye age by 8.7 years.

Conclusions: Therefore, improving CS and temporal processing (BM&RT) by PL may enable presbyopes to recover a reliable percept from the blurred and delayed image received from the aging eye, thus overcoming the bottleneck in the early visual cortex and providing normal output for the visual stream for further processing. The results suggest that the aging brain retains enough plasticity to overcome the natural biological deterioration and regain visual functions.

Cross-modal functional specialization in the ventral visual cortex of the congenitally blind

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Purpose: We examined several key questions surrounding the reading-selective Visual -Word-Form Area (VWFA): its selectivity for reading over other visual categories without visual experience, its feature-tolerance for reading in a novel sensory-modality and its plasticity for scripts and modalities learned in adulthood.

Methods: We used a visual-to-auditory sensory-substitution algorithm, and taught a group of congenitally fully-blind adults to successfully read and recognize complex visual stimuli using soundscapes– sounds topographically representing images. Following this unique training paradigm, we scanned the subjects using fMRI as they perceived soundscapes representations of images from different categories: textures, letters, faces, houses, objects and body-shapes.

Results: We find that the blind activated the VWFA specifically and selectively during letter-string processing relative to all tested “visual” soundscapes categories, including both simple “visual” textures and more complex stimuli categories. Further, VWFA recruitment for reading soundscapes emerged following as little as two hours of training on a novel script in a congenitally blind adult.

Conclusions: These results suggest that the reading-related selectivity of the left ventral-occipito-temporal cortex (LvOT) is feature-tolerant beyond sensory modality, does not depend exclusively on visual features or prior visual experience during early development, but reflects a flexible task-specific and sensory modality-independent computation, possibly linking letter shapes to their phonological meaning. Furthermore, our preliminary results demonstrate category selectivity for soundscapes in other areas of the visual ventral stream in the congenitally blind, mirroring the functional organization in the sighted. This suggests the preservation of functional specialization despite the robust plasticity in the visual cortex of the blind.

Interactions between perceptual learning and adaptation in texture discrimination

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Purpose: Perceptual learning and adaptation are two instances of perceptual plasticity in the visual system. Although the two phenomena are intermixed during the learning process, the dynamics of the reciprocal interactions between them is unclear. Intensive training on a texture discrimination task (TDT) leads to performance deterioration which has been suggested to result from sensory adaptation to the stimulus features. This study explicitly examines adaptation in TDT by measuring (1) behavioral tilt aftereffects (TAE) and (2) Electroencephalographic (EEG) adaptation effects.

Methods: Two groups of subjects were trained in the standard texture discrimination task. The first group performed additional tests to measure their perceived vertical at baseline, before training, and immediately after training. The magnitude of the TAE following training was calculated as the shift in subject's perceived vertical relative to the baseline condition. The second group had their EEG recorded continuously while performing the task.

Results: (1) Intensive training in TDT with a target composed of three bars tilted 20° clockwise from the vertical axis caused a repulsive TAE, in which a near-vertical test bar appeared to be tilted counterclockwise. The TAE was much stronger at the trained location. (2) Analyzing EEG signals recorded during training revealed significant differences in amplitudes of early-vision event related potentials (ERP) components between the early and later phases of within session training. The amplitude of occipital N1 decreased in later training compared to early training, while the amplitude of posterior P2 increased. Training the next day resulted in reduced adaptive changes in early ERP components.

Conclusions: Interactions between perceptual learning and adaptation exist in TDT. While adaptation deteriorates performance in TDT, sleep dependent consolidation of perceptual learning seems to reduce adaptation effects.

Visual Perception

Vision Programs

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Purpose: According to Turing's original definition, the universal computer is driven by a program tape, which determines the response to any read input on the data tape. Interestingly, and essentially, the program tape itself is also subject to change, a re-programming of the computer. The brain is certainly a universal computer in this sense, and a number of research directions touch on its re-programming aspect, including: attention, task-switching, executive control, and of course, perceptual learning. But even taken together, these elements do not contain the full nature of our brain's being a universal computer, rather than single-task machine. Choosing a program is necessary even when there is no competition for limited resources; (is "O" to be read as a number, as in O,1,2 or as a letter, as in M,N,O,P). Furthermore, choosing a program is also more than determining a set of stimulus-response associations, and it may entail also the choice of an appropriate computational algorithm.

Methods: I will try to define these terms to determine the programming and re-programming elements within each paradigm.

Results: I will demonstrate one example of a dual-task situation where participants actually get better at one task when the other gets too hard.

Conclusions: It is as if a central executive within the brain determines that it is wasteful to expend limited shared resources on a task that will fail anyway, and is more cost-effective to concentrate efforts on the task that is more likely to succeed.

How Can We Assist Forgetting?

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Purpose: In a primate behavioral experiment, we compared familiarity memory and identification memory.

Methods: We introduced a multiple-item memory task, where subjects report repetition of any stimulus in a sequence. Two primate groups participated.

Results: Group BT (n=2) trained with a fixed set of 16 images, where the same images were repeated thousands of times. To perform the task, monkeys need identification memory. Group BT showed very few False Positive (FP) errors (responding to an image which is not repeated within a current trial), and these drop off quickly with number of intervening trials since the original presentation (mean: 1-trial-back: 9%; 2-trials-back: 3%). We suggest presence of an inter-trial reset mechanism which forces “forgetting” of most of the previously-seen images. Such a reset mechanism is required because otherwise images frequently shown in previous trials would hinder detection of real repetitions. To check this hypothesis we trained another group of monkeys, Group DL (n=2) with an unlimited number of novel images, where in each trial new images were shown, so that there would be no need to establish a reset mechanism. Only in the final stage of training did we introduce “catch” trials with previously-seen images. Indeed Group DL had many FPs (1-trial-back: 80%; 2-trials-back: 66%). This also suggested that this group used familiarity memory rather than identification memory. When the tasks were switched, Group BT used its previously-learned reset mechanism also for novel images, and group DL now established reset. FPs were rare in both groups. Furthermore, Group DL, originally without a reset mechanism, afforded a unique opportunity to estimate memory decay without reset. We found that memory gradually decreases, with ~20% of images forgotten during each trial, so that ~10% of images remain in memory and produce FP errors even after 10 trials (about 2 minutes). We conclude that primates easily remember dozens of images, with a fixed gradual loss of image recognition over minutes.

Conclusions:

Primates easily remember dozens of images, with a gradual loss of image recognition over minutes. Familiarity memory differs from identification memory and may include only knowledge of having ever seen the image. Nevertheless, both memory types develop a reset mechanism, which may be shared between them.

Visual parsing using visual-to-auditory sensory-substitution vs. medically restored sight in early blind individuals

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Purpose: Individuals who had limited visual experience during development, and regained sight medically in adulthood, demonstrated that functional vision acquisition in adults is challenging. While dorsal stream functions recovered relatively fast, many ventral stream functions were impaired even years after the restoration. For instance, a recent study by Ostrovsky and colleagues (PSYCHOLOGICAL SCIENCE, 2009) reported poor behavior in static visual parsing (i.e. the segregation of the visual scene into distinct objects).

An alternative rehabilitation approach is to use non-invasive Sensory Substitution Devices (SSDs), which transform visual images into sounds while preserving the spatial topography of the image, thus theoretically enabling the blind to 'see' (though without qualia) using their intact auditory system. Many visual abilities were demonstrated using SSD, however no one tested 'visual' parsing with SSD, which is a critical ability for their use as practical daily aids.

Here we: (1) tested whether congenitally and fully blind adults can learn to perform a complex ventral visual task such as parsing using SSD. (2) Compared the SSD users' performance to that of sight restored individuals.

Methods: We replicated the static visual parsing test of Ostrovsky et al., using similar stimuli and tasks, but this time with the visual information delivered through SSD.

Results: Our congenitally blind subjects performed well above chance-level. Interestingly, they outperformed the individuals who regained sight in all tasks tested, although they experienced 'vision' through the SSD for only ~ 70 hours, compared to months of real vision in the sight-restored patients.

Conclusions: On a theoretical note, the results demonstrate that even the adult brain retains massive capacity for visual learning; and suggests that with adequate training and technologies high-order vision can be acquired, at least to some extent, in adulthood, despite visual deprivation during so-called developmental critical periods. Practically, the results support the potential use of SSDs as standalone aids for the blind in daily life, but also suggest a great potential for a synergic combination of SSDs and invasive restoration approaches to improve rehabilitation. We also suggest that invasive restoration might benefit from integration with SSD training before or after surgery.

Returning part of the sensory substitution spotlight from research to visual rehabilitation

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Sensory substitution devices have come a long way since first developed in the 70's for visual rehabilitation. They have been the source of exciting experimental results, and have deeply furthered our understanding of the human brain. However, while in the field of rehabilitation tactile-vestibular devices and others have made great progress, one of the first goals for visual-audio SSDs, of providing efficient practical devices for visual rehabilitation, has never been achieved. Furthermore, such devices have increasingly been treated as more relevant for lab settings and experiments following past failures with SSDs and the highly pessimistic general attitude to visualrehabilitation following the discouraging results previous such attempts bore. The outcome of tactile SSDs for high visual acuity information is even worse.

We suggest that the time has come to return part of the research spotlight to practical visual rehabilitation following a set of recent experiments with SSDs leading to changes in both practical and the theoretical basis of the understanding of the neural mechanisms behind visual restoration. Theoretically converging evidence suggest that brain areas can very quickly maintain or regain their task and function in vision with input arriving from audition and touch (e.g. from visual-to-auditory SSDs) suggesting the brain is a highly flexible task-machine rather than a pure sensory-machine.

This theoretical optimistic view is further strengthened by more practical advances.

The combination of a series of new more optimistic results in recent visual restoration studies, stemming mainly from improved and organized training protocols, new technological advances which make SSDs more practical and useful in the real world, and recent behavioral achievements using SSDs.

Blind in a virtual world - using distance information to accomplish virtual tasks

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Purpose: Distance information is critical to our understanding of our surrounding environment, especially in virtual reality settings. Unfortunately, as we gauge distance mainly visually, the blind are prevented from properly utilizing this parameter to formulate 3D cognitive maps and cognitive imagery of their surroundings. Our purpose is to increase the accessibility of virtual environments to the blind using distance information which they will receive as auditory information. We aim to create a setup which will enable the blind and visually impaired to experience novel environments virtually before travelling to them in the real world.

Methods: Blind and sighted-blindfolded subjects performed navigation and shape-discrimination tasks in virtual environments, using a simple transformation between virtual distance and sound, based on the concept of a virtual guide cane (paralleling in a virtual environment the "EyeCane", developed in our lab)

Results and conclusions: We show qualitatively that with no training it is possible for blind and blindfolded subjects to easily learn this transformation, enabling the discrimination of virtual 3D orientation and shapes and navigation in basic virtual environments using a standard mouse and audio-system.

Precise dynamic near visual acuity evaluation using mobile and PC screens

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Purpose: Our aim was to develop a tool for precise remote self-assessment of near visual acuity using dynamic stimulation in order to accurately and remotely estimate the functional reading acuity.

Methods: We used an application by Ucansi Inc., developed for iOS-based mobile devices (iPhone, iPad, iPod), based on the technology tested both on mobile devices and PCs (electronic visual acuity, eVA). Here we present part of the data, collected on 73 volunteers that were tested on iPhone 4, operating the application by themselves. The minimal measurable acuity is -0.18 logMAR, as determined by the pixel size of 0.078 mm. The stimuli were matrices composed of 25 letters "E" (5×5), each with a randomly chosen orientation out of 4 possibilities (left, right, up or down). Two variations of inter-letter spacing within the matrix were used (0.4 and 1 letter size). The task was to report the orientation of the central letter. The evaluation was performed using a staircase measuring the minimal detectable target size. For each staircase, the duration of target presentation (ranging between 240 to 30 msec) and the inter-letter spacing were changed. The results were compared to the standard clinical near visual acuity chart (ETDRS chart-based visual acuity, cVA) and to the required reading addition (measured using the fused cross-cylinder test, FCC).

Results: There was a significant correlation between the eVA and the cVA. Best correlation was found between monocular eVA and cVA ($R=0.85$, $p<0.01$; eVA: mean of 0.34 ± 0.02 logMar, ranging between -0.09 and 0.73 ; mean of 0.32 ± 0.02 ; cVA: ranging between -0.04 and 0.72). There was also a significant correlation with the FCC measurement ($R=0.73$, $p<0.01$; mean of 1.58 ± 0.07 , ranging between 0 and 2.75).

Conclusions: The remote self-assessment of near visual acuity using the iOS-based application is very accurate and may better predict the functional visual acuity due to the brief stimuli presentation similar in duration to a single fixation between saccades during reading. Moreover, measurements under the conditions of letter crowding induced by the letter matrix used by the application better estimate the functional reading acuity as opposed to single letter detection used in reading chart measurements. The assessment may be performed both monocularly and binocularly. Finally, VA improvement measured with eVA was highly correlated to the improvement measured by cVA.

Elimination of sensory adaptation during visual training allows for generalization of learning

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Purpose: Perceptual learning is improved visual detection ability gained by efficient training. This improvement was shown to be ubiquitously specific to the particular attributes introduced during training, limiting applications of perceptual learning as a therapeutic tool for humans with impaired vision. We recently suggested that retinal location specificity in texture discrimination task (TDT) is a result of sensory adaptation (selective sensitivity reduction) to the repeated visual stimuli during training. We showed generalization across retinal locations when adaptation was reduced during training and transfer test conditions. Here we aimed to examine whether transfer of perceptual learning following reduced adaptation applies for standard testing conditions where sensory adaptation is present.

Methods: A group of observers (n=6) was trained with reduced adaptation TDT paradigm. Subjects trained for four consecutive days and specificity was tested on the fifth day by changing the target's retinal location. Basing on previous adaptation studies, task-irrelevant ("dummy") trials with the texture oriented $\pm 45^\circ$ relative to the target's orientation were randomly interleaved with standard trials to remove adaptation during training. In the transfer testing condition (days 5-8), these dummy trials were removed to allow for adaptation to develop.

Results: During 4 days of training, thresholds improved from 179 ± 49 ms to 70 ± 7 ms (mean \pm SEM). Learning curves confirmed the absence of adaptation within training sessions. On the 5th day, with a new target location, threshold increased slightly to 101 ± 18 ms (mean \pm SEM) and remained stable during the 4 days of testing at this new location. This initial threshold at the new location is significantly lower ($p < 0.05$) than the initial transfer threshold in comparable adaptive training conditions (199 ± 44 ms, mean \pm SEM).

Conclusions: We showed that training without adaptation enables spatial generalization of learning in testing conditions allowing for adaptation.

Efficacy of primary collagen cross-linking treatment on Staphylococcus aureus induced corneal ulcer

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Purpose: To evaluate the efficacy of primary collagen cross-linking (CXL) therapy for Staphylococcus aureus induced corneal ulcer ,in a rabbit model.

Methods: The right eye of 40 New Zealand white rabbits was inoculated with Staphylococcus aureus to induce staph aureus ulcer in the center of the cornea. Rabbits were randomly assigned into 4 groups: Group A was treated with topical antibiotics (cefazolin 50 mg/ml, garamycin 14 mg/ml drops and chloramphenicol 5% ointment q 2 hr); Group B was treated with CXL only; Group C was treated with CXL combined with topical antibiotics (cefazolin 50 mg/ml, garamycin 14 mg/ml drops and chloramphenicol 5% ointment qid) ; Group D received no treatment and served as a control. Ulcer was induced on day 1, measured on day 5 and then treated according to the group assignment. Follow up examination was performed using biomicroscopy on day 5 and every week up to one month of follow up.

Main outcome measures included corneal ulcer or scar diameter, time to full recovery, time to full epithelization, and change in corneal thickness measurements.

Results: All animals developed corneal ulcers. Group B had significantly larger induced corneal ulcer on day 5 ($P = 0.03$) but achieved the most significant reduction of ulcer/scarred area ($P=0.002$) after 1 month of therapy; Group C showed the shortest ulcer healing time (16.7 days) followed by group A (19.7 days) , group D (21.8 days) and group B (23.7days); Group C also demonstrated the smallest ulcer size at day 30 (11.2 mm², $P=0.01$) followed by group A (13 mm², $P=0.04$).

Conclusions: Primary corneal CXL therapy combined with topical antibiotics seem to be effective in shortening ulcer healing time and ended up with the smallest corneal scar in our rabbit model. Further investigation of this mode of treatment as the primary treatment for infectious keratitis is mandatory.

The Role of lukSF-PV in Staphylococcus aureus Keratitis

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Purpose: To determine the prevalence, genetic diversity and clinical relevance of the lukSF-PV gene, encoding the bacterial toxin Panton-Valentine Leukocidin in a collection of Staphylococcus aureus isolates causing keratitis.

Methods: Multiplex polymerase chain reactions investigating the carriage of lukSF-PV and mecA were performed on S. aureus isolates collected from patients with bacterial keratitis in the United Kingdom. The lukSF-PV operon was sequenced to investigate its diversity within the study collection and multi locus sequence typing (MLST) was used to determine a clonal relationship between lukSF-PV isolates. Antimicrobial minimum inhibitory concentrations (MIC) values were determined. Clinical outcome data for cases; lukSF-PV+ve, mecA+ve, or lukSF-PV/mecA-ve were compared.

Results: Nine (9.5%) out of 95 S. aureus isolates were lukSF-PV+ve, 9 (9.5%) were mecA+ve, and one was positive for both. Five single nucleotide polymorphisms were found in the lukSF-PV genes of 7 strains. A smaller proportion of lukSF-PV+ve isolates were susceptible to the four fluoroquinolones tested, compared to lukSF-PV-ve isolates. All of the lukSF-PV+ve isolates were susceptible to vancomycin, teicoplanin, chloramphenicol, gentamicin, meropenem, linezolid and tigecycline. The healing and treatment times, ulcer and scar size and overall clinical score tended to be greater in the lukSF-PV+ve group, and the proportion of patients that required surgery was significantly greater amongst patients with lukSF-PV+ve isolates ($p=0.016$).

Conclusions: lukSF-PV was associated with a trend to worse clinical outcome, suggesting that it may be an important virulence factor in S. aureus associated keratitis. Antimicrobial testing suggested that fluoroquinolones may not be the treatment of choice in these patients.

The Anti-inflammatory Effects of Resolvin-D1 on Human Corneal Epithelial Cells

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Purpose: To evaluate the anti-inflammatory effects of Resolvin-D1 (RV-D1) and its mode of action on human corneal epithelial (HCE) cells in vitro.

Methods: Cultured HCE cells were incubated for different periods and at several concentrations of RV-D1. Oleic acid (OA) and Dexamethasone (DM) served as negative and positive controls, respectively. Cells were stimulated with polyriboinosinic : polyribocytidylic acids (poly I:C). The protein contents and mRNA expression levels of Tumor necrosis factor- α (TNF- α), Interleukin (IL)-6, IL-1 β and IL-8 were evaluated with multiplex fluorescent bead immunoassay (FBI) and real time-PCR, respectively. The expression of inhibitory factor- κ 1- κ 2 was evaluated with real time-PCR.

Results: The protein contents of the pro-inflammatory cytokines TNF- α , IL-6, IL-1 β and IL-8 were significantly increased after stimulation with Poly I:C. After incubation of the cells with RV-D1 at concentration of 1 μ M, the protein content of TNF- α decreased to 20.76 \pm 9.3% ($p < 0.05$), IL-6 to 43.54 \pm 14.16% ($p < 0.05$) and IL-8 to 51.15 \pm 13.01% ($p < 0.05$), compared with stimulation with poly I:C alone. Similar results were demonstrated for the mRNA levels of each of these cytokines. The anti-inflammatory effects of RV-D1 were comparable to those of DM. The effects of RV-D1 on Poly I:C stimulated HCE cells were dose dependent for the reduction in protein contents of TNF- α , IL-6, IL-1 β and IL-8. The decrease in the mRNA expression of TNF- α , IL-6, IL-1 β and IL-8 was shown to be related to a decrease in the expression of I- κ B.

Conclusions: RV-D1 may serve as a potent anti-inflammatory agent in ocular surface inflammation, as evaluated in cultured HCE. The anti-inflammatory effects of RV-D1 are comparable to those of DM, and are mediated through NF- κ B signal transduction.

Transplantation of Limbal Stem Cells Cultured on Contact Lenses for treatment of LSCD

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Purpose: Limbal epithelial cell sheets co-cultivated with 3T3 feeder-layer are used in order to promote corneal reconstruction following limbal epithelial stem cell deficiency (LSCD). The aim of the present study was to characterize the potential use of contact lenses (CL), with 3T3 feeder-layer, as a carrier of limbal cells for in-vivo transplantation in eyes displaying LSCD following sulfur mustard exposure.

Methods: Limbal epithelial cells were isolated from rabbit cornea and cultured with 3T3 cells on CL. Positive stem cell markers p63, p63 and ABCG2 and negative markers CK3, CK19 were used to characterize the culture phenotype. Colony forming efficiency (CFE) assay was performed in order to evaluate the percent of stem cells in cultures. Limbal epithelial cells grown on CL were labeled with the fluorescent dye PKH26 and transferred onto the denuded corneal surface of the damaged eye after superficial keratectomy, to remove fibrovascular in-growth. Transplanted limbal cell incorporation and survival, ocular surface re-epithelialization and clinical status were monitored.

Results: Proliferation and migration of limbal epithelial stem cells were observed on CL presenting a CFE of ~10%, showing a viable cell population on the CL also few days after transplantation. Viable fluorescent labeled cells were identified in regenerating corneal epithelium at one week when a complete re-epithelialization was observed.

Conclusions: Cultivation of limbal cells with 3T3 feeder-layer on a easy handling CL carrier, showed proliferation and preservation of stem or progenitor cells. This novel technique of engineered-construct may provide a cheap, available, easy handling and non-immunogenic carrier for transferring SC for ocular surface reconstruction in LSCD patients.

Study of corneal pathophysiology and therapy by induced pluripotent stem cells

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Purpose: Million individuals worldwide are suffering from corneal diseases. Corneal transplantation is commonly applied with high success at the short term but is limited by the shortage in post mortem cornea and immune-rejection. Therefore, there is a major need for alternative sources for corneal cell therapy. Moreover, there is a lack of cellular models for genetically linked corneal disease (e.g. PAX6-related aniridia and P63-related ectodermal dysplasia). Induced pluripotent stem cells (iPSCs) that are generated through somatic cell reprogramming have the remarkable capacity to differentiate into all types of tissues of our body. We employed iPSC technology to (1) investigate their potential to differentiate into corneal epithelial cells as an alternative source for therapy, and (2) for modelling defined genetic diseases of the cornea.

Methods: Skin biopsies were collected from healthy donors and ectodermal dysplasia patients. Normal and P63-mutated skin fibroblasts were isolated and reprogrammed into iPSC lines. A systematic analysis of different culture media and plate coating was performed to optimize the differentiation of iPSC into corneal cells (Western blotting, immune-staining, flow cytometer). The optimized method was used to test the effect of p63 mutation on corneal differentiation. The effect of APR-246 (a small chemical compound that rescued p53 activity in tumour cells) on corneal differentiation of iPSCs was evaluated.

Results: We successfully differentiate iPSCs into corneal epithelial cells by seeding the cells on collagen IV-coated dishes in the presence of corneal fibroblast-conditioned medium. Notably, several clones of p63-mutated iPSC displayed defects in differentiation into corneal epithelial lineage as indicated by the reduced expression of K14 (corneal progenitor marker) and genes that are involved in ectodermal dysplasia syndrome (GJB6, GJA1, Dlx5, Dlx6). Importantly, APR-246 could partially restore corneal epithelial lineage commitment and p63-related signaling pathway.

Conclusions: iPSCs can efficiently differentiate into corneal epithelial cells and therefore may serve in the future as a “ready-to-use” source for corneal transplantation. It would be of importance to evaluate the therapeutic potential of iPSC in animal models of limbal stem cell deficiency. This study illustrates the relevance of iPSC for p63-related disorders and paves the way for future therapy of ectodermal dysplasia.

Open-Capsule Device for PCO Prevention

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Purpose: To assess the ability of a novel open capsule device (PID) to reduce PCO rates using different IOLs materials

Methods: Thirty four New Zealand rabbit eyes were divided into 6 similar groups after crystalline lens evacuation. Group A: implantation of hydrophilic acrylic IOLs alone, Group B: implantation of hydrophobic acrylic IOLs alone, Group C: implantation of hydrophilic acrylic open capsule devices and hydrophilic acrylic IOLs, Group D: implantation of hydrophilic acrylic open capsule devices and hydrophobic acrylic IOLs, Group E: implantation of hydrophobic acrylic open capsule devices and hydrophilic acrylic IOLs, Group F: implantation of hydrophobic acrylic open capsule devices and hydrophobic acrylic IOLs. The rabbit were followed weekly for 6 weeks and then were scarified. The eyes were enucleated and sent for histological evaluation.

Results: The PID maintains an open capsule. A 75% decrease in the PCO rates was noticed in the tested groups in comparison with the control groups. An 80% reduction in the Soemmering's ring formation was noticed in the tested groups in comparison with the control groups. There was no difference between the results of the hydrophobic and the hydrophilic groups

Conclusions: Our results suggested primary PCO prevention by the PID, by reducing lens epithelial cells (LECs) proliferation, as was noticed by the inhibition of Soemmering's ring formation.

The inhibitory effects of bevacizumab (Avastin) on corneal neovascularization depends on timing of treatment

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Purpose: To determine the efficacy of bevacizumab (Avastin®) for the treatment of corneal neovascularization (NV) associated with Limbal Stem Cell Deficiency (LSCD) following chemical injury in rabbits.

Methods: Chemical burn was induced in the right eyes of NZW rabbits, using sulfur mustard (SM) vapor. Avastin (25 mg/ml, x2/day) was applied topically before and after the appearance of NV and was compared to the efficacy of 0.1% Dexamethasone (Dexamycin®, x4/day). Treatments were given for 3 weeks. Digital photographs of the cornea were taken and analyzed, using image analysis software. Vascular endothelial growth factor (VEGF) expression was studied by immunohistochemistry and ELISA.

Results: Corneal NV developed, as early as two weeks after exposure, associated with increased levels of corneal VEGF and delayed loss of limbal epithelial stem cells (Kadar et al., *Cur Eye Res* 2011;36). Avastin was beneficial in suppression of NV when given to neovascularized eyes. Yet, there was no improvement at all, when Avastin was given before the appearance of NV, a time point where VEGF increased but limbal stem cells were still intact. Anti-inflammatory steroidal treatment was more potent in diminishing the NV, either when administered before or after growth of blood vessels.

Conclusions: Symptomatic topical treatment with Avastin decreased SM-induced corneal NV in rabbits. The lack of effect of Avastin as a preventive therapy may be related to the additional role of VEGF as a trophic factor in the maintenance of corneal epithelial stem cells. Since the mechanism of action of Avastin and Dexamycin is different, a combined therapy is suggested for improving treatment of corneal neovascularization.

Cross-linking of rabbit sclera using riboflavin and UVA for the prevention of progressive myopia

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Purpose: Scleral crosslinking by the photosensitizer riboflavin and ultraviolet A have been shown to increase sclera rigidity. The aim of the study was to evaluate the effect of scleral crosslinking by the photosensitizer riboflavin and ultraviolet A on the development of axial myopia in rabbits eye myopia model.

Methods: Twenty two, 13 day old new zealand white rabbits were divided equally to control and study groups. Right eyes had surgery and left eyes had no surgical procedure.

All eyes had A-scan ultrasonography for axial length measurement at the beginning of the study. In the control group, eyes had 360 degrees conjunctival peritomy followed by tarrsorrhaphy. In the study group, eyes had 360 degrees conjunctival peritomy and scleral crosslinking followed by tarrsorrhaphy. In the sclera crosslinking procedure 0.1% riboflavin dextran free (Concept pharmacy Ltd. Kfar-Saba, Israel) was dropped onto the irradiation zone 20 seconds before the irradiation and every 20 seconds during the 200 sec. irradiation time. Each eyeball was divided to four quadrants and every quadrant had two or six irradiation zones (8 eyes had two and 3 eyes had six)– each zone had a radius of 4 mm and an area of 0.2 cm². UVA irradiation (370 nm) was applied over the sclera, which was irradiated at 570 mW/cm² for an area of 0.2 cm². This method provides a total UVA light dose of 5.7 J/cm². Fifty five days later, the tarrsorrhaphies were removed and the eyes had a second A-scan ultrasonography for axial length measurement.

Results: The mean axial elongation of the left (open and untreated) eyes in 55 days was 4.20±0.67 mm in the control group and 4.44+ 0.81 mm in the study group. In the control group (tarrsorrhaphy with no crosslinking), the mean right eye axial elongation was 5.19+ 0.85 mm (10.50+ 0.67 mm before tarrsorrhaphy and 15.69+ 0.39 mm 55 days later) In the study group (tarrsorrhaphy with crosslinking) the mean right eye axial elongation was 3.61+ 0.76 mm (10.68+ 0.74 mm before tarrsorrhaphy and 14.29+ 0.3 mm 55 days later). The difference between the mean right eye axial elongation of control group and the study group was statistically significant (p<0.01).

Conclusions: Scleral crosslinking by the photosensitizer riboflavin and ultraviolet A is an effective procedure to prevent axial elongation in rabbits eye lid suture myopia model. Scleral crosslinking may consider as a potential effective procedure to prevent axial elongation in myopia.

Collagen cross-linking as an adjunct to trabeculectomy surgery in a rabbit model.

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Purpose: To investigate the efficacy of collagen cross-linking as an adjunct to trabeculectomy surgery in a rabbit model.

Methods: 13 eyes of New Zealand white rabbits were divided into a study group (5 eyes) that underwent trabeculectomy with cross-linking irradiation and riboflavin 0.1% before surgery and control groups that underwent trabeculectomy with either riboflavin 0.1% (3 eyes) or mitomycin C 0.4mg/ml (5 eyes). Intra-ocular pressure was recorded before surgery. The postoperative weekly evaluation of the eyes included: intra-ocular pressure measurements and assessment of the trabeculectomy bleb morphology. All rabbits were sacrificed after 75 days and eyes were sent to histopathological studies. All specimens were stained with hematoxylin-eosin and Masson's trichrome for evaluation of cellularity and fibrosis.

Results: All the eyes had decreased intra ocular pressure after the trabeculectomy with no statistically significant difference in the measured pressure during the follow up time. Blebs from Cross-linking were flat diffuse with moderate vascularity. The riboflavin blebs were flat small and more vascular. The mitomycin blebs were elevated diffuse and avascular. Histopathological examination of the Cross-linking blebs showed moderate cellularity and collagen deposition and thickened conjunctival epithelium with a dense layer of fibrosis below. The riboflavin blebs were more cellular, had more collagen deposition and had healthy looking conjunctival epithelium. Mitomycin blebs were acellular with mild collagen deposition and had extensive disruption of the epithelium.

Conclusions: The use of Cross-linking as an adjunct to trabeculectomy surgery produces a flat, diffuse and functioning bleb with mild fibrotic reaction and may act as a potential adjuvant treatment when trabeculectomy alone is inadequate.

A novel approach for corneal stiffening using a bacteriochlorophyll derivative WST11 and near infrared light

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Purpose: To evaluate the efficacy and safety of photochemical corneal stiffening by WST11 and near infrared (NIR) illumination, using ex-vivo and in-vivo rabbit eye models.

Methods: Corneas of post mortem rabbits and corneas in living rabbits were topically pretreated with 2.5 mg/mL WST11 in saline or in 20% dextran T-500 (WST-D), washed and illuminated with a near infrared (NIR) diode laser (755nm, 10mW/cm²), (WST11/NIR or WST-D/NIR, respectively). Studies with corneas of untreated fellow eyes served as controls. Tensile strength measurements, histopathology, electron spin resonance and optical spectroscopy and fluorescence microscopy, were used to assess treatment effects. Comparative studies were performed with standard riboflavin/ UVA treatment.

Results: WST11/NIR significantly increased corneal stiffness, following ex-vivo or in-vivo treatment, as compared to untreated contralateral eyes. The incremental ultimate stress and Young's modulus of treated corneas increased by 45, 113, 115%, and 10, 79 and 174% following 10, 20, 30 minutes incubation with WST11, respectively. WST-D/NIR had a similar stiffening effect, but markedly reduced post-treatment edema and shorter time of epithelial healing. WST11/NIR and WST-D/NIR generate hydroxyl and superoxide radicals but no singlet oxygen in the cornea. Histology demonstrated a reduction in the keratocyte population in the anterior half of the corneal stroma, without damage to the endothelium.

Conclusions: Treatment of rabbit corneas, with either WST11/NIR or WST-D/NIR, increases their biomechanical strength through mechanism that does not involve singlet oxygen. The WST-D/NIR treatment showed less adverse effects, demonstrating a new potential for clinical use in keratoconus and corneal ectasia after refractive surgery.

Characteristics of 244 patients with keratoconus seen in an optometric contact lens practice

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Purpose: The purpose of this study was to describe the characteristics of keratoconic patients seen in a specialized contact lens practice from a general population with a high prevalence of the disease.

Methods: Patients attending a contact lens practice for keratoconus management were asked to complete a questionnaire. Data were collected on demographic characteristics, general health, family history, eye rubbing, allergy, asthma, eczema, education level, history of keratoplasty and smoking.

Results: 244 patients completed the questionnaire. There was a male bias (54.5%). 78.7% of the patients wore contact lens, of which 67.7% wore hard, 13%, soft and 4.2% scleral contact lenses. 21.3% of the patients had undergone corneal graft surgery. 18% had an associated systemic disease, the most common of which was diabetes (type 2), although this disease was less, but not significantly, prevalent in the KC sample than in the general population ($p = 0.19$). The prevalence of eye rubbing (65.6%) was similar to other studies. Compared to the general population asthma (13.2%) was slightly, but not significantly, less prevalent ($p = 0.17$), eczema (6.6%) was significantly less ($p = 0.001$) and allergy (34.4%) was more prevalent ($p = 0.001$). A high proportion of patients reported a family history of the disease (27.9%) and most were better educated than the general population.

Conclusion: The results of this survey concur with those of other studies with regard to most known characteristics of keratoconus. However the proportion of asthma and eczema tended to be less than in other surveys and may be linked to the environmental influence of a hot and sunny country. The high prevalence of positive family history of the disease in this cohort suggests a genetic influence.

The long-term outcome of the refractive error in hypermetropic children

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Purpose: To unveil the natural history of high hypermetropic refractive errors in childhood.

Methods: We retrospectively reviewed data from the medical charts of 131 children with high spherical equivalent hypermetropic refractive errors in 3 medical centers collected over 29 years. Children with hypermetropic refractive errors between +1.00 and + 3.00 were classified as mild hypermetropes and those +5.00 or greater were classified as high hypermetropes .Four variables studied were, age, refractive error, strabismus and gender. The rate of reduction of the hypermetropic refractive error was calculated over time in years. We used the mixed model to test for statistical significance.

Results: Eighty one high hyperopic children and 51 mild hypermetropic children were included. High hypermetropes were detected at a mean age of 3.3 years, while mild hypermetropes were detected at 4 years. The mean follow-up was 6.5 years. Younger children, boys (45.2-93.9%) more than girls (15.7-75.3%), with mild refractive errors tended to reduce the refractive error over time. High hyperopes tended to remain highly hyperopic with no gender predisposition.

Conclusions: Children with hypermetropia higher than 5D will need glasses throughout childhood and adulthood.

The effect of accommodation on Maddox Rod phoria testing at distance

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Purpose: Two methods of subjectively determining the amount and direction of the phoria are the Von-Graeffe technique and the Maddox Rod technique (Elliot, 2007). The Maddox Rod technique is performed with a penlight in the dark, and therefore includes tonic accommodation (Heath, 1956). The Von Graeffe technique is done in a lighter room with an accommodative target. In this research, our objective is to compare the effect of which the accommodation has on the Maddox Rod test and on the Von Graeffe technique at distance. We assumed the results of the Maddox Rod technique would be more esophoric than the results of the the Von Graeffe technique, due to tonic accommodation.

Method: 30 healthy patients (mean age of 24.86 ± 3.17) without binocular anomalies (Cover Test and Steropsis were tested) participated in the study. Four procedures were performed and compared while the patients were fully corrected at distance: Von Graeffe, Von Graeffe with a fogging +0.50D lens, Maddox Rod, and Maddox Rod with a fogging +0.50D.

Results: We found an average of $0.61D \pm 3.54D$ esophoria with Maddox Rod compared to $0.50D \pm 2.50D$ exophoria with the von-Graeffe however the difference between the 2 tests was not significant (T-test; $p=0.082$, correlation; $r=0.85$). however, the averages of Maddox +0.50D and Von-Graeffe +0.50D were significantly different ($0.48D \pm 3.36D$ esophoria and $1.13D \pm 2.58D$ exophoria respectively; T-test; $p<0.02$, correlation; $r=0.78$).

Conclusions: Maddox Rod showed more eso tendency when compared with Von Graefe, however, this difference was not significant. The high correlation between the two methods questions any significant clinical effect of tonic accommodation on the Maddox Rod test. Additionally, both the Maddox Rod test and the Von Graeffe test are influenced by the added plus lens.

Intracameral Tissue Plasminogen Activator (tPA) in the management of severe fibrinous anterior chamber reactions in Toxic anterior segment syndrome (TASS)

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Purpose: To describe the use tPA in the treatment of severe fibrinous anterior chamber reactions in TASS after cataract surgery.

Methods: In a retrospective study, 26 eyes of 26 patients with severe fibrinous anterior chamber reaction as part of TASS received 25 mcg tPA intracamerally through a temporal paracentesis. The main outcome measures were rate of complete fibrinolysis, time of maximal effect, visual acuity and complications

Results: TASS appeared 11.5 ± 5.2 days after cataract surgery. There was no report of any complications during the injection of tPA. Fibrin lysis was observed 1 to 3 days after TPA injection. In 15 patients, the membrane had dissolved almost completely by the following day. In 4 eyes fibrin was reduced significantly, albeit sometimes only slowly with the need of topical steroid treatment. In three cases a second injection was needed. Visual acuity was significantly improved one week after the tPA injection ($P=0.041$). No hemorrhage or other complications occurred. No patient had an increase in intraocular pressure. Eleven eyes (42.3%) had corneal edema that lasted less than one month. The mean follow-up duration after tPA administration was 5 months

Conclusions: Intracameral application of tPA appears to be a safe and efficacious therapeutic approach in the management of severe fibrinous reactions in TASS after cataract surgery. Treatment was well tolerated and gave excellent results with no serious complications except for transient corneal edema.

Comparison Between Manual and Automated Interpupillary Distance Measurements in the Israeli Population

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Purpose: Interpupillary distance (IPD) is important in developmental anatomy and genetics, in optical prescribing instrumentation and display devices and in ocular diagnostics. This study compared manual (anatomic) IPD measurements and two types of automated (physiologic) ones in a sample of Israeli subjects to determine population norms and the precision of the measurement methods.

Methods: The mean of two manual millimeter ruler measurements and Essilor pupillometer measurements were recorded by two experienced examiners. Outcome variables included: distance and near monocular and binocular IPDs (DMonoIPD, NMOIPD, DBinoIPD, NBinoIPD). Two other examiners recorded the DMonoIPD using the L80+Wavefront aberrometer. Outcome variables were compared using correlation and Bland-Altman (B&A) analyses, and sub-divided according to gender and ethnicity (Jew/Arab) to compare between and determine population norms.

Results: 219 subjects (mean age: 24.2±4.6; range: 19-53) participated in the study. The pupillometer and manual methods were significantly correlated ($R(\text{DMonoRightEye}\&\text{LeftEye})=0.8$, $R(\text{NBino,DBino})=0.9$), though the L80+ measurements were not significantly correlated with the other methods ($R(\text{DMonoLeftEye}\&\text{RightEye (Manual,Pupillometer)})=0.3$). The B&A analysis found the instruments interchangeable only for binocular variables (Dmean difference(manual and pupillometer) (MD)=1.14mm; 95% CI: (-6.7)-9.5mm; NMD(manual and pupillometer)=1mm; 95% CI: (-6.7)-8.7mm; MD(manual and Aberrometer (RightEye+LeftEye))=1.14mm; 95% CI: (-10)-7.8; MD(pupillometer and Aberrometer (RightEye+LeftEye))= 0.004mm 95% CI: (-8.6)-7.8). The standard deviation of the pupillometer (1.85mm) and L80+ measurements (4.5mm) was larger than the manual measurements (1.5mm), indicating that averaging the values of two manual measurements is more precise. For all measured values, the differences between the Jewish (N=165) and Arab (N=54) populations were not clinically significant (1mm or less). The male manual and pupillometer DBinoIPD and NBinoIPD were 1.8mm, 2.0mm, 2.3 mm and 2.3mm wider than the female IPD, respectively.

Conclusions: The varying IPD methods were found to not be interchangeable. Based on to the lower standard deviation values obtained with the manual measurements, it is recommended for clinicians to manually measure the IPD twice and calculate the average IPD rather than performing automatic measurements for IPD determination.

Identification of miR-450b-5p as a new repressor of Pax6

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Purpose: PAX6 gene is a critical regulator of eye development and maintenance. A precise dosage of Pax6 protein is required for normal corneal development and integrity while over expression or down regulation of Pax6 results in various eye and corneal abnormalities. Loss of function mutations of PAX6 cause a severe panocular disease named aniridia. MicroRNAs (miRNA) are a group of non-coding RNAs that repress gene expression through specific binding to complementary sequences at the 3'-untranslated region (UTR) of their target genes. The purpose of this study is to identify miRNAs involved in PAX6 regulation using a model of induced pluripotent stem cells (iPSCs) that are able to differentiate into corneal epithelial-like cells and recapitulate embryogenesis.

Methods: In-silico analysis of the 3'UTR of PAX6 gene using TargeScan algorithm was used to identify new miRNAs that may bind and inhibit Pax6. Expression profiling of miRNAs and Pax6 was performed in vitro (during corneal commitment of iPSCs) and in vivo (in mouse embryos). Finally, lentiviral infection was performed to express miR-450b-5p in iPSCs or in mouse embryos ex vivo and the level of Pax6 and corneal markers was examined.

Results: We identified that miR450b-5p which is expressed in the cornea in vivo can bind to the 3'UTR of Pax6 and attenuate Pax6 protein expression. Interestingly, miR-450b-5p and Pax6 were reciprocally expressed during corneal differentiation of iPSCs in vitro and in mouse embryogenesis in vivo. While Pax6 was restricted to the head surface ectoderm that is committed to ocular lineage, miR-450b-5p displayed a photo-negative profile and was expressed in the ectoderm that will form the epidermis. Furthermore, over-expression of miR-450b-5p reduced Pax6 expression in iPSCs and in mouse embryos ex-vivo.

Conclusions: miR-450b-5p is a new repressor of Pax6 in corneal lineage specification. Since Pax6 is involved in the development and maintenance of various other ocular tissues (e.g. iris, lens and retina), nervous system and pancreas, it is possible that miR-450b-5p and PAX6 interactions have significance to the pathophysiology of these tissues as well.

Contralateral lateral rectus muscle recession in patients with Duane retraction syndrome type 3

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Purpose: To evaluate motor, sensory, functional and head posture results due to recession of the lateral rectus muscle contralateral to the involved eye in patients with Duane retraction syndrome (DRS) type 3.

Methods: A retrospective longitudinal, observational study of a consecutive clinical case-series was conducted. Of 11 patients with DRS type 3 operated from 1977 to 2012 at a tertiary medical center, 8 underwent recession of the lateral rectus muscle contralateral to the involved eye. Full ophthalmic, orthoptic and neurological examination was performed before and after surgery. Postoperative changes in distance/near exodeviation, abnormal head turn, ocular upshoot, and stereopsis were analyzed. Intragroup changes in motor misalignment (distance/near), abnormal head turn, ocular upshoot and binocular functions were calculated.

Results: Mean patient age was 8.75 ± 3.14 years at surgery. Mean exodeviation for distance was -17.3 ± 3.5 prism diopters (PD) preoperatively and

-4.0 ± 6.10 PD postoperatively; corresponding values for near were -23.13 ± 7.2 PD and

-5.9 ± 8.68 PD. Motor deviation improved by 77% for distance ($p=0.017$) and 74.5% for near ($p=0.01$). In 7/8 patients, the postoperative residual exodeviation (distance and near) was <8.0 PD. There was an 80% improvement in head turn, from 15.63 ± 4.2 degrees before surgery to 3.1 ± 5.3 degrees after ($p=0.01$).

Conclusions: Contralateral lateral rectus muscle recession for the treatment of moderate unilateral DRS type 3 is associated with significant motor and functional improvement and a decrease in head turn. Further collaborative multicenter studies are needed to confirm these findings.

Wavefront Aberrations in RGP vs. Soft Toric Contact Lenses for Corneal Astigmatism

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Purpose: Rigid gas permeable (RGP) contact lenses (CLs) create a liquid tear lens between the back surface of the RGP lens and the front surface of the cornea forming a refractive layer that is almost devoid of aberrations. As such, RGPCLs are expected to provide a better correction than soft toric CLs (STCLs) in subjects with a corneal astigmatism. The quantification of on-eye wavefront aberrations induced by various CL designs is important because of potential effects of the wavefront on visual acuity and visual quality. We assessed this by comparing the entire wavefront in subjects with corneal astigmatism fitted with STCLs and RGPCLs.

Methods: The on-eye wavefront aberrations of five eyes of three healthy subjects with an astigmatic refractive error that is primarily corneal (mean astigmatism: -1.85 D; range: -1.00-(-2.50) D) that were corrected with RGPCLs and STCLs were assessed. The corneal astigmatic component of the prescription was determined using the keratometry function of the L80+ Wavefront Aberrometer (Visionix, Luneau, Chartres, France) and tangential topography maps obtained from the Shin-Nippon topographer (Shin-Nippon Commerce Inc., Japan). The subjects were examined by two licensed Optometrists and fitted with STCLs (Filcon II 2, Soflex, IL) and RGPCLs (HDS, Soflex, IL). The entire ocular wavefront was measured with both CLs and without correction using the L80+'s Hartmann-Shack device. Root mean square (RMS) was calculated for the entire wavefront, lower order astigmatism, coma, trefoil, tetrafoil, HO astigmatism, and spherical aberration. The RMS values were compared using a student's paired t-test.

Results: Both CLs significantly improved the total RMS error (Uncorrected: 4.03 ± 1.05 ; STCL: 0.88 ± 0.51 , $p < 0.003$; RGPCL: 0.48 ± 0.17 , $p < 0.001$). However, RGPCLs significantly improved the low order astigmatism RMS (Uncorrected: 0.72 ± 0.15 ; RGPCLs: 0.31 ± 0.08 , $p < 0.01$), whereas the STCLs did not (0.75 ± 0.46 , $p = 0.86$).

Conclusions: RGPCLs provide a superior correction of corneal astigmatism, as demonstrated by their significant reduction of the low order astigmatism term.

Single Nucleotide Polymorphism Signature in Behcet's Uveitis

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Purpose: Behcet's disease is an idiopathic systemic inflammatory disease often involving the eye causing severe inflammation. However, ocular and systemic disease do not always coincide. Current pathogenic hypothesis of inflammatory diseases include environmental triggers affecting genetically vulnerable individuals. In an attempt to identify genetic predisposing targets, a recent genomic wide association studies (GWAS) found high association of single nucleotide polymorphism (SNP) in the IL-10I and L-23-IL-12RB2 loci, with behcet's disease. The purpose of our study is to validates these associations and to determine their frequencies in Israeli behcet's patients.

Methods: Blood samples were collected from behcet's patients, with and without uveitis. Patients with uveitis of other etiologies served as a control group. Genomic DNA was extracted from peripheral blood leukocytes using iPrep™ Purification Instrument according to manufacturer's instructions. Primers and probes relevant for SNP genotyping assays (rs1518111, rs1800872, rs1800871, rs1495965) were custom designed. Results were obtained by genotyping.

Results: For each genotyping assay, 26 samples were analyzed. Of them 7 were behcet's uveitis patients, 11 were behcet's patients, and the remaining 8 had other uveitis entities. For the 3 genotyping assays of IL-10, rs 1518111, rs 1800872, rs 1800871, the variant genotypes were A/A. None of the control group harbored this variant. In contrast, 9% of the Behcet's patients and 30% of the Behcet's uveitis patients harbored this genotype. In the IL-23-IL12RB2 the variant allele G/G was present in 28 % of Behcet's uveitis patients, in 36% the Behcet's disease patients and in only 12% of the control group.

Conclusions: These data are in accord with previously published studies. If confirmed in a large group, these data may suggest the role of reduced IL-10 in the pathogenesis of Behcet's disease and specifically in Behcet's uveitis.

Rapid Fire 2

Black and white and in-between

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Purpose: To assess visual quality following cataract surgery with positive and negative aspheric intraocular lenses (IOL) implantation.

Methods: Contrast sensitivity and MTF were measured at 3 months following cataract surgery with positive or negative aspheric IOL implantation. Contrast sensitivity was measured with best corrected distance correction using the OPTEC 6500 device at 5 different spatial acuities (1.5, 3, 6, 12 and 15CPD) under photopic (85 cd/m²) and mesopic (3 cd/m²) conditions. MTF was measured using the iTrace with a naturally occurring pupil.

Results: Fifty eight eyes of 42 subjects were implanted with a positive aspheric IOL and compared with 21 eyes implanted with a negative aspheric IOL. Contrast sensitivity values for positive and negative IOLs at the 5 spatial frequencies under photopic conditions were 63.3, 105.4, 114.5, 46.4, 18.9 and 55.8, 101.6, 123, 50, 1.43, respectively. None of the frequencies showed a significant difference of contrast sensitivity between the groups under photopic or mesopic conditions. Mean area under the MTF curve for eyes was 0.41 and 0.40 for eyes with positive and negative IOLs.

Conclusions: Subjective contrast sensitivity performance and objective MTF following a positive aspheric IOL implantation are comparable with a negative aspheric IOL

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The protective effect of TLR4 KO knock out mice against corneal chemical burn

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Purpose: Chronic inflammation of the cornea leads to neovascularization. TLR4 knock out (KO) mice are known to be resistant to inflammation. The aim of this study was to determine the resistance of TLR4 KO mice to the development of corneal neovascularization following chemical injury, as compared to wild type mice.

Methods: Corneal neovascularization induced by chemical burn (75% silver nitrate, 25% potassium nitrate) in TLR4 KO mice (n=12) and Wt (n=12). Clinical evaluation, digital photos, fluorescein angiography (FA) and measurement of the vascular area in flat mount corneas and histological sections were taken on days 2,4,8 and 10. Image J was used for statistical calculation. Immunohistochemistry was performed to detect the inflammatory and angiogenic reaction using CD31 ,CD11b, CD45 and VEGF antibodies.

Results: Neovascularization developed in all the corneas following chemical burns as shown clinically, by FA and in flat cornea samples. The maximal area of neovascularization measured on day 8, was smaller in TLR4 KO. There were no differences between the TLR4 KO and Wt mice on earlier days. Immunostaining revealed angiogenesis and inflammatory infiltration to the damaged corneas.

The inflammatory reaction that increased towards day 4 and that was reduced on day 8, was more prominent in the burn area and Wt mice compared with TLR4 KO. The angiogenesis that increased from the limbus towards the burn shown by maximal staining (CD11 and VEGF) on day 8, was greater than in the Wt mice.

Conclusions: An inflammatory and angiogenic reaction started from the limbus toward the central burn of the cornea in both TLR4 KO and Wt mice, but in the Wt mice both responses were greater. In both groups, maximal infiltration of inflammatory cells occurred on day 4, and angiogenesis on day 8. We assume that the inflammation leads to secondary cytokine secretion causing angiogenesis as part of the healing procedure. TLR4 KO exhibit an inflammatory reaction but a reduced one compared to Wt.

Signaling between macrophages and trabecular meshwork cells in-vitro and their potential contribution to glaucoma

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Purpose: Cytokines and chemokines have a role in Modulation of Aqueous Outflow in the ocular Immune privilege, through trabecular meshwork cells. Glial cells have an important role in release and recruitment of many cytokines and chemokines and as well as immunoregulatory functions. The present research aim is to investigate the ability of macrophages to influence human trabecular meshwork cells (NTM) changes in-vitro.

Methods: Differentiated monocyte cell line (THP-1) PMA treated, resulted in "glia like" macrophages cells (gL). NTM cells were co-cultured with the differentiated THP-1 cells for various times (2,4,8,12 and 24 hr). The effects of gL cells over NTM cells were examined by the following methods: Zymography for MMP's activity; Western blot analysis for MAPK expression and DIMFUP for phosphatases activity.

Results: The exposure to gL cells increased MMP-9 levels in human NTM cells over time up to 1.5 fold vs. the control (peak at 4 hr). Phosphorylate Erk/ total-Erk ratio increases in a time dependent manner up to 8hr and decrease at 24hr post co-culture.

Conclusions: Our preliminary data indicates that exposing the NTM cells to "glia like" macrophages stimulated protein expression and an increased MMP-9 activity. These results suggest the involvement of glial cells in the regulation of the NTM homeostasis might be, subjected to further research, an intervention point for glaucoma treatment.

Do signaling between the ciliary epithelium and the trabecular meshwork has a role in intraocular pressure maintenance?

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Purpose: Ciliary epithelium (CE) includes neuroendocrine and steroidogenic activities. The neuropeptides released by the CE to the Aqueous humor can serve as messengers to communicate with trabecular meshwork cells and regulate intraocular pressure. The aim of the study is to test the hypothesis that TM cells are affected via the Aqueous humor by unknown factors released by the CE, resulted in changes in human trabecular meshwork HTM cells morphology, MMP&phosphatase activity.

Methods: Co-culture model of human cell lines, ODM, derived from the nonpigmented ciliary epithelium and the HTM cell line were used. HTM cells were cultured with ODM cells for 0.25 0.5, 1, 2, 4 and 8 hr. The effects of ODM cells on HTM cells were examined, focusing on activation of extracellular signal regulated kinase (Erk1/2) and the activity of MMPs. Erk1/2 phosphorylation was measured by Western blot analysis with anti-phospho-Erk1/2 antibodies. The activity of MMPs in HTM was determined by gelatinase zymography enabling the detection of MMP-2 and MMP-9.

Results: MMP-9 activity following co-culture with ODM demonstrated higher activity vs. their match controls (NTM-NTM co-culture). HTM- ODM following intermediate or long incubation time (2,4&8hr) showed higher levels of MMP-9 in compare to short co-culture incubation (0.25&0.5hr). The HTM-ODM resulted in a time dependent activity elevation of MMP-9 that was measurable as early as 15 minutes and reached a maximum by 8 hr. MMP-2 activity along the experiment did not change significantly.

pErk/tErk ratio following ODM-NTM exhibited an decrease at the short incubation time periods vs. NTM-NTM co-culture. At 2hr to 8hr the pErk/tErk ratio was higher for the ODM-NTM.

Conclusions: Our results demonstrates that TM cells affected by CE, resulted in increased MMP-9 activity and activation of the Erk1/2 pathway. Manipulation of this and related TM signal-transduction pathways may provide targets for developing improved glaucoma treatments.

Chromatic pupillometer-based perimetry in glaucoma patients

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Purpose: To objectively evaluate visual field defects in patients with glaucoma using a custom-built chromatic pupillometer.

Methods: Thirty participants were recruited (19 healthy subjects and 11 patients with glaucoma). A computerized infrared video pupillometer was used to record changes in pupil diameter in response to short- and long-wavelength stimuli (peak 485 nm and 640 nm, respectively) size V, at light intensities of 15-100 cd-s/m² and duration of 1000 ms at 11 different points of the visual field. Percentage change of pupil diameter was calculated. Correlation between pupillometer and Humphrey-based perimetry was estimated by calculations of Pearson's correlation coefficients for each point of the visual field. Receiver operating characteristic (ROC) curves were constructed for the different visual point locations. Intra-individual variability was estimated.

Results: Significantly reduced pupillary responses were recorded in glaucoma patients under testing conditions that emphasized ganglion cell contribution (short-wavelength stimuli at high intensity) in all perimetric locations (P

Chromatic components in underwater targets do not affect Great cormorants (*Phalacrocorax carbo*) visual resolution

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Purpose: Light scatter and absorption impair image formation underwater. Scatter and absorption are wavelength dependent and it is expected that visual resolution for targets with different chromatic components, will differ. Great cormorants pursue prey (fish) underwater, facing visual constraints in their frequent transitions between air and water. Visual resolution of cormorants for achromatic targets has been previously established yet the effects of chromatic components have remained open.

We aimed here to determine the underwater visual resolution of cormorants for square wave gratings comprising chromatic and achromatic components

Methods: Hand-reared Great cormorants (N=6) were trained and tested for their resolution, in an underwater Y-maze. The visual targets comprised square-wave gratings that were achromatic (black&white) or chromatic (black&color). Colors ranged from “reds” through “yellow greens” to “blues”. Targets with vertically oriented bars were “positive” and targets with horizontally oriented bars were “negative”. Gratings frequencies ranged from 1.4 to 12 cpd. Illumination was diffuse daylight and water turbidity ranged 0.3-5.6 NTU. The cormorants’ choice was made at 1.4m from the targets. Each individual provided results from ca. 30 tests on chromatic and ca. 7 tests on achromatic gratings. The proportion of correct choices was used to determine resolution (at $p=0.75$ level).

Results: Over all cormorants (grouped) the mean maximal underwater visual resolution for achromatic and chromatic gratings was ca. 8cpd. Resolution for achromatic gratings was consistently higher than for chromatic gratings the yet difference was not significant. Chromatic components did not have a significant effect while the effects of gratings frequency and of individual differences on resolution were significant. Individuals showing high resolution reached 6.1-12.2 cpd while individuals showing low resolution reached 3.0– 4.0 cpd.

Conclusions: Under the experimental conditions here, the chromatic components in the targets did not affect visual resolution. It may well indicate that color patterns of fishes, such as alternating black and chromatic bars, may not significantly affect their detection by foraging cormorants. Marked and consistent individual differences in visual resolution must play a role in prey detection and capture success.

Air-pulse corneal applanation signal curve parameters for the characterization of astigmatic corneas

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Purpose: To test the parameters from ocular response analyzer (ORA) to distinguish the biomechanical properties between emmetropic eyes with normal topography and eyes with moderate to high with-the-rule astigmatism (WTA) and against-the-rule astigmatism (ATA) with symmetric bow tie topography

Settings: Enaim private refractive surgery center, Tel-Aviv, Israel

Methods: A total of 172 patients were included in our study (344 eyes): the control group consisted of 35 emmetropic patients (70 eyes) with a normal topography and the group with astigmatism which was divided into 2 groups, 62 patients (124 eyes) with WTA astigmatism and 67 patients (134 eyes) with ATA astigmatism. We tested the correlation of 42 parameters that describe the applanation curve during ORA measurements with maximum simulated keratometry (Sim K max) values in all groups. Finally we tested the significant parameters in order to find any difference in biomechanical properties of the cornea between these groups.

Results: Of the 42 parameters, 26 were correlated with Sim K max reading value. The correlations r coefficients were moderately low between -0.3848 to 0.0939. The best correlated 8 parameters were p1area, p2area, dslope1, h1, dive1, p1area1, p2area1, and h11. All were negative correlated with Sim K max. The group with the highest number of significant difference parameters was ATA compare to control group.

Conclusions: Some of the new waveforms parameters can distinguish between patients with ATA, WTA and normal topography patterns and may point out a difference in biomechanical properties between these groups.

Ocular anterior segment changes during pregnancy

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Purpose: To describe the changes that occur in the cornea, anterior chamber and intraocular pressure (IOP) during pregnancy.

Methods: Anterior segment anatomy and IOP were measured in healthy pregnant and non-pregnant women with The Ocular Response Analyzer and the Pentacam HR. Biometric and IOP parameters were compared..

Results: Sixty four pregnant and 67 non-pregnant women were enrolled. Goldmann correlated intraocular pressure (IOPg) and corneal compensated IOP (IOPcc) were significantly lower in the pregnant group (11.05 vs 13.05 mmHg, $P < 0.001$; 10.9 vs 13.15 mmHg, $P < 0.001$, respectively).

Corneal front steep keratometry value was statistically significantly higher in the pregnant group (44.77 vs 44.12 D, $P = 0.037$).

No significant difference was found in corneal hysteresis, corneal resistance factor, corneal posterior curvature, central corneal thickness and volume, or anterior chamber depth, volume and angle.

Conclusions: This study suggests that pregnancy can influence measured corneal curvature and IOP. Longitudinal studies are needed to verify these findings and clarify if they result from changes in corneal biomechanical stability during pregnancy.

Functional Macrophage Heterogeneity in Experimental Autoimmune Uveitis

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Purpose: Macrophages displaying diverse functions are well accepted outside the ocular system, in cancer and wound healing. We previously showed that monocyte-derived macrophages display anti-inflammatory features required for neuroprotection and renewal of progenitor cells following glutamate-induced retinal damage. However, in experimental autoimmune uveitis (EAU) macrophages have mostly been perceived deleterious and their functional heterogeneity was largely overlooked. In this study we addressed macrophage heterogeneity in this ocular autoimmune condition.

Methods: EAU was induced in male C57BL/6J mice by injection of human interphotoreceptor retinoid binding protein (IRBP)-derived peptide 1-20. Monocyte-derived macrophages in this disease were traced in CX3CR1-GFP bone marrow chimeric mice. Depletion of the infiltrating macrophages and subsequent effect on disease severity was performed at different stages of EAU in order to evaluate the different functions of these cells along the disease course.

Results: EAU induction resulted in the recruitment of monocyte-derived macrophages to the diseased retina. The frequency of CX3CR1-GFP^{high} infiltrating macrophages that express markers associated with inflammation-resolving activity increased along the disease course, together with a decrease in the frequency of inflammation-associated, Ly6C⁺ macrophages. Depletion of monocytes at the induction phase of EAU prevented disease onset, whereas such depletion at the resolution phase resulted in a decrease in Foxp3⁺ regulatory T cells, and in exacerbated disease.

Conclusions: Monocyte-derived macrophages display distinct phenotypes along the course of an experimental inflammatory autoimmune disease, reflecting their differential roles in disease induction and resolution, thus pointing to functional macrophage heterogeneity in such condition.

Specular microscopy findings in early well controlled diabetes

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Purpose: To compare specular microscopy findings in patients with and without diabetes and determine possible association with age, diabetes duration, and glycemic control.

Methods: Retrospective, clinic based, cross sectional comparative study. Patients files were reviewed retrospectively, specular microscopy findings including CCT and endothelium features were compared between diabetic and non diabetic population, statistical analysis of possible association between specular microscopy findings and age as well as diabetes characteristics was performed. One hundred and eighteen eyes of 68 patients with type 2 diabetes and 194 eyes of 112 non-diabetic age matched patients were identified.

Results: Diabetes duration was 7.8 ± 6.2 years, HbA1C $7.2 \pm 1.2\%$. Mean Cell density and Central Corneal thickness (CCT) were 2467.8 ± 334.5 cells/mm² and 558.8 ± 48.8 μ m respectively in diabetic patients, compared to 2553.5 ± 289.2 cells/mm² and 547.1 ± 44.6 μ m in non diabetic patient ($p < 0.05$). Statistically significant association was found for diabetes existence and Cell density and diabetes existence and (CCT) $p < 0.05$, and borderline association between diabetes duration and (CCT) $p = 0.05$. No other associations showed statistical significance.

Conclusions: Diabetic corneas are different from non diabetics even in early disease and good glycemic control.

New technique of phacodonesis induction and anterior capsule adjustment in enucleated pig eyes for wet lab training.

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Purpose: To introduce a novel technique for adjustment of anterior capsule and induction of graded phacodonesis in enucleated pig eyes for wet lab training of residents.

Methods: Two hundred fresh post mortem enucleated pig eyes were assessed. The following substances were injected: Formaldehyde, Ethanol, Methanol, Acetone, Urea, Chlorine based disinfectants. Injections were performed intracamerally, into crystalline and intravitreally. The eyes were evaluated at measured intervals lasting from 1 minute till 1 hour using the uniform system for all subgroups by the same observer and phacoemulsification was performed by the same surgeon. As an outcome these parameters were evaluated: corneal transparency, anterior capsule similarity to human eye, formation of cataract and degree of phacodonesis.

Results: Urea injection provided graded reproducible phacodonesis. Chlorine derived substances achieved anterior capsule similarity to human.

Conclusions: A novel technique for induction of reproducible and graded phacodonesis, as well as anterior capsule consistency adjustment to the human capsule is described. These findings can help in the wet lab training systems.

The role of PPM1A in early corneal wound healing response

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Purpose: Protein phosphatase magnesium dependent 1A (PPM1A) is a protein phosphatase with an important role in different signaling pathways which down-regulate inflammatory and fibrosis processes following cellular stress. In the current study we evaluated the role of PPM1A in the early inflammatory reaction following corneal wound by comparing wild type (WT) mice with mice that are knockout (KO) for the PPM1A gene and do not express this protein.

Methods: A standardized corneal alkali burn was performed in one eye of 13 mice, the other serving as control (8 KO for PPM1A and 5 WT). Corneas were harvested 6 hours following the alkali burn. Expression levels of key Cytokine / chemokine players (IL1 α MCP-1, PDGF-B) in the corneal healing process were evaluated using RT PCR. The corneas of 7 more mice (3 KO, 4 WT) treated in the same way were processed for ELISA testing to evaluate IL-6 protein levels.

Results: Evidence of inflammatory induction as indicated by increased levels of cytokine expression in the treated group as compared with the control group was demonstrated, and was statistically significant for IL-6 ($p=0.0495$). There was a non-statistically significant increased level of IL1- α (1.006354 KO vs. 0.954947 WT) and PDGF-B (2.105282 KO vs. 1.634252 WT) in the treated knockout group as compared to the wild type group. IL-6 protein levels as determined by ELISA tests were significantly higher ($p=0.052$) in the KO group as compared to the WT group following corneal alkali burn.

Conclusions: The results indicate that PPM1A participates in the initial inflammatory process following corneal wound, as early as 6 hours. This may be used in developing treatment aimed to reduce post-traumatic and post-surgical corneal inflammation.

Endothelial survival after DSAEK in eyes with retained anterior chamber intraocular lenses

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Purpose: To evaluate endothelial cell survival after Descemet-stripping automated endothelial keratoplasty (DSAEK) for the treatment of endothelial dysfunction in the presence of an anterior chamber intraocular lens (AC IOL).

Methods: This study comprised eyes with endothelial failure that had DSAEK in the presence of an AC IOL. Donor central endothelial cell density (ECD) was recorded 6 months and 1 year postoperatively and compared with preoperative ECD donor values.

Results: The study evaluated 11 eyes with ACIOL and 50 eyes with PCIOL that were operated between March 2009 and June 2012 at Rabin Medical Center. The mean preoperative ECD was 2558 ± 477 cells/mm² in the ACIOL group and 2545 ± 339 cells/mm² in the PCIOL group. ($P=0.87$) At 1 year, the mean ECD was 1611 cells/mm² ± 266 (SD) and 1555 ± 380 , representing a mean cell loss from preoperative measurements of $37\% \pm 12\%$ and $39\% \pm 10\%$, respectively. ($p=0.24$)

Conclusions: DSAEK in the presence of a well-centered AC IOL, with a deep anterior chamber, had a mean postoperative donor endothelial cell loss of 37% at 1 year. There was no significant difference in cell loss in the ACIOL and PCIOL groups.

Sodium Iodate-Induced Model for Retinal Degeneration Secondary to RPE Injury

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Purpose: Dysfunction, injury, and loss of retinal pigment epithelium (RPE) cells are prominent features of AMD, Best disease, and subtypes of Retinitis Pigmentosa. Animal models of RPE injury and degeneration are scarce. Sodium Iodate (NaIO₃) was shown to induce specific damage to RPE cells, resulting in secondary dysfunction and loss of photoreceptors. The purpose was to establish and characterize the course of retinal degeneration secondary to selective RPE injury induced by NaIO₃ in adult naïve mice. It is expected that this model will allow testing of different therapies aimed at supporting and replacing dysfunctional RPE cells.

Methods: Single intraperitoneal injections of NaIO₃ (50-100mg/kg) were performed in 7-8w old C57Bl6 mice. Littermate mice served as controls. To evaluate retinal function, scotopic and photopic full-field electroretinography (ERG) was performed 14d following NaIO₃ injection. Retinal structure was assessed using ocular coherence tomography (OCT) immediately and 14d after NaIO₃ injection, as well as by histological and IHC techniques 1,3,7,14d post-injection.

Results: Two week following NaIO₃ injection, scotopic ERG responses were non-detectable at lower stimulus intensities. Mean b-wave amplitude at the highest intensity was severely reduced ($271\pm 45\mu\text{V}$ vs. $536\pm 47\mu\text{V}$ in controls, $p=0.002$). Interestingly, photopic cone ERG showed a trend for super-normal responses in NaIO₃-treated retinas (mean b-wave amplitude at highest stimulus intensity $114\pm 20\mu\text{V}$ vs. $63\pm 5\mu\text{V}$ in controls, $p=0.12$). Structural retinal changes were time-dependent and progressed from loss of RPE nuclei 1d after NaIO₃ injection to severe retinal disorganization and thinning of the photoreceptor layer accompanied by macrophage activation by 14d. In-vivo OCT findings were well correlated with the histological observations. IHC staining of NaIO₃-treated retinas revealed increased amount of Blue and Red/Green cone opsins that were mislocalized to photoreceptor cell bodies, axons and pedicles whereas in controls, opsins were localized to the outer segments only.

Conclusions: Injection of 50mg/kg NaIO₃ leads to RPE damage followed by dysfunction and loss of photoreceptors. Interestingly, at 2w post-injection, cone photoreceptors demonstrate super-normal ERG responses, enhanced opsins production and mislocalization throughout the cell. NaIO₃ can thus provide an easily induced, reproducible, non-inherited model for retinal degeneration caused by RPE injury.

Human CNGA3 Gene Therapy Rescues Cone Function in a Sheep Model of Achromatopsia

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Purpose: Congenital achromatopsia (ACHM) is a currently incurable hereditary disorder primarily affecting cone photoreceptors. In the Israeli population, mutations in the CNGA3 gene are by far the most prevalent cause of disease, accounting for over 85% of cases. Recently, we reported prominent improvement in retinal function following mouse CNGA3 gene therapy in achromatopic sheep. The purpose of this study was to determine efficacy of gene therapy using the normal human gene (hCNGA3) in the sheep model of CNGA3 ACHM.

Methods: AAV5-hCNGA3 under control of the red-green opsin promoter was injected unilaterally into the subretinal space of four 5-6m old day-blind lambs. Animals were assessed preoperatively and then several times up to 3 months following gene therapy. Behavioral assessment included scotopic and photopic maze testing under standardized conditions. Passage times and number of collisions were recorded. Electroretinography (ERG) was used to evaluate cone function, and photopic responses to low frequency and flicker (10-80Hz) stimuli were recorded at 4 intensities (1-10cd•sec/m²). Age-matched normal and non-treated day-blind sheep served as controls.

Results: Pre-operatively and post-operatively there was no difference in passage time between affected (n=18) and control (n=14) animals under scotopic conditions, which was on the average 5.7±0.4sec and 4.1±0.5sec (mean±SEM), respectively. On the other hand, pre-operatively, affected lambs demonstrated marked impairment of photopic visual function as evaluated by the behavioral maze test. Twelve of 18 affected animals were not able to pass the maze at all, and the other 6 experienced multiple collisions and needed significantly ($p < 0.05$) longer time for passing as compared with control lambs (26±2sec vs. 5.6±0.9sec, respectively). Gene therapy dramatically improved results of photopic maze tests – passage time shortened to 6.8±1.1sec, and number of collisions dropped significantly. 1.5-2 months following subretinal delivery of hCNGA3, cone ERG responses showed shorter implicit times and higher flicker fusion frequencies.

Conclusions: Subretinal delivery of the human CNGA3 gene significantly improves cone-mediated visual function in the sheep model of achromatopsia. Long-term follow-up of the animals is in progress as an important step towards an eventual human trial.

Incidence of Demodex parasites in Chronic Blepharitis and Controls

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Purpose: Many studies tried to determine the pathogenic relation between the parasite Demodex in the lids lashes and chronic Blepharitis. Results are not conclusive, possibly due to the lack of accurate diagnosis of the parasite in some of the studies.

Recently, Tea-Tree Oil was suggested as a beneficial treatment when blepharitis is associated with Demodex. The purpose of this study is to determine the incidence of Demodex parasites in blepharitis patients versus controls, and to investigate the effectiveness of Tea-Tree Oil treatment for demodex-associated blepharitis.

Methods: 112 patients were included in this case-control study. They were divided into 2 groups: Group A- included 61 patients with chronic blepharitis (anterior or posterior). Group B- included 51 patients without signs of blepharitis (Controls).

6-8 lashes were epilated from each patient, and the presence of Demodex and eggs was recorded under a light microscope. The study was conducted in a blinded fashion.

The efficacy of Tea-Tree Oil treatment for eradicating the parasite was evaluated in a subgroup of 11 patients

Results: 44/61 (72.1%) patients of group A and 20/51 (39.2%) patients of group B had either Demodex or eggs at their eyelashes. (P=0.0009)

7/11 patients (63.6%) treated with Tea-Tree Oil had Demodex at their lashes following treatment and 77.8% (7/9) denied improvement in symptoms following this treatment.

Conclusions: Demodex species were more prevalent in blepharitis patients when compared to the controls. Treatment with Tea-Tree Oil did not significantly contribute to relieve symptoms neither eradicated Demodex from patient's lashes.

Higher levels of IL-8 in tear fluid preceded the clinical manifestation of corneal neovascularization following chemical ocular injury in rabbits

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Purpose: To monitor the changes in tear fluid biomarkers throughout the dynamic course of chemical ocular injury in the rabbit model.

Methods: Rabbit eyes were exposed to sulfur mustard (SM) vapor and a clinical follow-up was carried out up to 4 weeks. Tear fluid and corneal samples were collected at different time points for measurement of MMP-2 and MMP-9 activities by zymography and VEGF, IL-8, IL-6, TNF α and IL-1 β levels by ELISA.

Results: Typical SM-induced ocular injury was developed including a partially healed acute phase, clinically expressed by corneal erosions and severe inflammation, followed by a delayed pathology in 50%-80% of the eyes, characterized mainly by chronic inflammation and corneal neovascularization (NV). In the tear fluid, elevation in MMP-9 activity and IL-8 level was seen. While MMP-9 activity remained high throughout the follow-up period in all of the exposed eyes, IL-8 levels decreased with the healing of the acute clinical symptoms. Moreover, in the tear fluid from eyes that developed a delayed pathology, relatively higher IL-8 levels preceded NV clinical manifestation. Elevated levels of corneal IL-8 and MMP-9 activity were found during the acute phase as well as in vascularized eyes, indicating a possible source for these proteins in the tear fluid.

Conclusions: Different profiles of IL-8 and MMP-9 in the tear fluid were found during the dynamic course of the ocular injury. Although both factors may point towards therapeutic strategies and serve as a tool for treatment evaluation, only IL-8 level was indicative of the future clinical outcome.

EMM - Eyelid Motion Monitor

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Purpose: Neuro-Ophthalmologists and Oculoplastic Surgeons analyze the eyelid movements to assess and monitor many ocular and systemic diseases. So far, static metrics and levator function are performed routinely for evaluation of eyelid movements. Yet no clinical device is available for routine clinical practice that allows evaluation of the kinematics of eyelid movements.

Goals: Develop a device that facilitates the monitoring of the upper eyelids motion, acquires the eyelid vertical movement and enables analysis and graphic presentation of the results. It should allow the patient to move freely in his/her natural environment.

Methods: The system consists of three components: (1)glasses for the patient including magneto-sensitive (Hall) probes. (2)Hardware– digital and analog cards that select, process, store or transmit the data. (3)Dedicated software allows a user friendly interface for the doctor. It includes portable, “plug and play” system and well defined physician-patient work flow, for measuring amplitude, velocity, rise and fall-time, and time duration between two blinks of each eye separately. Essentially, four Hall-probes monitor the magnetic field generated by a tiny magnets attached to the upper eyelids. They are placed on glasses-like frame which contains a pre-amplifier and attached to them is a digital card consisting of a micro-processor and 2GB of data storage capability. Two modes of operation are conceived, on or off-line. When on-line, the device is connected to PC and the data is displayed instantaneously and stored on the HD. If off-line, the data is stored in the internal memory of the device. At the end of the day, week or month, the data can be downloaded to the PC where the software may store, assist analyzing and presenting the data.

Results: A fully operational prototype is reported. Currently direct and separate monitoring of each eyelid is possible. Based on present performance it is possible to set the time between two blinks, rise and fall time. In the near future, full analysis of each eyelid dynamics will be possible.

Conclusions: A novel device has been developed which may provide the medical community with a new methodological asset that enables to trace the eyelid motion. In due course, the system will enable us to examine and monitor many ocular and systemic diseases including ptosis, cranial nerve palsies, myasthenia gravis, degenerative neurological diseases, stability disorders and many others.

Parafoveal processing of semantic information

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Purpose: : To use a Stroop-like task to assess automatic semantic processing of words appearing in the center of the visual field and at 3.9 visual degrees (the outer limits of the parafovea).

Methods: Participants performed a gender identification task by means of a button press in response to briefly flashed (180 msec) stick figures. The Figures were located at 3.9 and 7.9 degrees to the right or left of center. In addition to the figure a word was flashed that was either congruent (e.g., “gever” for male picture) or incongruent (e.g., “gever” for female picture) to the figure. The word appeared medial to the picture, either at the center of at 3.9 degrees. Eye position was recorded using the ISCAN Infra-red eye tracker and only correct trials with central fixation immediately prior to stimulus onset were analyzed for response time.

Results: A two-way repeated measures ANOVA revealed a significant effect ($p < 0.05$) at both positions for all subjects ($N=9$). A significant interaction occurred whereby the difference between congruent and incongruent responses was greater when the word appeared at center (congruent=478 ms, incongruent=516 ms) and smaller when it appeared at 3.9 degrees (congruent=477 ms, incongruent 543 ms).

Conclusions: The existence of a stroop effect suggests that words are semantically processed even parafoveally. The interaction related to position was driven by the processing of incongruent words, which caused more interference in the center than at 3.9 degrees. Thus although the contribution of congruent words was the same at both positions, it seems that it was easier to ignore the incongruent word parafoveally. The overall result does not suggest a “winner takes all” model, i.e., if parafoveal stimuli are processed semantically they are processed as well as they are in the fovea. Rather, it seems that parafoveal processing can be influenced by attentional strategy.

Incidence and Causes of Blindness in Israel between 1999 and 2010

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Purpose: We have previously shown that the age-standardized incidence rate of newly registered legal blindness in Israel was halved in the decade between 1999 and 2008, declining from 33.8 to 16.6 per 100 000 in 2008. This dramatic decrease was attributed to a decreased incidence of blindness from age-related macular degeneration (AMD), glaucoma, diabetic maculopathy and retinopathy, and cataract. The aim of the current study was to analyze the data for the years 2009 and 2010 and to determine whether there is a continuation of the decline in the incidence of blindness from all major causes.

Methods: Data was retrieved from the 2009 to 2010 annual reports of the National Registry of the Blind in Israel and retrospectively reviewed. Specific rates by age, gender, calendar year and cause of blindness were calculated. Total and cause-specific annual age-standardized rates were calculated as well. Findings were evaluated by the use of Poisson regression models.

Results: The overall rate of blindness per 100.000 people declined from 16.6 in 2008 to 14.8 in 2010. The disease-specific rates for the corresponding years were: 3.51 and 2.84 for AMD; 2.52 and 2.36 for diabetic maculopathy and retinopathy, and 1.84 and 1.68 for glaucoma. The number of individuals recognized as blind due to cataract increased from 78 to 129.

Conclusions: There was a distinct continuation of the rapid decline in the incidence of new cases of blindness from all major causes except cataract in the years 2009-2010. This continuing reduction is attributable to the use of the effective contemporary ophthalmic technologies and widely available universal free access to modern healthcare.

The Correlation between Visual Acuity, Refraction and Cognitive Function in the Elderly

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Purpose: To study the correlation between visual acuity, refraction and cognitive state in an elderly population, with no known dementia or Alzheimer's disease.

Methods: A cross sectional study was conducted, comprising of 200 subjects age 75 and older from adult day care centers. Near visual acuity was tested using the Jaeger chart and refraction was examined by a portable auto-refractometer. Cognitive function was evaluated with the mini-mental state examination (MMSE). The eye with better visual acuity and no cataract or refractive surgery was used for analysis. Patients that underwent cataract or refractive surgery in both eyes were excluded. Correlation tests were used to find association between visual acuity, refraction, wearing eyeglasses for near or far vision and cognitive functions.

Results: One hundred and ninety five subjects (mean age 81.6 ± 5.1 years, 70.3% females) fulfilled the inclusion criteria and comprised the study population. The mean period of education was 9.2 ± 4.6 years (range 0-25). Mean Jaeger near visual acuity was $J3.3 \pm 3.1$ (range J1-J16). Mean refractive error was 0.52 ± 2.33 (range +4.625 to -5.625). Eyeglasses for near vision were used by 124 (63.6%) participants and 128 (65.6%) participants used eyeglasses for distance vision. Mean MMSE was 24.9 ± 4.0 points (range 15-30). Good near visual acuity (J3 or lower) was found to be associated with high MMSE score (>24) (OR=3.74, 95% CI=1.86-7.52, $p<0.001$) and remained significant after adjustment for sex, age and years of education. Wearing eyeglasses for near or far vision were found to be correlated with high MMSE score after adjustment for sex and age (OR=1.95, 95% CI=1.06-3.57, $p=0.03$, OR=1.94, 95% CI=1.05-3.59, $p=0.04$, respectively) but did not after adjustment for years of education. A trend was found toward correlation between myopia and better MMSE score ($r=-0.12$, $p=0.09$, Pearson's correlation) although it did not remain so after adjusting for sex, age or education.

Conclusions: Good near visual acuity and wearing eyeglasses for far or near vision seem to be correlated with better cognitive function. The nature of the relationship between visual and cognitive functions and possible causality needs to be further investigated.

Knockdown of the UNC119 paralog in zebrafish ; an animal model for core rod dystrophy?

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Purpose: Mammalian UNC119 is a polypeptide involved in ciliary vesicular trafficking in retinal photoreceptors. UNC119 interacts with GTPase Arf-like 3 (ARL3) leading to release of myristoylated cargo and recycling of UNC119. We examined the role of an UNC119 paralog (UNC119c) in zebrafish vision and retinal organization.

Methods: The expression patterns of the three zebrafish UNC119 and ARL3 orthologs were determined by whole mount in-situ hybridization. Visual development was studied through optomotor response analysis in UNC119c knockdown, compared to wild-type zebrafish, and rescue controls.

Results: The three *unc119* zebrafish orthologs (UNC119a-c) and *arl3l2* were cloned, and their expression patterns were determined by whole mount in-situ hybridization. UNC119c and ARL3l2 are specifically expressed in photoreceptive tissues (pineal and retina). At 24 hours post fertilization (pf), a specific expression of *unc119c* was found in the pineal gland of the embryo and by 3 days pf, *unc119c* mRNA was first evident in the ventral patch of the retina. The expression of *unc119c* within the retina expanded with the expansion of the developing retina. In addition to their co-localization, *unc119c* was found to specifically interact with ARL3L2 by co-immuno precipitation.

Following injection of morpholino-modified antisense oligonucleotides (MO) directed to block *unc119c* expression, UNC119MO larvae displayed impaired visual acuity when compared to wild-type controls and to MO-controls as indicated by their optomotor response to grating motion.

Conclusions: Zebrafish UNC119c is a novel ortholog of the mammalian UNC119. UNC119c and ARL3l2 interact and are highly expressed in photoreceptive tissues (pineal and retina). Knockdown of the *unc119c* resulted in early onset visual impairment despite the existence of other UNC119 isoforms in zebrafish. Further research on the role of ARL3 and the interactions of ARL3 and UNC119c in the zebrafish model of cilopathies is currently underway.

Inhibition of NFkB in Uveal Melanoma: in vitro vs. in vivo

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Purpose: To describe the differential response of uveal melanoma to NFkB inhibition in vitro vs. in vivo.

Methods: The C918 uveal melanoma (UM) cell line was grown in culture without and with 1 μ /ml of the BMS-345541 NFkB inhibitor. Cells were grown under normoxic and hypoxic conditions (0.5% O₂) for 72 hours with viability and Caspase3 measurements every 24 hours using the Fluorescent Cell Viability and Caspase-Glo 3/7 Assays (Promega, Madison, WI, USA). Later, C918 cells were transfected with the luciferase (luc) gene and cells that stably expressed luc were selected. The new C918-Luc cell line was trypsinized, washed in 1xPBS and injected either subcutaneously or directly into the livers of SCID mice through a small (1 cm) abdominal wall incision via a 0.5 cc insulin syringe (29 gauge needle) in a non-reflux technique. Injected cells were visualized with an IVIS bioluminescence (BioL) camera (Caliper Life Sciences, Hopkinton, MA, USA) after injecting the mice with luciferin (IP 3 mg/0.3 cc). Cells were allowed to settle for 1 week before BMS-345541 (0, 2, 10, 20, and 50 mg/kg) was administered IP 3 times / week for 3 weeks, and tumor growth was monitored via BioL twice weekly. The experiment was terminated following euthanasia and the livers were harvested for histopathologic evaluation. The research reported herein was conducted in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Results: Cell viability diminished similarly either with addition of BMS in normoxia or without it in hypoxia, and was abolished with BMS in hypoxia. A similar increase in Caspase3 was noted at 72 hours. In SCID mice, bioluminescence started decreasing after administration of BMS, but then turned into a remarkable growth spurt which increased with higher doses of BMS. Histopathology of treated tumors showed a central area of necrosis surrounded by viable tumor vs. a completely viable tumor in untreated animals.

Conclusions: Inhibition of NFkB reduces cell viability and increases apoptosis in vitro and in vivo. However, this effect is reversed by yet unknown mechanisms in vivo, possibly triggered by the necrotic tumor. These mechanisms may lie behind UM's unresponsiveness to chemotherapeutics.

MuLV-based replication-competent retroviruses (RCR) Target Uveal Melanoma Response to Hypoxia

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Purpose: Tumor hypoxia is considered to be a potential therapeutic problem because it renders solid tumors more resistant to ionizing radiation and chemotherapeutic drugs. We describe a recombinant Murine leukemia virus (MuLV)-based replication-competent retroviruses (RCR) delivery system that infects only growing cells. This results in a persistent viral knockdown of the expression of the regulators of the hypoxia responding genes CREB, HIF1, and HIF2, via shRNA targeting of these genes separately and all together from a single polycistronic RNA.

Methods: C918 uveal melanoma cells were stably infected with RCR expressing shRNA targeting CREB, HIF1, and HIF2 separately and all together from a single polycistronic RNA. Knockdown of the target genes was analyzed using qRT-PCR and Western blot. Infected cells co-transfected with either CRE or HRE mediated luciferase (luc) gene expression vector, pCREluc or pHREluc, respectively, served for functional analyses of the transcription factors. Cell viability and caspase 3 activity were determined using the Fluorescent Cell Viability and Caspase-Glo 3/7 Assays (Promega) after 0-72 hours under normoxic and hypoxic (0.5% O₂) conditions.

Results: The different RCRs efficiently infect the C918 cells and efficiently knockdown the mRNA and protein levels of CREB, HIF1 and HIF2. Knockdown of these genes by the recombinant RCRs reduced VEGF secretion, reduced tumor cell proliferation, and increased Caspase 3 activity in hypoxia. We found that CREB, more than HIF1 and HIF2, plays a pivotal role in the survival of C918 under hypoxia in vitro while HIF1 affects VEGF in vitro.

Conclusions: MuLV-based RCRs affecting the response of UM to hypoxia, specifically affecting CREB and HIF1, have potential as a novel therapeutic approach for metastatic UM.

Recovery of visual function following gene therapy using the mouse CNGA3 gene in a sheep model of achromatopsia. One year follow-up.

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Purpose: Recently, we reported on novel hereditary dayblindness in sheep caused by a mutation in the CNGA3 gene, and proposed it as a cone-enriched, large animal model to evaluate safety and efficacy of CNGA3 gene therapy. At the 2012 ISVER meeting we presented electroretinographic (ERG) and behavioral improvement in visual function in dayblind sheep 2 months following subretinal delivery of Adeno-Associated Viral vector carrying a mouse CNGA3 gene. We now present results of one year follow-up in treated animals.

Methods: Unilateral surgery was conducted in three dayblind lambs. Animals were assessed preoperatively and 2, 6&12 months post-operatively. Cone function was measured by ERG following light adaptation (10min, 30 cd/m²). Photopic responses to low frequency and flicker (10-80Hz) stimuli were recorded at 4 intensities (1-10 cd/sec/m²) after light adaptation. Thus, 20 ERG parameters (a- and b-wave amplitudes and implicit times, and flicker frequency fusion) were assessed for each eye. Behavioral assessment included scotopic and photopic maze testing under standardized conditions. Passage times and number of barrier collisions were recorded. Age-matched normal and untreated day-blind sheep served as controls.

Results: Two months post-operatively, significant improvement was noted in 4/20 ERG parameters, mostly b-wave amplitudes and a-wave implicit times in response to the higher intensities. Interestingly, the improvement was observed in both operated and untreated fellow eyes. Six months post-operatively, significant improvement was noted in most (16/20) ERG parameters in operated, but not in fellow eyes. One year post-operatively, the number of improved ERG parameters in operated eyes declined back to 4/20, mostly reflecting shortened implicit times. Behaviorally, treated dayblind sheep navigated the photopic maze without collisions, similar to normal controls. The improvement was noted 2 months post-operatively, and persisted at least one year.

Conclusions: Gene therapy improves cone-mediated visual function in CNGA3 dayblind sheep. The behavioral improvement is long-lasting, while electrophysiological improvement peaks at 6 months. The long-term improvement in this naturally-occurring large animal model paves the way for clinical trials using the human CNGA3 gene.

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TGF- β 1 Mediates RPE Cells Apoptosis through Caspase-3 Activation

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Purpose: Programmed cell death (apoptosis), is an essential process for the homeostasis of multi cellular organisms. However, apoptosis can also occur during pathological events and is associated with neurodegeneration, ischemia-reperfusion injury and age related macular degeneration (AMD). Dry AMD is characterized by progressive apoptosis of the overlying photoreceptor cells, the choroidal capillary layer and the retinal pigment epithelium (RPE) cells. RPE cells can undergo apoptosis upon exposure to transforming growth factor- β 1 (TGF- β 1) that is known to play a key role in RPE cells homeostasis. This study aimed to examine the signaling pathways activated by TGF- β 1 during apoptosis of RPE cells.

Methods: Human ARPE-19 cells were treated with or without transforming growth factor β activated kinase-1(TAK1) inhibitor (5Z-7 oxozeaenol) followed by TGF- β 2.5ng/ml) stimulation for all experiments. Caspase-3 protein expression and subcellular distribution were determined by immunofluorescence staining. Finally, cell proliferation was measured with an XTT assay.

Results: Immunofluorescence staining of RPE cells stimulated by TGF- β demonstrated caspase-3 activation 6 hours after stimulation. Eighteen hours after stimulation the levels of caspase-3 remained higher as compared to the control levels. Finally, XTT assay has demonstrate that addition of 5Z-7 prior to TGF- β stimulation reduces cells death

Conclusions: The progression of AMD is known to be involved with RPE cells apoptosis. This study demonstrates that RPE cells apoptosis is TGF- β and mediated through caspase-3 activation. It is known that TGF- β induce RPE cells apoptosis. However, we suggest that the mechanism is TAK1 dependent. This study demonstrates that TGF- β induce apoptosis through TAK1 and caspase-3 activation.

Towards ultrasonic excitation of retina in controlled spatio-temporal patterns

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Purpose: Ultrasound (US) waves have been shown to stimulate and suppress neuroal activity, opening new possibilities for therapeutic, non invasive neuro-modulation. When attempting to mimic physiological activation patterns, accurately controlled spatio-temporal patterns of excitation are required. Our study is aimed at demonstrating US spatio-temporal patterned stimulation of the retina.

Methods: 1) We studied the full-field US stimulation of the retina in-vivo in and in-vitro. In-vivo, US pulse trains were transmitted to eyes of anesthetized rats, while measuring the evoked potentials (EPs) via subcutaneous electrodes. A preliminary safety study was conducted using electroretinograms and histological sections. In-vitro, isolated rat retinas were placed on multi-electrode-arrays and local field potential and extracellular spike responses were measured.

2) We adapted algorithms from optical holography to use in ultrasonic phased arrays, addressing the generation of sparse and continuous patterns. The algorithms were tested in simulations and resulting fields were measured using serial hydrophone scanning. Generalizations of the method have been formulated, bringing the method closer to operation in a realistic environment.

Results: 1) In-vivo US stimulation led to EPs with a power of ~25% that of flash EPs, in contrast to control conditions. No damage was found to the stimulated retinas' structure or function. In-vitro preliminary data show responsiveness to the US stimuli.

2) Simulations and field measurements show that sparse and continuous arbitrary US fields can be generated, with a sub-mm resolution and on a cm-scale field of view. The fields generated by the GSW-type algorithm were found to be efficient and uniform.

Conclusions: These results indicate that US waves are capable of exciting the retina, possibly without damage, and that US fields can flexibly patterned. Thus, vision restoration strategies based on US excitation of the retina may lead to non-invasive prosthetic devices.

Repetitive Magnetic Stimulation Improves Retinal Function in a rat model of Retinal Dystrophy

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Purpose: To evaluate the effect of repetitive magnetic stimulation (RMS) on retinal functions in Royal College of Surgeons (RCS) rats.

Methods: Four weeks-old RCS and control Spargue Dawley (SD) rats underwent RMS treatment (12 sessions for 4 weeks) at intensity of either 150% or 100% of the average resting motor threshold (8 RCS and 5 SD rats or 6 RCS and 3 SD rats, respectively) over the right eye. 14 RCS and 8 SD rats received sham treatment as control. Retinal functions were examined weekly by electroretinogram (ERG) under dark and light adaptation prior to treatment and for 7 weeks following end of treatment. H&E histopathology analysis was used for assessing retinal structure.

Results: RMS treatment at intensity of 150% of the average resting motor threshold significantly increased ERG b-wave responses by up to 6-fold or 10-fold in the left and right eye respectively, 3-5 weeks following end of treatment. This treatment resulted in a short and transient reduction in ERG response in the right eye, 2 weeks following end of treatment. RMS treatment at intensity of 100% of the average resting motor threshold significantly increased ERG b-wave response by 8-15 fold in both eyes 5 weeks following end of treatment with no adverse effect on ERG response or retinal structure of SD rats.

Conclusions: RMS treatment induces delayed improvement of retinal functions in a rat model of retinal degeneration. These results suggest that RMS treatment may induce neural plasticity in the neuroretinal tissue. This non-invasive treatment may possibly be used in the future as a primary or adjuvant treatment for retinal dystrophy.

Responder analysis of the effect of 9-cis β -Carotene rich powder on ERG and visual field in patients with retinitis pigmentosa

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Purpose: To compare the efficacy of oral treatment with 9-cis β carotene on visual functions of responders to non responders patients with retinitis pigmentosa.

Methods: Randomized, double-masked, placebo-controlled, crossover trial of 34 patients. Twenty nine completed the study and included in analysis. Patients were treated daily for 90 days with capsules containing 300 mg of 9-cis β carotene-rich alga *Dunaliella bardawil* (β carotene ~20 mg) or placebo (starch). Following a 90-day washout period, they were treated for 90 days with the other capsules. The outcome measures were changes in light-adapted maximal b-wave amplitude, changes in dark- and light-adapted maximal a-wave amplitude, dark- and light-adapted visual-field and best-corrected visual acuity (BCVA).

Results: Ten participants (34.5%) demonstrated an increase of more than 10microV for both eyes (range of 11-42microV) in dark-adapted b-wave following 9-cis β carotene treatment vs. none following placebo. These 10 participants were considered to be "responders". The "responders" demonstrated significantly improved light-adapted b-wave responses as well as dark- and light-adapted a-wave responses following 9-cis β carotene treatment compared to placebo. The group of patients receiving 9-cis β carotene treatment first demonstrated better correlation between improved dark-adapted visual field following 9-cis β carotene treatment vs. placebo than the group receiving placebo first.

Conclusions: 9-cis β carotene treatment increased both a-wave and b-wave ERG responses in one third of retinitis pigmentosa patients under the tested conditions. The genetic defect of patients may underlie their response to treatment. The optimal therapeutic regimen is being determined in a larger clinical trial. 9-cis β carotene may represent a new therapeutic approach for some patients with retinitis pigmentosa.

Exome sequencing identifies mutations of both MYO7A and PDE6B in three siblings with retinitis pigmentosa

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Purpose: Retinitis pigmentosa (RP), a group of pigmentary retinopathies characterized by night blindness followed by visual-field loss, is the most genetically heterogeneous disorder in humans. RP can appear as either syndromic or nonsyndromic. One of the most common forms of syndromic RP is Usher syndrome (USH), characterized by the combination of RP and hearing loss. The current work aimed to identify the underlying cause for the appearance of both syndromic and nonsyndromic RP in three siblings from a consanguineous Israeli Muslim Arab family.

Methods: Patients underwent a detailed ophthalmic examination, including funduscopy, electroretinography (ERG), optical coherence tomography, visual field and color vision testing. Affected individuals were studied by whole-genome homozygosity mapping followed by whole exome sequencing.

Results: The family was found to segregate novel mutations of two different genes: MYO7A, causing USH1, and PDE6B, causing nonsyndromic RP. One affected child was homozygous for both mutations. Since the retinal phenotype seen in this patient results from overlapping pathologies, one might expect to find a very severe retinal degeneration. Indeed, he was diagnosed with RP based on an abnormal ERG at a very young age (9 months). However, this early diagnosis may be biased, as two of his older siblings have already been diagnosed, leading to increased awareness. At the age of 32 months he had relatively good vision with normal visual fields.

Conclusions: Here we present a rare case of three siblings with the same retinal phenotype (RP) and three different genotypes (MYO7A deficiency, PDE6B deficiency or both). This report further exhibits the genetic heterogeneity of RP, and demonstrates how consanguinity could increase intrafamilial clustering of multiple hereditary diseases. Moreover, it provides a unique opportunity to study the clinical implications of co-existence of null mutations in two RP-causative genes in a human patient.

Are Monocular Retinoblastoma Patients Safe? Lessons learned from Genetics Characterization among 232 Patients

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Purpose: To describe the association between the existence of a germline mutation and disease characteristics in patients with retinoblastoma.

Methods: The study included 232 patients with retinoblastoma who were treated at a single center between 1988 and 2012. Genetic testing for RB1 mutation was performed in 107 patients. Patients with a RB1 mutation were compared to patients without a mutation, in terms of epidemiological factors and clinical presentation. Several parameters were compared among groups by distribution analysis and Pearson correlation.

Results: Among 107 families, whose genetic status was evaluated, 62 patients had a RB1 germline mutation and 45 did not have a mutation (57.94% vs 42.06%). Mutations were found in 92.00% of the patients with bilateral disease, 28.07% of the patients with unilateral disease and in 3 of 4 patients with unilateral multifocal disease (Pearson correlation, $p < 0.0001$). Six patients with mutations showed mosaicism (5 monocular and 1 binocular). The most common type of mutation was a stop codon mutation (41.94%). 85.0% of the patients with macular involvement had a mutation (Pearson correlation, $p = 0.0106$). No significant differences were found in gender, age or reason for referral.

Conclusions: As expected, mutations were found in most of the patients with bilateral disease. Surprisingly, our genetic tests also revealed mutations in 28.07% of patients with unilateral retinoblastoma. These patients have an increased risk for other cancers throughout their life, and their first-degree relatives have an increased risk for retinoblastoma. Therefore, genetic testing for RB1 mutation should be offered to all patients, including the unilateral cases.

Achromatopsia - More than Meets the Eye

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Introduction: Achromatopsia (ACHM) is an inherited congenital heterogeneous autosomal recessive (AR) condition characterized by the absence of cone function, reduced visual acuity, nystagmus, photophobia, and color blindness. Mutations in 4 genes cause ACHM: CNGB3 (the most common cause of disease), CNGA3, GNAT2, PDE6C.

Methods: Clinical evaluation included family history, ophthalmologic exam, full-field electroretinography and color vision testing. Affymetrix whole-genome SNP arrays were used to genotype markers. Mutation analysis of specific genes was performed by direct sequencing. Whole exome sequencing was performed on one sample producing over 4 million mapped reads with an average base coverage of 49.

Results: We recruited 322 families with cone-dominated diseases (mainly cone-cod dystrophy (CRD), ACHM, Stargardt disease), 266 of which (82.6%) show an AR mode of inheritance. One of the most common diagnoses was ACHM with 142 patients (from 52 families). Aiming to identify the genetic etiology of ACHM in the Israeli population we chose three complementing approaches: 1. Screening of known genes in patients with a clear clinical diagnosis. 2. Homozygosity mapping in patients with more than one possible clinical diagnosis. 3. Exome sequencing. This comprehensive analysis enabled us to find mutations in 47 families. Mutations in CNGA3 are the most common cause of ACHM (40 cases, 85%) in our cohort. We identified 16 CNGA3 mutations (5 of which are novel) and 5 CNGB3 mutations (1 novel). One of the CNGA3 mutations (p.V529M) was published by us previously as it is common in both Muslim and oriental Jewish patients. Six out of the 21 mutations identified explain 33 (70%) of cases, a high fraction that is explained by the high percentage of intra-community marriages and population specific founder mutations. A few patients who clinically showed a CRD phenotype proved to have CNGA3 mutations as the cause of their disease, suggesting this gene can be associated with a range of phenotypes.

Conclusions: ACHM is one of the most common cone-dominated disorders in the Israeli and Palestinian populations and CNGA3 is the most prevalent cause of this disease. Our results allow a better definition of the clinical spectrum due to CNGA3 and CNGB3 mutations and allow accurate genetic counseling. Successful gene therapy experiments in mice and sheep with CNGA3 mutations provide hope that treatment will become available for many of our patients.

Whole Exome Sequencing as a Tool for Identification of Genes Causing Autosomal Recessive Retinitis Pigmentosa

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Purpose: Over 200 genes are known or suspected to cause inherited retinal diseases, and the number is likely to rise within the coming years. This is mainly due to next generation sequencing (NGS) techniques and whole exome sequencing (WES) in particular. The aim of this study is to use WES to identify the genetic cause of autosomal recessive (AR) retinitis pigmentosa (RP) in 30 Israeli index cases.

Methods: Patients with ARRP who agreed to participate in the study were recruited at Hadassah medical center. Clinical data included family history, ocular examination and imaging. Genomic DNA was extracted from blood samples and analyzed using Affymetrix whole genome single nucleotide polymorphism (SNP) microarrays and/or WES (Otogenetics Corporation).

Results: We selected for this study a set of 30 index cases with ARRP. The DNA sample of each patient was prescreened for all mutations known to cause retinal degeneration in the appropriate ethnic group. We obtained an average of about 50 million sequences per sample and assembled them to the reference human genome sequence. Each WES sample was initially analyzed to detect mutations in known retinal degeneration genes. In seven samples we have identified mutations, most of which are novel, in known RP genes (RP1, CNGA1, CNGB1, CYP4V2, C2orf71, RDH12, and ABCA4). In a nonconsanguineous family with three siblings affected by nonsyndromic RP, we identified compound novel mutations in the BBS2 gene known to cause Bardel-Biedl syndrome. In three additional families we identified likely disease causing mutations that are currently being evaluated. Interestingly, seven out of the 30 index cases carried single heterozygous null mutations in known disease-causing genes, that are unlikely to be the cause of disease but might affect disease severity. The analysis of the remaining exome samples is being performed mainly using homozygosity data obtained by whole genome SNP arrays.

Conclusions: We present here the first comprehensive WES analysis in Israeli and Palestinian patients with RP. Pre-screening for known founder mutations and the availability of homozygosity mapping data improve WES efficiency as a tool for identification of novel disease-causing genes.

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Prenatal Molecular Diagnosis of Oculocutaneous Albinism (OCA) and Additional Congenital Eye Diseases in a Large Cohort of Israeli Families

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Purpose: To present the prenatal molecular test results of OCA types 1, 2 and 4 caused by mutations in the tyrosinase (TYR), P and SLC45A2 genes, respectively, in a large cohort of Israeli albino families. Prenatal test results of families with aniridia, cone-rod degeneration (CRD) and X-linked retinitis pigmentosa (RP) will also be presented.

Methods: Clinical evaluation of subtypes of OCA included hair skin and eye examination. Detailed genetic investigation included pedigree analysis and ethnic origin of all 4 grandparents. Genetic counseling was performed after the completion of molecular tests of the propositus and parents, prior to, and after each prenatal test. Following prenatal molecular test genetic counseling included prediction of the spectrum of expected phenotypes based on diagnosed genotypes. Molecular prenatal tests were performed on extracted DNA using the combination of PCR followed by direct mutation screen, direct sequencing, and haplotype analysis. The same parameters were used for clinical diagnosis, genetic counseling, and molecular diagnosis of other inherited eye diseases.

Results: 77 prenatal tests were performed in 48 families affected by OCA; in 35- the propositus was the child and in 13- a parent or a close relative. In 39 families TYR mutations were diagnosed, in 8 families P mutations, and in one family a SLC45A2 mutation was identified. 19 albino fetuses were diagnosed. Following further genetic counseling most couples elected to terminate the pregnancy. Two couples (3 pregnancies) elected to continue the pregnancy of an albino fetus due to the possibility of a mildly affected fetus. Several additional pregnancies were terminated for other reasons.

Prenatal tests, using the same approach, were performed also for aniridia, caused by PAX6 mutations, CRD caused by ABCA4 mutations, and X-linked RP caused by mutations in the RP2 and RPGR genes.

Conclusions: Families with increased risk for an albino child with severe visual handicap seek prenatal genetic counseling and testing for the prevention of affected offspring. Unless mild phenotype of albinism is predicted, couples elect to terminate the pregnancy of an albino fetus. Molecular genetic testing at our center enables a nationwide approach for the prevention of a severe phenotype of albinism, as well as severe phenotypes of additional congenital eye diseases.

Homozygosity for a novel missense mutation in the GUCY2D gene causes Leber Congenital Amaurosis

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Purpose: Leber Congenital Amaurosis (LCA) is a severe retinal degenerative disease that first manifests in early life. Until now, 16 LCA genes (mostly autosomal recessive) have been identified, which account for 55% of LCA cases. The purpose of this study was to clinically characterize and identify the cause of disease in a large inbred Bedouin family with multiple members affected by LCA.

Methods: Thirty individuals, 8 of whom are affected with LCA, were recruited for this study. We collected clinical data including visual acuity, eye movements, anterior and posterior segment findings. Electroretinography (ERG) was performed in a subset of patients. Molecular analysis included homozygosity mapping with polymorphic markers, as well as sequencing of candidate genes.

Results: The pedigree was compatible with autosomal recessive inheritance with a founder effect. Affected subjects had visual acuity of finger counting or less in both eyes. Nystagmus was documented in five of eight subjects. Three patients showed bilateral keratoconus. Cataract appeared in 5 of 16 eyes. ERG done in 5 patients was non-detectable.

Linkage analysis excluded all except one gene known to be associated with LCA. Sequencing of that gene, GUCY2D, revealed a homozygous new missense mutation (c.C2129T) resulting in substitution of the amino acid arginine by valine at position 710 of the retina-specific enzyme guanylate cyclase 1 (GC1). The GC1 protein, encoded by GUCY2D, is one of the key enzymes in the phototransduction cascade. The mutated arginine at position 710 is highly conserved and occurs within the catalytic domain of protein kinases.

Conclusions: To the best of our knowledge, this is the first documentation of the p.Arg710Val mutation in GC1 and the second ever described mutation in its protein kinase domain. Our findings will allow prevention of further transmission of disease in this large family. They also enlarge the scope of genetic variability of LCA and provide hope for therapy in patients with this congenital blinding disease.

Novel mutations in the NHS gene among congenital cataract Ashkenazi Jews

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Background: To date, more than forty genetic loci and genes have been associated with congenital cataracts, including the NHS gene on chromosome X, mutations of which may be associated with the rare Nance-Horan Syndrome (NHS).

Purpose: In the present manuscript we demonstrate that an oriented physical examination can help in identifying subtle extraocular defects that may accompany syndromatic familial cataracts, hence facilitating the molecular search for the underlying genetic defect.

Methods: Two small Ashkenazy Jewish congenital cataract families underwent a detailed ophthalmological and oriented physical examination. Mutation analysis of the NHS gene was performed by direct sequencing of PCR amplified exons.

Results: Among patients examined, affected male patients harbored a more severe clinical picture regarding the onset point and severity of cataracts, as well as the existence of extra-ocular findings. Dental anomalies included abnormally shaped teeth and supernumerary mandibular incisors. Facial anomalies included large, posteriorly rotated low set ears. In some female carriers we found mainly mild sutural cataract of late onset, without significant visual impairment. No dental or facial anomalies were identified among female carriers. No subjects, male or female, were found to suffer from marked developmental delay.

Mutation screening of the NHS gene identified the novel null mutations; p.R71X and p.S994X in each of the families.

Conclusion: Two novel truncating NHS gene mutations were identified in Ashkenazy Jewish families whose major manifestations were congenital cataract. A thorough oriented clinical examination for extraocular manifestations can ease the search for an underlying molecular defect in congenital cataract patients.

Cone Dystrophy with Supernormal and Delayed Rod Response: An Under-Diagnosed Phenotype Caused by Mutations in KCNV2

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Purpose: To characterize genotype and phenotype in Israeli patients manifesting cone dystrophy with supernormal rod response (CDSRR).

Methods: Two hundred and twenty Israeli index patients with cone-dominated diseases, as well as unaffected relatives, were recruited. Patients underwent a full ophthalmologic exam, electroretinography (ERG), and retinal imaging studies. Genomic DNA was extracted using the FlexiGene DNA kit (QIAGEN). Homozygosity mapping was performed using whole genome single nucleotide polymorphism (SNP) arrays (10K or 250K Affymetrix platforms). Mutation analysis was performed by Sanger sequencing of the KCNV2 gene.

Results: Among the 220 index cases with cone-dominated diseases, two carried the clinical diagnosis of CDSRR. Mutation screening of KCNV2 revealed two compound heterozygous mutations in two affected sisters in one family and a homozygous mutation in the other family. To examine whether KCNV2 is the cause of disease in patients with other cone-dominated diseases, we performed whole genome homozygosity mapping in 52 consanguineous families (out of the initial 220), two of which had homozygous genomic regions encompassing KCNV2. Mutation analysis revealed a different novel homozygous mutation in each family. In addition, KCNV2 was screened for mutations in four families where clinical data suggested a CDSRR phenotype misdiagnosis. The analysis revealed two compound heterozygous mutations in one of these families. Following the genetic results and the review of the clinical findings, the diagnosis was revised to CDSRR in all patients with KCNV2 mutations. Clinical data of 12 patients from these families was collected, suggesting that while in some cases the classic phenotype of CDSRR is present, other patients with KCNV2 mutations may present with dark-adapted ERG responses that are within normal range in terms of amplitudes at ISCEV standard flash intensity. The delay in rod responses may be a more reliable indicator.

Conclusions: This is the first report of genetic and clinical analysis of CDSRR in the Israeli population, and five KCNV2 mutations that were not previously reported were identified. Our results support recent studies showing that CDSRR is often misdiagnosed. Therefore, screening for mutations in the KCNV2 gene should be considered in patients with cone-dominated diseases, particularly if a delay in rod ERG implicit times is present.

Whole Exome Sequencing (WES) in Age-related macular degeneration (AMD) Patients Identifies Novel Mutations in Complement Pathway Genes

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Purpose: AMD is the leading cause of blindness in the developed world. The association of AMD with variants on chromosome 1 (complement factor H (CFH)), chromosome 6 (CFB; C2), chromosome 10 (LOC387715/ARMS2), and chromosome 19 (C3) has clearly marked the primary role of the complement pathway in disease pathogenesis. At Assaf-Harofeh Medical Center retinal clinic we noticed a high prevalence of AMD patients among a subgroup of North African Jewish AMD patients. In light of this observation we hypothesized that focusing on this subgroup may increase the chance of identifying AMD-related mutations and genes. The purpose of this study was to use WES aiming to explore the genetic component of AMD in this sub-population, and to shed light on AMD mechanism.

Methods: We performed whole exome sequencing (OtoGenetics Corporation) of four AMD patients (two sets of sibs from families Famd4700601,03 and Famd4700701-02) and searched for potentially disease-causing genetic variants in previously identified macular degeneration related genes. Follow-up Sanger sequencing was performed for confirmation and mutation screening.

Results: Whole exome sequencing did not identify a common disease causing mutation shared by all four AMD subjects; nevertheless a probable causing mutation was identified for each family. Participants were diagnosed during age 50-60 displaying a wide variety in clinical presentation, ranging from limited large drusen to extensive basal laminar drusen (BLD) in the posterior pole as well as peripheral retina. Severe visual impairment due to extensive geographic atrophy and/or CNV was common by age 75. Approximately, 400,000 genomic variants for each DNA sample passed quality filters and were included in the downstream Bio-informatic analysis. Overall the filtering pipeline, publication parsing, pathway and biological relevance, ranked a novel deleterious mutation c.4162delC in Fibulin-6, a known AMD related gene (FBN6;HMCN1;MIM:603075), as the most probable candidate mutation in Famd47007, and a novel missense mutation p.V412M in the Complement Factor I gene (CFI), in Famd47006.

Conclusions: Two novel mutations in Complement pathway genes (Fibulin6, and CFI) were identified. This is the first report of a mutation affecting the coding sequence of CFI gene in AMD patients, and the first null FBLN6 mutation. The present report illustrates both the genetic complexity and the pivotal role of complement variations in AMD.

Silicon Oil Tamponade and Intraocular Pressure

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Purpose: Silicone oil has been used as a tamponade for over 40 years. Since it was first introduced, it is used in eyes with marked proliferative vitreoretinopathy, and eyes with retinal detachment (RD) refractory to other treatment methods. Its most common complications include: high intra-ocular pressure (IOP), cataract, band shape keratopathy and emulsification. The purpose of this study was to examine the influence of intra-ocular silicone on the IOP in patients who underwent silicone oil tamponade and to find out how many patients develop high IOP and glaucoma during follow-up after silicone tamponade.

Methods: A retrospective cohort study. Medical files of all patients who underwent silicone oil tamponade for RD during pars plana vitrectomy between October 2006 and October 2011 at the Kaplan Medical Center in Rehovot were examined.

Results: 106 patients underwent silicone oil tamponade, of them 93 cases met the research criteria and were included in the study. Fifty four (60%) were men, the mean age at the time of treatment was 60.9 (SD 17.6). Out of 93 eyes, 23 (25%) developed high IOP during follow up. Fourteen of them (61%) developed IOP elevation within 1 month from silicone oil injection; the rest developed increased IOP only after more than 1 month from injection. In most patients the silicone was removed within 3 months after insertion. In this group 4 (29%) developed persistent high IOP and 1 (7%) developed glaucoma. In 9 patients the silicone tamponade was not removed for various reasons— all 9 developed persistent elevation of IOP, 7 patients (78%) developed glaucoma.

Conclusions: The present study shows an incidence of 25% of elevated IOP after treatment with silicone oil tamponade, of which most will occur within the first month. Removal of the silicone is beneficial for prevention and treatment of persistent high IOP and silicon induced glaucoma.

Cryo therapy for neovascular and other refractory glaucoma

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Purpose: Glaucoma that is refractory to conventional therapy remains a therapeutic challenge for ophthalmologists. Cryo ablation treatment causes ciliary body fibrosis. As a result it reduces production of aqueous humour and decreases intraocular pressure (IOP). Most cases of refractory glaucoma are due to neovascular glaucoma (NVG). Cryo ablation treatment has been proven effective in lowering intraocular pressure in those patients. The Purpose of this study is to evaluate the extent of the impact of cryo ablation treatment for glaucoma that is refractory to conventional therapy.

Methods: A retrospective cohort study. Medical files of all patients who underwent cryo therapy treatments during the years 2002-2012 at the Kaplan Medical Center in Rehovot were examined. Patients were divided into three groups according to the type of cryo therapy: cyclo-cryo therapy, Pan-cryo therapy and combination of cyclo and Pan-Cryo therapy.

Results: Twenty four patients who underwent 26 cryo therapy treatments were included in the study. Most patients suffered from NVG which was refractory to medicinal therapy and were not candidates for filtration surgery. Thirteen (54%) were men, the mean age at the time of treatment was 70.4 (SD 8.96). In all patients a decrease in IOP was observed. Mean IOP before and after treatment was 40.2 mmHG and 19.3 mmHG, respectively. The difference in IOP was greatest among the group that underwent combined therapy, compared with patients who received cyclo or Pan-cryo therapy alone. In most patients the iris neovascularization disappeared or at least diminished significantly after treatment.

Conclusions: Our study shows that treatment of neovascular glaucoma with cryo therapy is recommended and significantly reduces IOP in NVG. In addition, a trend of advantage for combined treatment over each method alone was observed.

Trans Scleral (External) Laser Trabeculoplasty (SLT): A novel treatment for Open Angle Glaucoma (OAG)

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Purpose: To assess the efficacy of a direct trans-scleral SLT in OAG.

Methods: A randomized, masked, controlled trial. Laser trabeculoplasty (LTP) candidates diagnosed with primary OAG, pigment dispersion glaucoma and pseudoexfoliative glaucoma were randomly assigned to an external SLT or a standard internal SLT treatment. Identical laser irradiation parameters were used in both groups. The study group underwent a peri-limbal laser treatment performed on the sclera overlying the trabecular meshwork (TM) whereas the TM of the control group was traditionally treated using a gonioscopic Latina lens. IOP was measured and side effects were evaluated at 1, 7, 30, 60 and 180 days after treatment. No changes were made in the medical regimen. Short term success was defined as 20% IOP reduction at 2 months visit as compared to baseline.

Results: In the trial group (N=11), IOP decreased from an average of 20.9 mmHg before treatment to 15.9 at 2 months and 15.0 at 6 months. The corresponding numbers for the control group (n=10), were 20.5 mmHg, 14.7 and 7 (one patient) respectively, with no statistical difference between groups ($P=0.757$, Fisher). Short term success was attained in 7 patients of either group. No significant side effects were documented in both groups.

Conclusions: Intermediate term results suggest that trans-scleral SLT is as effective as the traditional SLT treatment using a gonioscopy lens. While external SLT depends on laser energy in order to penetrate the scleral tissue, the mechanism of action on the TM is probably similar in both methods. As it simplifies and shortens the SLT procedure as well as eliminates the gonioscopic-induced side effects, this novel treatment may be considered as an optional treatment for eligible glaucoma patients.

Blood Flow Velocity in Glaucoma Patients Measured with the Retinal Function Imager

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Purpose: Circulatory abnormalities in the retina, optic nerve and choroid have been detected by various technologies in glaucoma patients. However, there is no clear understanding of role of blood flow in glaucoma and blood flow measurement is not a routine clinical parameter. The Retinal Function Imager (RFI, Optical Imaging Ltd., Rehovot, Israel) is a non-invasive diagnostic approach for measuring blood flow velocity. The purpose of this study was to compare retinal blood flow velocities between glaucoma patients and healthy subjects.

Methods: Fifty nine eyes of 46 patients with primary open angle glaucoma (POAG), 51 eyes of 31 healthy individuals and 28 eyes of 23 patients with glaucomatous optic neuropathy (GON) but normal perimetry were recruited for this study. All patients were scanned by the RFI with analysis of blood flow velocity of secondary and tertiary branches of arteries and veins. Differences among groups were assessed by mixed linear models.

Results: The average retinal blood flow velocity in the arteries of the POAG eyes was 4.3 mm/sec and 4.2 mm/sec in the healthy eyes ($p=0.7$). The average venous velocity was also similar in the POAG and healthy eyes (3.3 vs. 3.0 mm/sec, $p=0.3$). The arterial velocity in the GON group was not different from any of the other study groups. However, in veins, the velocity in the GON (3.8 mm/sec) group was significantly faster than in the glaucoma ($p=0.03$) and healthy ($p=0.005$) groups. A subgroup of the glaucoma group (12 patients) had perimetric glaucoma in 1 eye and GON in the fellow eye. Paired analysis of the velocity between the eyes discovered significant changes in arteries ($p=0.04$) and veins ($p=0.03$), although not in the same direction in all patients. Such inter-eye asymmetry was not found in the healthy group.

Conclusions: Changes in retinal blood flow velocity were detected only in early glaucoma state but not in perimetric glaucoma. Inter-eye asymmetry in blood flow velocity was detected in glaucoma patients, due to the complex effect of the glaucoma state and its treatment on the retinal vascular function.

A novel semi-computerized technique to reproducibly quantify the cup/disc ratio in glaucoma patients

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Purpose: An integral part of the clinical assessment of a glaucoma patient is the evaluation of the optic disc damage. The importance of accurate measurement of the cup-to-disc ratio (CDR) cannot be overemphasized in glaucoma as well as ocular hypertensive patients. Disagreement among observers regarding the CDR may occur. We developed a user friendly computer software program "CDRCalculator" that allows the clinician to rapidly measure the CDR of digital images of the optic disc.

Methods: The CDRCalculator loads and displays pre-scanned images stored in power point slides. Using the Screen-Vu Stereoscope (Eyesupply USA, Inc., Tampa, FL), the observer marks the respective diameters of the cup and disc with a blue and green line respectively. These colors provided the best contrast when viewed with the optic disc in their background. Several functions in the software facilitate delineation of the cup and disc edges for the inexperienced observer. The light green line was intentionally designed to be wider than the dark blue line to ensure that the measurements are on the same meridian. The software automatically calculates and displays the vertical and horizontal CDR.

Results: We herein describe the novel prototype software named CDRCalculator for measuring the CDR of 3D digital disc photos. At present, a study evaluating the inter-observer&intra-observer variation using the CDRCalculator to measure the CDR is ongoing.

Conclusions: As the CDRCalculator optimizes the ability to evaluate the CDR it may assist the clinician in correctly assessing the cupping of the disc.