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

PROGRAM & ABSTRACTS

34th Annual Meeting

Avenue Congress Center, Airport City

26th-27th March, 2014

תכנית ותקצירים

הכינוס השנתי ה-34

מרכז הכנסים Avenue, קרית שדה התעופה

26-27 במרץ, 2014

עריכת התוכנית:

פרופ' אבי סלומון, פרופ' איתי חוברס

מזכירות הכנס:

עיצוב והבאה לדפוס: יעקב אלבז, דבורה מרקס אוחנה

ISRAELI SOCIETY FOR VISION AND EYE RESEARCH

The 34th Annual Meeting, March 26-27, 2014

Program at a glance - תוכנית הכנס

Wednesday, March 26th , 2014

Session	Location	Time	Page
Coffee & Exhibition	Exhibition Hall	08:00 – 08:30	10
Opening Remarks	Lecture Hall	08:30 – 08:35	10
Retina 1: Retinal cell biology	Lecture Hall	08:35 – 10:00	10-13
Coffee & Exhibition	Exhibition Hall	10:00 – 10:30	13
Oncology	Lecture Hall	10:30 – 11:20	13-15
Cornea 1: Corneal Transplantation	Lecture Hall	11:20 – 12:00	16-17
Guest lecture 1	Lecture Hall	12:00 – 12:30	17
Lunch break	Dining Room	12:30 – 13:30	17
Refractive and Cataract Surgery	Lecture Hall	13:30 – 14:20	18-19
Cornea 2	Lecture Hall	14:20 – 15:15	20-22
Coffee & Exhibition	Exhibition Hall	15:15 – 15:45	22
Glaucoma	Lecture Hall	15:45 – 17:00	22-24

Thursday, March 27th , 2014

Session	Location	Time	Page
Coffee & Exhibition	Exhibition Hall	08:00 – 08:30	25
Retina 2: Retinal degenerations	Lecture Hall	08:30 – 10:00	25-29
Coffee & Exhibition	Exhibition Hall	10:00 – 10:30	29
Retina 3: AMD	Lecture Hall	10:30 – 11:40	29-31
Awards & ISVER update	Lecture Hall	11:40 – 12:00	31
Guest lecture 2	Lecture Hall	12:00 – 12:30	32
Lunch break	Dining Room	12:30 – 13:30	32
Visual Function and Perception	Lecture Hall	13:30 - 14:45	32-35
Coffee & Exhibition	Exhibition Hall	14:45 – 15:15	35
Animal Vision	Lecture Hall	15:15 - 16:00	36-37
Retina 4: Clinical studies and Imaging	Lecture Hall	16:00 – 17:00	38-40

יושבי-ראש של האגודה הישראלית לחקר העין והראיה

CHAIRMEN OF THE ISRAELI SOCIETY FOR VISION & EYE RESEARCH

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Prof. Mordechai Rosner	2007-2009	פרופ' מרדכי רוזנר
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Prof. Avi Solomon	2013-	פרופ' אבי סלומון

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

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מרצים המקבלים פרס על עבודות שהוצגו בכינוס השנתי ה-33, 14-15 במרץ, 2013

AWARD RECIPIENTS FOR THE BEST PRESENTATIONS AT THE 33rd ANNUAL MEETING, MARCH 14-15, 2013

מלגות נסיעה לכנס ARVO במאי 2014 ניתנות בעזרת מענקים שנתרמו באדיבות עמותת "לראות"; באדיבות משפחת מרין לזכרו של פרופ' שאול מרין ז"ל (מילגות 1-2); ובאדיבות עמי דברת לזכרה של פרופ' אהובה דברת ז"ל.

1. **Daniel Rappoport**: **Intravitreal injection of Bevacizumab may be neuroprotective in a mouse model of optic nerve crush.**
   Department of Ophthalmology, Kaplan Medical Center, Rehovot
2. **Ifat Sher**: **Repetitive Magnetic Stimulation improves retinal function in a rat model of retinal dystrophy.**
   The Maurice and Gabriela Goldschleger Eye Research Institute, Sheba Medical Center, Tel-Hashomer
3. **Adi Hanuka**: **EMM – Eyelid Motion Monitor.**
   Department of Electric Engineering, Technion, Haifa
4. **Shachar Maidenbaum**: **Blind in a virtual world – using distance information to accomplish virtual tasks.**
   Department of Medical Neurobiology, Institute for Medical Research Israel-Canada, Faculty of Medicine, The Hebrew University of Jerusalem

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

ARVO CHAPTER AFFILIATE

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

תודה לעמותת "לראות"

לראות

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

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לראות

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

אודות עמותת "לראות"

מטרות עמותת "לראות"

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

המועצה המדעית של עמותת "לראות"

מורכבת מהשורה הראשונה של רופאים וחוקרי עיניים בישראל וכן גורמים 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 על פי סדר עדיפויות מוגדר. המועצה פועלת לגיוס מיטב החוקרים מתחומים רלוונטיים וכן להקמת רשות מחקרית בינלאומית.

בין יוזמות עמותת "לראות" בשנת 2013

"לילה של בריאות בפארק הרצליה" - קיום בדיקות סקר לילדים.
"נבדקים היום כדי לראות את המחר" - חודש מודעות בריאות העין החמישי שכלל בדיקות ראיה ללא עלות בכל רחבי הארץ, הפצת מוסף בריאות העין לכל המשפחה המופץ בתפוצה ארצית עם ישראל היום וקמפיין בתקשורת.
"פרויקט הניידת לבדיקות עיניים של קשישים נזקקים" – מאות אנשים נבדקו במרכזי יום, בתי אבות ומתנ"סים. קשישים רבים הופנו להמשך טיפול רפואי בקופות החולים.
פרטים נוספים באתר עמותת לראות – www.eyes.org.il.

תכנית פעילות של עמותת "לראות"לשנת 2014

<u>פעילויות שוטפות</u>

1. תכנית למימון מחקרים במוסדות מחקר רפואיים בישראל ובארה"ב
2. מתן יעוץ רפואי ב5 פורומים של רופאים מומחים ומנהלי מחלקות עיניים
3. ארגון חודש המודעות השישי לבריאות העין
4. ניידת בדיקות עיניים לקשישים נזקקים

<u>פרויקטים מתוכננים</u>

1. קידום פעילות סקר ראיה לילדים עם הפוטו סקרינר
2. המשך גיוס משאבים למחקר רפואי בארץ ובחו"ל
3. גיוס חולים למחקר מיפוי גנטי של מחלות רשתית

לראות

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

המחקרים הממומנים ע"י עמותת "לראות" בשנת 2013

השנה קבלו כ-13 מחקרים מימון, כתוצאה מהפעילות של עמותת "לראות".
בין החוקרים המקבלים מענקי מחקר של עמותת "לראות"
באמצעות המדען הראשי :

פרופ' אריה סולומון, פרופ' רון עופרי, ד"ר שחר פרנקל, פרופ' דרור שרון, ד"ר חטיב סאמר, פרופ' איתי חוברס, ד"ר חיים כהן, ד"ר אברהם קציר, ד"ר עדי ענבל, ד"ר תמר בן-יוסף, פרופ' איתן גלון ופרופ' אדו פרלמן.

חברי ועד המנהל של עמותת "לראות"

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מנכ"ל: נדין הולנדר

www.eyes.org.il

הרצאות אורח בכינוס השנתי 2014

Keynote Lectures at ISVER 2014

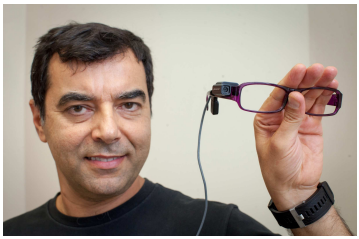
Wednesday, March 26th, 2014; 12:00-12:30

Prof. Chaim Cedar - Harry and Helen L. Brenner Professor of Molecular Biology; Chairperson, Developmental Biology & Cancer Research, IMRIC; The Faculty of Medicine, The Hebrew University of Jerusalem.

"**Annotation of the Genome**."

Thursday, March 27th, 2014; 12:00-12:30

Prof. Amnon Shashua - Sachs Professor of Computer Science, School of Engineering and Computer Science, The Hebrew University of Jerusalem; Co-founder and Chairman, Mobileye Vision Technologies.



"**Harnessing Computer Science for the Visually Impaired: the OrCam Device."**

Program

Wednesday, March 26th , 2014

Coffee & Exhibition 8:00 - 8:30

Opening Remarks: Prof. Avi Solomon 8:30 – 8:35

* **Retina 1: Retinal Cell Biology** 8:35 - 10:00

Moderators:
Dr. Zeev Dvashi
Dr. Nitza Goldenberg-Cohen

1. **Combination of staining techniques to differentiate venous endothelial cells in mouse optic nerve.** 8:35 p. 43
James D. Nicholson 1,2, Orkun Muhsinoglu 3, Nitza Goldenberg-Cohen 1,2,4
1Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Israel, 2The Krieger Eye Research Laboratory, FMRC, Rabin Campus, Tel Aviv University; 3Department of Ophthalmology, Rabin Medical Center, Beilinson Campus, Petach Tikva; 4Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petach Tikva

2. **Demonstration of retinal vasculature in diabetic mice** 8:40 p. 44
Moshe Ben Hamou,1,2 James D. Nicholson,1,2 Orit Barinfeld,1,2 Orkun Muhsinoglu,3 Nitza Goldenberg-Cohen.1,2,4
1Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Israel, 2The Krieger Eye Research Laboratory, FMRC, Rabin Campus, Tel Aviv University; 3Department of Ophthalmology, Rabin Medical Center, Beilinson Campus, Petach Tikva; 4Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petach Tikva

3. **Monocyte entry and function in ocular repair** 8:45 p. 45
Inbal Benhar and Michal Schwartz
Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

4. **The effects of the APOE genotype on murine retinal vasculature and VEGF expression during development** 8:50 p. 46
Idit Maharshak1,2, Tami Livnat3, Yael Nisgav3, Mordechai Rosner4, Arieh S. Solomon4, Dov Weinberger5,2, Carol A. Colton6, Daniel M. Michaelson1.
1Department of Neurobiology, Faculty of Life Sciences, Tel Aviv University; 2Department of Ophthalmology, Sackler School of Medicine, Tel-Aviv University; 3Laboratory of Eye Research, Felsenstein Medical Research Center, Rabin Medical Center, Petach Tikvl; 4Goldschleger Eye Institute, Tel-Aviv University, Tel-Hashomerl; 5Department of Ophthalmology, Rabin Medical Center, Petach Tikva; 6Division of Neurology, Duke University Medical Center, Department of Medicine, Durham, NC

5. **VEGF as a novel therapeutic target for counteracting the neuronal and vascular effects of apoE4** 8:55 p. 47
Shiran Salomon-Zimri, Ran Antes and Daniel .M. Michaelson
Sagol School of Neuroscience, Tel Aviv university, Israel

6. **The roles of Lim-domain binding proteins in mammalian retina** 9:00 p. 48
Keren Gueta-Milshtein1, Tsadok Cohen2, Heiner Westphal2, Ruth Ashery-Padan1
1. Sackler Faculty of Medicine, Tel-Aviv Universit., 2. Laboratory of Mammalian Genes and Development, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, HHS, Bethesda, MD, USA

12. **Therapeutic potential of adipose tissue derived mesenchymal stem cells for atrophic RPE- migration, yrophic anti-apoptotic effects and differentiation** 9:30 p. 54
Aya Barzelay, Ran Levy, Anat Loewenstein, Adiel Barak
Ophthalmology laboratory, Department of Ophthalmology Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

13. **Two-photon in-vivo imaging of retinal micro-structures** 9:35 p. 55
Adi Schejter, Nairouz Farah and Shy Shoham
Technion Israel Institute of Technology, Haifa, Israel

Discussion 9:40 - 10:00

Coffee & Exhibition 10:00 - 10:30

* **Oncology** 10:30 - 11:20
Moderators:
Prof. Jacob Pe'er
Prof. Mordechai Rosner

14. **A biological tissue adhesive and dissolvent system for intraocular tumor plaque radiotherapy** 10:30 p. 56
Ido Didi Fabian, Vicktoria Vishnevskia-Dai, Michael Belkin, Ofira Zloto
The Goldschleger Eye Institute, Sheba Medical Center, affiliated to Tel Aviv University

15. **sIL-2R: an immuno-biomarker for prediction of metastases in uveal melanoma** 10:35 p. 57
Barak V, Pe'er J, Kalickman I, Frenkel S.
(1)Immunology Laboratory for Tumor Diagnosis and (2) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

16. **The impact of thyroid hormone levels on survival in a uveal melanoma murine model: an experimental study** 10:40 p. 58

Fabian I.D.1,2,3, Rosner M.1,3, Fabian I.3,4, Vishnevskia-Dai V.1,3, Zloto O.1,3, Shinderman E. 3,5,6, Cohen K. 3,5,6, Ellis M. 3,6, Davis P.J. 7,8, Hercbergs A. 9 and Ashur-Fabian O. 3,5,6

1 Goldschleger Eye Institute, Sheba Medical Center, Ramat-Gan, Israel, 2 Dr. Pinchas Borenstein Talpiot Medical Leadership Program 2012, 3 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, 4 Department of Cell and Developmental Biology, 5 Department of Human Molecular Genetics and Biochemistry. 6 Translational Hemato-Oncology Laboratory, The Hematology Institute and Blood Bank, Meir Medical Center, Kfar-Saba, Israel. 7 Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, Albany, New York, USA, 8 Department of Medicine, Albany Medical College, Albany, New York, USA. 9 Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio, USA.

17. **MuLV-based replication-competent retroviruses (RCR) target uveal melanoma response to hypoxia in a variety of cell lines** 10:45 p. 59

1Esther Houri-Levy, BScMed, 1,2Dudi Shneor, MSc, 2Alik Honigman, PhD, 1Jacob Pe'er, MD, 1Shahar Frenkel, MD, PhD

1Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, 2Department of Biochemistry and Molecular Biology, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

18. **Ruthenium-106 plaque brachytherapy in the primary management of ocularmedulloepithelioma** 10:50 p. 60

Ehud Reich 1,2, Daniel S. Poon 2, Mandeep S. Sagoo 1,2,3, Judith Kingston 2,4, M. Ashwin Reddy 1,2

1 Moorfields Eye Hospital, London, 2 Royal London Hospital, London, 3 UCL Institute of Ophthalmology, 4 Great Ormond Street Hospital, London

19. **Mutation analysis of MYB, MYBL1 and FGFR1 in grade I and diffuse pediatric glioma** 10:55 p. 61

Orit Barinfeld,1,5 James D. Nicholson, 1,5 Helen Toledano2,5 Shalom Michowiz, 3,5 Mali Salmon-Divon 6 Nitza Goldenberg-Cohen. 1,4,5

1The Krieger Eye Research Laboratory, 2Department of Pediatric Oncology, 3Neurosurgery and 4Ophthalmology, Pediatric Unit, Schneider Childrens' Medical Center, Petah Tiqwa; 5Sackler School of Medicine, Tel Aviv University, Tel Aviv; Israel; 6Functional Bioinformatics Laboratory, Molecular Biology , Ariel University, Ariel, Israel

20. **Periocular pilomatrixoma: a retrospective analysis of 16 Cases** 11:00 p. 62

Ofira Zloto, MD, Ido D. Fabian, MD, Vicktoria Vishnevskia Dai, MD, Guy J. Ben Simon, MD, Mordechai Rosner, MD

Goldschleger Eye Institute, Sackler Faculty of Medicine, Tel-Aviv University, Sheba Medical Center, Tel Hashomer, Israel

21. **Comparison of treatment modalities for circumscribed choroidal hemangioma** 11:05 p. 63

Vasilios P. Papastefanou 1, Ehud Reich 1, Efthymia Pavlidou 1, Nicholas P. Plowman 2, John L Hungerford 1, Victoria ML Cohen 1, Mandeep S Sagoo 1 3

1. Ocular Oncology Service, St Bartholomew`s Hospital and Moorfields Eye Hospital, 2. Radiotherapy Service, St Bartholomew`s Hospital, 3. UCL Institute of Ophthalmologyc

Discussion 11:10 – 11:20

* **Cornea 1: Corneal Transplantation, Keratoconus** 11:20 – 12:00

Moderators:
Dr. Arie Marcovich
Dr. Irina Barequet

22. **Comparing the incidence of ocular hypertension after penetrating keratoplasty and deep anterior lamellar keratoplasty** 11:20 p. 64
Shirin Hamed- Azzam1, Raneen Shehadeh-Mashor2, Daniel Briscoe1, Modi Naftali 3
1 Department of ophthalmology- Haemek Medical Center, Afula, Israel., 2 Department of ophthalmology- Bnai-Zion Medical Center, Haifa, Israel2., 3 Department of ophthalmology- Padeh Medical center, Poria, Israel3.

23. **DSPEK - Descemet's Stripping Pseudo Endothelial Keratoplasty** 11:25 p. 65
Daphna Ofer 1, Bahar Irit 1, Marcovich Arie 2
1 Rabin Medical Center, Petah Tiqva, Israel, 2 Kaplan Medical Center, Rehovot, Israel

24. **Objective and subjective assessment of the KBA contact lens for keratoconus.** 11:30 p. 66
Gantz Liat, Abousaid Arige, Serero Gad, Gordon-Shaag Ariela, Fine Phillip
Department of Optometry and Vision Science, Hadassah Academic College

25. **Objective and subjective comparison of three fitting approaches for the Rose K2 lens for keratoconus** 11:35 p. 67
Gantz Liat, Arbiv Gabi, Tiri Niva, Gordon-Shaag Ariela, Fine Phillip
Department of Optometry and Vision Science, Hadassah Academic College

26. **Corneal biomechanical properties in keratoconic, myopic and hyperopic eyes as measured with a Scheimpflug-based tonometer** 11:40 p. 68

Nadav Shoshany (1), Ran Rotenberg (2), Irina S. Barequet (3), David Zadok (1)

(1) Assaf Harofe Medical Center, (2) Tel Aviv University, (3) Sheba Medical Center, "Enaim" Medical Center, Tel Aviv

27. **Stiffening of rabbit sclera by bacteriochlorophyll derivative WST11 using near infrared light** 11:45 p. 69

Arie Marcovich1,4, Alexander Brandis1, Ilan Feine2, Iddo Pinkas1, Daniel Wagner3, Yoram Salomon2, Avigdor Scherz1

Departments of 1Plant Sciences, 2Biological Regulation, 3Materials and Interfaces, The Weizmann Institute of Science, 4 Ophthalmology, Kaplan Medical Center, Rehovot

Discussion 11:50 – 12:00

* **Guest lecture 1** 12:00 – 12:30

Prof. Chaim Cedar

Harry and Helen L. Brenner Professor of Molecular Biology; Chairperson, Developmental Biology & Cancer Research, IMRIC; The Faculty of Medicine, The Hebrew University of Jerusalem.

"Annotation of the genome."

Lunch break 12:30 – 13:30

* **Refractive and Cataract Surgery** 13:30 – 14:20

Moderators:
Prof. Igor Kaizerman
Dr. David Varssano

28. **Photorefractive keratotomy for high myopic patients surgery outcomes** 13:30 p. 70
Eyal Cohen, MD (1), Gur Munzer Llb,(2) David Varssano, MD (1), Igor Kaiserman, MD (2), Amir Rosenblatt, MD, MPH (1), Yaziv Yosef, MD (1)
(1)Tel-Aviv Sourasky Medical Center, Sackler, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, (2)CARE VISION, Inc.

29. **Corneal Haze following photorefractive Keratectomy- prevalence and risk factors** 13:35 p. 71
Naava Sadi 1, Tzahi Sela 3, Gur Munzer 3, Shmuel Levratovsky1 2, Igor Kaiserman 1 2 3.
1Department of ophthalmology Barzilai medical center Ashkelon Israel. 2 Ben Gurion University- faculty of health science, Be'er Sheva, Israel. 3 Care Vision Laser Center, Tel Aviv- Israel

30. **Simultaneous photorefractive keratectomy and collagen crosslinking for patients with an increased risk profile** 13:40 p. 72
Oded Ohana (1), Yuval Domnitz (2), Gur Munzer Llb. (2), Eyal Cohen (1), David Varssano (1)
(1) Ophthalmology department, Tel Aviv Medical Center, Israel, (2) Care vision clinic, Tel-Aviv, Israel

31. **Pain control after excimer laser photorefractive keratectomy: tetracaine 0.3% versus benoxinate 0.15%.** 13:45 p. 73
David Ben david, Shmuel Levartovsky, Tzahi Sela, Gur Munzer, Igor Kaiserman.
Barzilai Medical Center, Ashkelon, Israel, care vision laser centers,tel-aviv, israel.

* **Cornea 2: Ocular Surface, Stem Cells, Neovascularization** 14:20 – 15:15

Moderators:
Prof. Irit Bahar
Dr. Tamar Kadar

36. **MicroRNA-184 is essential for corneal commitment and limbal stem cell homeostasis** 14:20 p. 78
Daria Putin1, Noora Dbayat2, Laura Serror1,3, Beatris Tiosano2 Daniel Aberdam3 and Ruby shalom-Feuerstein1
1Rappaport Faculty of Medicine of the Technion, Israel; 2Department of ophthalmology – Hillel Yaffe Medical center, Hadera, Israel; 3INSERM UMR-S976, Université Paris Diderot, Hôpital Saint-Louis, Paris, France.

37. **In-vivo characterization of the ocular surface following transplantation of limbal stem cells on contact lenses: Towards treatment of LSCD** 14:25 p. 79
Gore A., Horwitz V., Cohen-Jacob O., Gutman H., Cohen M., Cohen L., Turetz J., Dachir S. and Kadar T
Israel Institute for Biological Research

38. **Time dependent changes in biomarkers in the tear fluid following ocular chemical injury in rabbits** 14:30 p. 80
Horwitz Vered, Cohen Maayan, Gore Ariel, Gutman Hila, Cohen Liat, Dachir Shlomit, and Kadar Tamar
Department of Pharmacology, Israel Institute for Biological Research, Ness Ziona

39. **The effects of Nerve Growth Factor (NGF) on corneal injury associated with LSCD in a chemical burn model in rabbits** 14:35 p. 81
Tamar Kadar, Ariel Gore, , Adina Amir, Liat Cohen, Maayan Cohen, Hila Gutman, Patrick McNutt, Vered Horwitz and Shlomit Dachir
Department of Pharmacology, Israel Institute for Biological Research, Ness Ziona

Discussion 15:05 – 15:15

Coffee & Exhibition 15:15 - 15:45

* **Glaucoma** 15:45 – 17:00

Moderators:
Dr. Elie Beit- Yannai
Dr. Yaniv Barkana

45. **Cross-talk of Ciliary Epithelium cells and Trabecular Meshwork cells: a new insight in understanding Glaucoma.** 15:45 p. 87
Natalie Karpenko, Elie Beit- Yannai
Clinical Biochemistry and Pharmacology Department of; Ben-Gurion University of the Negev.

46. **RPTP- σ over expression in Trabecular meshwork cell line as a model for phosphatases role in the ocular drainage system evaluation** 15:50 p. 88
Michal Zaiden and Elie Beit-Yannai
Ben-Gurion University of the Negev

47. **Ciliary derived exosomes and their roles within the drainage system as a pharmacological intervention target for glaucoma.** 15:55 p. 89
Natalie Karpenko(1), Reut Singer(2), Elie Beit-Yannai(1)
(1) Department of Clinical Biochemistry and Pharmacology; Ben-Gurion University of the Negev., (2)Department of Ophthalmology, Barzilai Medical Center, Ashkelon

48. **Signaling between macrophages and trabecular meshwork cells and their potential contribution to glaucoma pathophysiology** 16:00 p. 90
Matan Shmilovich, Elie Beit-Yannai
Clinical Biochemistry&Pharmacology Department, Ben-Gurion University of the Negev.

54. **Assessment of a combined tropicamide and oxime treatments against miosis and visual dysfunction following ocular exposure to the nerve agent sarin** 16:30 p. 96

Gore A. Brandeis R., Egoz I. And Bloch-Shilderman E
Israel Institute for Biological Research

Discussion 16:35 – 17:00

Thursday, March 27th , 2014

Coffee & Exhibition 8:00 – 8:30

* **Retina 2: Retinal degenerations: Genetics, Diagnosis and Therapy** 8:30 - 10:00

Moderators:
Dr. Ygal Rotenstreich
Prof. Eyal Banin

55. **A new method for subretinal transplantation of human cells as a thin layer in rabbit and porcine eyes** 8:30 p. 97

Rotenstreich Ygal.(1,2), Kalish Sapir (1,2), Sher Ifat (1), Tzameret Adi (1,2), Belkin Michael (1,2), Treves Avraham (3), Nagler Arnon (4).
Goldschleger Eye Research Institute, Tel-Hashomer, Israel; (2) The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, (3) Cancer Reserch Center, Tel-Hashomer, Israel; (4) Hematology Division, Tel-Hashomer, Israel.

56. **Gene therapy in a sheep model of CNGA3 achromatopsia: long term functional rescue and expression of the vector-delivered CNGA3 mRNA and protein** 8:35 p. 98

Ayala Ejzenberg (1), Alexey Obolensky (1), Lina Zelinger (1), Edward Averbukh (1), Alexander Rosov (2), Raaya Ezra-Elia (3), Esther Yamin (1), Hen Honig (2), Dror Sharon (1), Ron Ofri (3), William Hauswirth (4), Elisha Gootwine (2), Eyal Banin (1).
Department of Ophthalmology, Hadassah-Hebrew University Medical Center., (2) Agricultural Research Organization, The Volcani Center., (3) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, (4) Department of Ophthalmology, University of Florida

65. **A nonsense mutation in CEP250, a mammalian-specific homolog of Rootletin, causes a new type of Usher syndrome** 9:20 p. 107

Samer Khateb (1), Lina Zelinger (1), Liliana Mizrahi-Meissonnier (1), Carmen Ayuso (2), Robert K. Koenekoop (3), Uri Laxer (4), Menachem Gross (5), Eyal Banin (1), Dror Sharon (1)

Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem; (2) Department of Genetics, Instituto de Investigacion Sanitari Fundacion Jimenez Diaz (IIS-FJD), CIBERER, ISCIII, Madrid, Spain; (3) Departments of Human Genetics, Paediatric Surgery and Ophthalmology, McGill University Health Centre, Montreal, Quebec, Canada; (4) Department of Pulmonology, Hadassah-Hebrew University Medical Center, Jerusalel; (5) Department of Otolaryngology - Head and Neck Surgery, Hadassah-Hebrew University Medical Center, Jerusalem

66. **Isolated foveal hypoplasia is associated with a homozygous SLC38A8 mutation** 9:25 p. 108

Libe Gradstein(1), Yonatan Perez(2), Hagit Flusser(3), Barak Markus(2), Idan Cohen(2), Yshaia Langer(2,4), Mira Marcus(1),Tova Lifshitz(1), Rotem Kadir(2), Ohad Birk(2,4)

Department of Ophthalmology, Soroka Medical Center and Clalit Health Services, Ben Gurion University, Beer Sheva, (2) The Morris Kahn Laboratory of Human Genetics at the National Institute of Biotechnology in the Negev, Ben Gurion University, Beer Sheva, (3) Zussman child development center, Soroka Medical Center, Faculty of Health Sciences, Ben-Gurion University, Beer Sheva, (4) Genetic Institute, Soroka Medical Center, Beer Sheva

67. **Advantages and pitfalls of whole exome sequencing** 9:30 p. 109

Avigail Beryozkin (1), Rinki Ratnapriya (2), Gal Levi (1), Linn Gieser (2), Csilla Lazar (2), Mousumi Mutsuddi (2), Itay Chowers (1), Eyal Banin (1), Dror Sharon (1), Anand Swaroop (2)

(1) Dept. of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.,(2) Neurobiology-Neurodegeneration&Repair Laboratory (N-NRL), National Eye Institute, National Institutes of Health, Bethesda, MD, USA.

68. **Identification of genetic defects in cone-rod degeneration by whole exome sequencing** 9:35 p. 110
Adva Kimchi (1), Csilla Lazar (2), Lina Zelinger (1), Mousumi Mutsuddi (2), Avigail Beyozkin (1), Liliana Mizrahi-Meissonnier (1), Eyal Banin (1), Dror Sharon (1), Anand Swaroop (2)
Hadassah-Hebrew University Medical Center, Jerusalem, Israel., (2) Neurobiology-Neurodegeneration&Repair Laboratory (N-NRL), National Eye Institute, National Institutes of Health, Bethesda, MD, USA.

69. **Single nucleotide polymorphic changes in patients with adult onset foveal vitelliform dystrophy** 9:40 p. 111
Michelle Grunin, Liran Tiosano, Tareq Jaouni, Shira Hagbi-Levi, Dror Sharon, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center

Discussion 9:45 – 10:00

Coffee & Exhibition 10:00 – 10:30

* **Retina 3: AMD** 10:30 – 11:40
Moderators:
Prof. Adiel Barak
Dr. Ori Segal

70. **Ranibizumab and Bevacizumab decrease macular ganglion cell complex thickness measured with Fournier-domain optical coherence tomography in AMD** 10:30 p. 112
Shulamit Schwartz, MD (1,2), Adiel Barak, MD (1), Anat Loewenstein, MD (1), Hugo Quiroz-Mercado, MD (2)
1.Ophthalmology Department, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel, 2. Ophthalmology Department, Denver Health Medical Center, Anschutz school of Medicine, University of Colorado, Aurora, CO

76. **Characterizing the phenotype of differentiated macrophages from patients with age related macular degeneration** 11:00 p. 118
Shira Hagbi-Levi, Michelle Grunin, Tareq Jaouni, Paula Mosqueda, Liran Tiosano, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center

77. **Analysis of gene expression in monocytes from patients with age-related macular degeneration** 11:05 p. 119
Michelle Grunin, Shira Hagbi-Levi, Paula Mosqueda, Gala Beykin, Radgond Amer, Itay Chowers
Department of Ophthalmology, Hadassah-Hebrew University Medical Center

78. **Prevalence of CFH Y402H and ARMS2 A69S polymorphism among Israeli intermediate AMD patients towards genotype-directed therapy** 11:10 p. 120
Nadav Shoshany, MD, Isaac Avni, MD, Eran Pras, MD
Assaf Harofeh Medical Center, Zerifin, Israel

79. **BRCA1/2 mutations may play a role in developing neovascular AMD in Ashkenazi Jews** 11:15 p. 121
Shirel Rossnewasser Weiss,1,2 Mohammed Azab,3 Sivan Gershanov ,1,4 Mali Salmon-Divon, 4 Yoram Cohen,3,5 Nitza Goldenberg Cohen. 1,2,3
1The Krieger Eye Research Laboratory, 2Ophthalmology, Pediatric Unit, Schneider Children's Medical Center, Petah Tiqwa; 3Sackler School of Medicine, Tel Aviv University, Tel Aviv; Israel; 4 Functional Bioinformatics Laboratory, Molecular Biology, Ariel University; 5Department of Gynecology, The Gynecology Research Laboratory, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

Discussion 11:20 – 11:40

Awards & ISVER update 11:40 – 12:00

* **Guest lecture 2** 12:00 – 12:30

Prof. Amnon Shashua
Sachs Professor of Computer Science, School of Engineering and Computer Science, The Hebrew University of Jeusalem. Co-founder and Chairman, Mobileye Vision Technologies..
"Harnessing computer science for the visually impaired: the OrCam device".

Lunch break 12:30 – 13:30

* **Visual Function and Perception** 13:30 – 14:45
Moderators:
Prof. Amir Amedi
Dr. Uri Polat

80. **Objecive chromatic pupillometer - pupillary responses of healthy subjects to chromatic stimulation from small 2.5-mm-diameter spots** 13:30 p. 122
Soad Haj Yahia (1), Ron Chibel (1,2), Mohamad Mahajna (1,2), Tom Kornhauser (1) , Ifat Sher (1), Michael Belkin(1,2), Ygal Rotenstreich (1,2)
Sheba Medical Center, Goldschleger Eye Research Institute, Israel, (2) The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv

81. **Beyond the eye - behavioral and cortical assessment in posterior cortical atrophy (PCA)** 13:35 p. 123
Haya Shames ,Noa Raz,& Netta Levin
fMRI unit, Neurology Department, Hadassah Hebrew University Hospital, Jerusalem Israel

90. **The time course of ocular parameters in ADHD during a continuous performance task (CPT) and the effect of medication** 14:20 p. 132
Fried M(1), Bonneh Y(2), Sterkin A(1), Polat U(1)
Faculty of Medicine, Tel-Aviv University, Goldschleger Eye Research Institute, Sheba Medical Center, 2Department of Human Biology, University of Haifa, Haifa, Israel.

91. **Improving visual functions in TBI patients by perceptual learning** 14:25 p. 133
Sterkin Anna (1,2), Lev Maria (1), Doron Ravid (1), Fried Moshe (1), Mandel Yossi (3), Dobin Genady (1)Ruth Huna-Baron(1,4) , Polat Uri (1,2)
(1) Faculty of Medicine, Goldschleger Eye Research Institute, Sheba Medical Center, Tel Aviv University, Israel, (2) GlassesOff Inc., USA, (3) The Mina&Everard Goodman Faculty of Life Sciences, Bar Ilan University, Ramat Gan, Israel, (4) Neuro-Ophthalmology Unit Goldschleger Eye Institute, Sheba Medical Center, Israel

92. **Grating acuity is reduced in children with acute papilledema** 14:30 p. 134
Eedy Mezer, MD, Carol Westall, PhD, Ronit Yagev, MD, Tamara Wygnanski-Jaffe, MD, J Raymond Buncic, MD
Rambam Healthcare Campus, Hospital for Sick Children, Toronto, Canada, Sheba Medical Center

Discussion 14:35 – 14:45

Coffee & Exhibition 14:45 – 15:15

* **Animal Vision** 15:15 – 16:00
Moderators:
Prof. Gadi Katzir
Dr. Amit Lerner

97. **A bio-inspired stereo compound-eye imaging device based on the visual system of the praying mantis.** 15:35 p. 139
Tomer Baum(1), Ehud Rivlin(2), Joao Barreto(3), Gadi Katzir(4)
(1) Mathematics Department, Technion , Israel Institute of Technology 32000, Haifa,Israel, (2) Computer Science Department, Technion , Israel Institute of Technology 32000 Haifa,Israel,(3) Departament,University of Coimbra 3030 Coimbra, Portugal, (4) Department of Evolutionary and Enviromental Biology, Department of Marine Biology, University of Haifa, Mount Carmel 31905, Israel

98. **Cone function in normal and day blind sheep. A large animal model for CNGA3 achromatopsia patients** 15:40 p. 140
(1) Raaya Ezra-Elia, (2) Eyal Banin, (3) Hen Honig, (3) Alexander Rosov, (2) Alexey Obolensky, (2) Edward Averbukh, (4) William W Hauswirth, (3) Elisha Gootwine, (1) Ron Ofri
(1) Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot, Israel, (2) Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, (3) Agricultural Research Organization, The Volcani Center, Beit Dagan, Israel, (4) Department of Ophthalmology, University of Florida, Gainesville, FL

99. **Polarization vision - why animals and not humans?** 15:45 p. 141
Amit Lerner
Israel Oceanographic and Limnological Research

Discussion 15:50 – 16:00

* **Retina 4: Clinical studies and Imaging** 16:00 – 17:00

Moderators:
Dr. Shulamit Schwartz
Prof. Itay Chowers

100. **The sealing effect of external diathermy on leaking sclerotomies after small gauge vitrectomy surgery - a clinico-pathological report** 16:00 p. 142

Yoreh Barak, M.D. (1), Elizabeth Summers Lee, B.A. (2), Shlomit Schaal, M.D., Ph.D. (2)
1- Department of Ophthalmology, Rambam Medical Center, 2- Department of Ophthalmology and Visual Sciences University of Louisville, Louisville, Kentucky, USA

101. **New application of hydrogel-sealant to close retinal breaks** 16:05 p. 143

Tilda Barliya1,2 Tami Livnat1,2 and Dov Weinberger1,2,3
1.Division of Ophthalmology , Rabin Medical Center- Beilinson campus, Petah Tikva, Israel., 2 Laboratory of Eye research Felsenstein Medical Research Center (FMRC)., 3 Sackler School of Medicine, Tel-Aviv university, Israel

102. **Seasonal airsoft gun-related ocular injuries and macular OCT follow up of one case with macular edema.** 16:10 p. 144

Hilo Wasseem MD, Haneen Jabaly-Habib MD, Yaron Lang MD, Daniel Briscoe MD.
Ophthalmology Department, Emek Medical Center, Afula, Israel

103. **Computerized analysis of OCT images: segmentation and measurement of retinal layers thickness** 16:15 p. 145

Boris Rosin and Eyal Banin
Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel

108. **Hyperbaric oxygen treatment reduced stroke damage and improved vision in a child and perfusion after middle cerebral artery occlusion in mice** 16:45 p. 150

James D. Nicholson,3,4 Dennis Pushkov,1* Shalom Michowiz,1,3* Shirel Weiss,3,4 Dana Morzaev,3,4 Nitza Goldenberg-Cohen.2,3,4*
1Department of Neurosurgery, Rabin Medical Center, Beilinson Campus; 2Pediatric Ophthalmology Unit, Schneider Children's Medical Centerl; 3Sackler Faculty of Medicine, Tel Aviv Universityl, 4The Krieger Eye Research Laboratory, FMRC, Rabin Campus, Tel Aviv University

109. **Long-term outcome of intravitreal dexamethasone implant for the treatment of noninfectious uveitic macular edema** 16:50 p. 151

Zohar Habot-Wilner (1,2), Nir Sorkin (1,2), Dafna Goldenberg (1,2), Anat Loewenstein (1,2), Michaella Goldstein (1,2)
(1)Department of Ophthalmology, Tel Aviv Medical Center., (2)Sackler Faculty of Medicine, Tel Aviv University

Discussion 16:55 – 17:00

Concluding Remarks: Prof. Avi Solomon 17:00

ABSTRACTS

תקצירים

Combination of staining techniques to differentiate venous endothelial cells in mouse optic nerve.

James D. Nicholson 1,2, Orkun Muhsinoglu 3, Nitza Goldenberg-Cohen 1,2,4

1Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Israel, 2The Krieger Eye Research Laboratory, FMRC, Rabin Campus, Tel Aviv University; 3Department of Ophthalmology, Rabin Medical Center, Beilinson Campus, Petach Tikva; 4Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petach Tikva

Purpose: In our previous work using the rodent model of optic nerve stroke (rAION) initiated via photoactivation of rose bengal dye, we imaged the perfused and ischemic areas of the optic nerve (ON) using fluorescent vascular filling. Previous results in rat suggest that the ischemic event begins immediately behind the globe, as in human non-arteric anterior ischemic optic neuropathy (NAION), where the capillary bed is the most dense. However, in mice the capillary density has previously been reported to be much lower than in rat or human. We would like to know if there are substantial variations in mouse optic nerve vasculature between mouse strains that would allow comparisons of stroke susceptibility to be made between mouse strains. We report here our preliminary work on the staining technique for vascular measurement across mouse strains.

Methods: ON from C57Bl/6 mice were fixed post-mortem in 4% paraformaldehyde and cryosectioned to 50Âµm thickness. Serial sections from the optic nerve head to ~2 mm behind the globe were mounted on slides for staining. Sections were then sequentially stained and imaged, first with alkaline phosphatase substrate which only stains arterial endothelial cells and capillary endothelial cells, then de-coverslipped and stained with Gomori lead stain which stains all vessels. Additional staining can be optionally performed using luxol blue to image the initiation of myelination.

Results: Capillaries were expected to stain uniformly with alkaline phosphatase while the veins did not stain, however, there were periodic areas of dropout in capillary alkaline phosphatase staining where the capillaries are proximal to pial veins.

Conclusions: Our multi-staining technique will allow us to compare the vasculature of mouse strains where the eyes are removed without special preparation. We have also discovered an unexpected difference in endothelial cell population in the optic nerve capillaries based on alkaline phosphatase expression that indicates two populations of endothelial cells line the ON capillaries

Demonstration of retinal vasculature in diabetic mice

Moshe Ben Hamou,1,2 James D. Nicholson,1,2 Orit Barinfeld,1,2 Orkun Muhsinoglu,3 Nitza Goldenberg-Cohen.1,2,4

1Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; Israel, 2The Krieger Eye Research Laboratory, FMRC, Rabin Campus, Tel Aviv University; 3Department of Ophthalmology, Rabin Medical Center, Beilinson Campus, Petach Tikva; 4Pediatric Ophthalmology Unit, Schneider Children's Medical Center of Israel, Petach Tikva;

Purpose: Dysfunction of the retinal vasculature is the most prominent aspect of diabetic retinopathy (DR), including thickening of the vascular layers, capillary non-perfusion, plasma protein leakage, ischemia, and hypoxia. Eventually, proliferative growth of new vessels, tractional retinal detachment, and macular edema can occur, leading to severe visual loss. The aim of this study is to describe histological staining and perfusion techniques used to demonstrate the retinal vasculature of diabetic mice.

Methods: Non-obese diabetic (NOD) mice aged 4-8 months (6 per group) were examined. Their blood glucose level was measured to confirm diabetic status and in vivo fluorscein angiography was performed to detect neovascularization or pathological vascular leakage. Twelve retinae were dissected post-mortem from NOD mice, 6 diabetic and 6 non-diabetics. The retinae were analyzed using the following **Methods:** Periodic acid–Schiff (PAS), ADPase, immunostainng with anti TLR4, isolectin, von Willebrand (vW) and CD11 antibodies. Six mice were perfused with fluorescent gelatin to establish co-localization of vascular stains with vessel lumens.

Results: The thickening of the vascular basal membrane was demonstrated by PAS staining. The retinal vessels were best demonstrated with ADPase and but these vessels were less prominent when stained with anti TLR4 antibodies. The other staining methods failed to demonstrate the vessels in the NOD mice, although they were successful in C57Bl/J6 retinae. Perfusion showed microaneurism. None of the in vivo FA, fluorescein gel perfusion or histological staining revealed neovascularization in the retinae.

Conclusions: We demonstrated the thickening of the vascular basement membrane of diabetic retinal vessels, in line with the literature. We failed to detect retinal neovascularization in any of the mice, even with long staining diabetes, in contrast to previous reports. Gelatin perfusion is a novel method, better than FA, that enables analysis of pathological retinal vessels difficult to perform in albino mice. Despite the difficulties in immunostaining, we developed a method to demonstrate the retinal vasculature.

Funds: partially supported by the Krieger Fund.

Monocyte entry and function in ocular repair

Inbal Benhar and Michal Schwartz

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

Purpose: We recently demonstrated the heterogeneity of macrophages and their important roles in immune resolution and repair following glutamate-induced retinal damage and in experimental autoimmune uveitis. As the eye is an immune-privileged site, endowed with specialized barriers and molecules to preserve its integrity, the route by which monocytes enter the eye is likely to dictate their phenotypes so as to become beneficial or destructive. Here we hypothesized that healing monocytes enter the eye through the ocular epithelial rather than endothelial barrier.

Methods: Adult mice were subjected to retinal insult in a model of glutamate intoxication or optic nerve crush (ONC). In some experiments, ONC was preceded by protective autoimmune vaccination with MOG-45D. Effects of monocyte depletion or augmentation were tested using the anti-CCR2 antibody, MC-21, or adoptive transfer of monocytes, respectively. CX3CR1-GFP transgenic mice were used as donors of monocytes to enable their tracking in the eye. Survival of retinal ganglion cells (RGCs), the phenotype of the recruited monocytes and their contribution to the local retinal milieu were analyzed by immunohistochemistry and flow-cytometry.

Results: Monocytes injected after glutamate intoxication either intravenously or intravitreally localized to the site of damage, but were also found in the subretinal space, adjacent to the retinal pigment epithelium. The injected monocytes expressed an array of immune mediators, including IL-10 and TGF-β. ONC resulted in immune cell infiltration into the retina, which was augmented in animals that were vaccinated with MOG-45D prior to the crush.

Conclusions: Monocyte-derived macrophages maintain their capacity to mediate neuroprotection in different modes of application, indicating that the eye, as an immune privileged site, has the ability to select and regulate the activity of infiltrating cells. The presence of monocyte-derived macrophages distal to the site of injury and in proximity to the retinal pigment epithelium suggests that their interaction with this barrier may influence their phenotype.

The Effects of the APOE Genotype on Murine Retinal Vasculature and VEGF Expression during Development

Idit Maharshak1,2, Tami Livnat3, Yael Nisgav3, Mordechai Rosner4, Arieh S. Solomon4, Dov Weinberger5,2, Carol A. Colton6, Daniel M. Michaelson1.

1Department of Neurobiology, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel; 2Department of Ophthalmology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; 3Laboratory of Eye Research, Felsenstein Medical Research Center, Rabin Medical Center, Petach Tikva, Israel; 4Goldschleger Eye Institute, Tel-Aviv University, Tel-Hashomer, Israel; 5Department of Ophthalmology, Rabin Medical Center, Petach Tikva, Israel; 6Division of Neurology, Duke University Medical Center, Department of Medicine, Durham, NC.

Purpose: Our working hypothesis is that APOE4, the most prevalent genetic risk factor of Alzheimer's disease, affects both murine retinal vasculature and murine retinal VEGF expression during neonatal development.

Methods: Retinal whole mounts and cryo-sections of neonatal targeted replacement mice which express either human APOE4 or APOE3 were stained for endothelial cells and VEGF. Confocal images of the retinas were analyzed and quantitated.

Results: The results obtained revealed that retinal vascular density is higher in APOE4 compared to APOE3 neonate mice (post-natal days 4, 7, 12). Two-Way ANOVA revealed a significant effect for genotype ($p=0.035$) and for age ($p<0.01$). Further analysis revealed that the increased vascular density in APOE4 neonate mice was associated with increased arterial branching ($p=0.043$). The extent to which the increased vascular density of APOE4 neonate mice was associated with increased levels of VEGF was examined next by immunohistochemical staining of VEGF in retinal cryosections. Quantitation of these results at the GCL layer revealed increased VEGF expression for APOE4 compared to APOE3 mice at the center of the retina and even more so at the retinal periphery (post-natal days 4, 7, 12). Higher levels of VEGF in APOE4 mice versus APOE3 mice were found also at the IPL, INL and OPL layers.Unlike the VEGF protein, VEGFA mRNA expression levels were not affected by the APOE genotype.

Conclusions: Our results revealed a denser vasculature and more branching in neonate APOE4 mice vs. APOE3 mice which correlate with the increased VEGF levels in APOE4 mice versus APOE3 mice. Expression levels of vascular related genes were unaffected by the APOE genotype in comparison to VEGF levels measured by immunohistochemical methods**.**

VEGF as a novel therapeutic target for counteracting the neuronal and vascular effects of apoE4

Shiran Salomon-Zimri, Ran Antes and Daniel .M. Michaelson

Sagol School of Neuroscience, Tel Aviv University, Israel.

Purpose: Alzheimer's disease (AD) is associated with neural and vascular dysfunction. ApoE4, the main genetic risk factor for AD is associated with increased neurodegeneration and vascular impairments. The extent to which these pathologies are mediated by a common factor is unknown. The vascular endothelial growth factor (VEGF) has been shown to play an important role in both the neuronal and vascular systems. The objective of the present study is to test whether the apoE4 pathological effects on these systems are mediated by VEGF and to identify novel therapeutic targets utilizing the brain and the eye as complementary model systems.

Results: Our previous results revealed neuronal and synaptic impairments in hippocampi of young naïve apoE4-targeted replacement mice, which correlated with cognitive deficiencies. Similar results were obtained under stress conditions after activation of the amyloid cascade. In contrast, no gross effect was observed on the vasculature. This study shows that these apoE4-induced pathological effects are associated with lower VEGF levels. The eye, with its unique structure in which the neuronal and vascular systems are spatially separated, provides an excellent model to approach our research question. Examination of young naïve apoE4 neuro-retina revealed synaptic impairments and functional deficiencies. This was also found to be associated with down regulation in VEGF levels, with no gross effect observed in the choroid vasculature. Stress conditions generated by laser-induced choroidal neurovascularization, resulted in apoE4 hyper-angiogenesis, associated with an elevation of VEGF levels in both the retina and the choroid.

Conclusions: These findings show differential effects of apoE4 on the neuronal and vascular systems. VEGF levels are associated with neurodegeneration in the neuronal system and angiogenesis in the vascular system. This sets the stage for a novel therapeutic anti-VEGF treatment to counteract apoE4 pathologies.

The roles of Lim-domain binding proteins in mammalian retina

Keren Gueta-Milshtein1, Tsadok Cohen2, Heiner Westphal2, Ruth Ashery-Padan1

Sackler Faculty of Medicine, Tel-Aviv University, Ramat Aviv, Tel Aviv, Israel., 2. Laboratory of Mammalian Genes and Development, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, HHS, Bethesda, MD 20892, USA.

Background & Aims: The generation of the neuroretina during embryogenesis occurs through gradual differentiation of multipotent retinal progenitor cells (RPCs) to the diversity of retinal cell types. Members of the LIM family of transcription factors are known to play important roles in the transition of progenitors to differentiated cell types throughout the CNS. Most members of this family were shown to play role during retinal development for the establishment of retinal identity (Lhx2) and differentiation of specific retinal lineages (Islt1, Lhx3, Lhx4, Lhx6). The LIM-domain binding proteins (Ldbs) are essential cofactor-proteins for the activity of the LIM factors. The composition of Ldb complexes influences cell-fate and differentiation depending on the developmental context. Despite their importance, the role of Ldbs in retinal development is currently unknown. The aim of this study is to investigate the roles of Ldb proteins during retinal development.

Methods: We established the Ldb1loxP/loxP;Ldb2-/-;Î±-Cre mice in which Ldb1 was deleted exclusively in the retinal progenitors populating the optic cup prior to onset of cell differentiation. The phenotype of the Ldb1/2 deficient retina was analyzed for determining changes in tissue morphology, cell fate, proliferation and survival employing histology, immunohistochemistry and in-situ hybridization technologies.

Results: The loss of Ldb1/2 from RPCs resulted in premature cell cycle exit followed by an early depletion of the retinal progenitor cells and elevation in the number of post-mitotic precursors of early born retinal lineages (ganglion and amacrine cells). Furthermore, the photoreceptor precursors and late born retinal cell types failed to be specified in the Ldb1/2 deficient optic cup.

Conclusion: Our findings reveal crucial function for Ldb proteins as regulators of RPCs characteristics by maintaining their pluripotency, regulate cell cycle exit and determine cell fate. The study further suggests a role for Ldb proteins in specification of the photoreceptor lineage in mammals.

PAX6 regulates melanogenesis in the retinal pigmented epithelium through feed-forward regulatory interactions with MITF

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Purpose: During organogenesis, PAX6 is required for establishment of most ocular lineages. Accordingly most eye structures are affected when Pax6 activity is compromised as seen in Anridia patients who suffer from pan-ocular syndrome due to Pax6 haploinsufficiency. The expression of Pax6 is maintained in a variety of cell types within each structure, although its role in each lineage and how it acquires cell-specific activity remains elusive. Herein, we aimed to determine the roles and the hierarchical organization of PAX6 dependent gene regulatory network during the differentiation of the retinal pigmented epithelium.

Methods: Somatic mutagenesis of Pax6 exclusively in the differentiating RPE was obtained through conditional mutagenesis. The phenotype was analyzed by determining alteration in tissue morphology and gene expression. Biochemical studies were employed for determining direct association with the DNA and with interacting partners.

Results: The phenotype and the biochemical studies revealed that Pax6 functions in a feed-forward regulatory loop with MITF during onset of melanogenesis of the retinal pigmented epithelium. PAX6 both controls the expression of an RPE isoform of Mitf, and synergizes with MITF to activate expression of genes involved in pigment biogenesis.

Conclusions: This study exemplifies how one central gene, which is pivotal for organ formation, accomplishes a lineage-specific role in course of terminal differentiation of a single lineage of the ocular pigmented epithelium.

TAK-1 plays a key role in RPE cell senescence, a possible cause leading to dry AMD

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Purpose: This study aimed to investigate the role of the transforming growth factor-beta-activated kinase 1 (TAK-1) in cellular senescence and apoptosis of the retinal pigment epithelium (RPE) cells, as a model for dry age-related macular degeneration (AMD).

It is well known that RPE cells are subjected to a high level of oxidative stress from several sources, which can contribute to the development of early AMD. However, the precise mechanism is unclear. One possible pathway involves cellular senescence of the RPE cells that share similar feature to cell atrophy. Interestingly, TAK-1 was reported to be involved in the response to stress in variety of cells. Therefore, we focused on the role of TAK-1 in RPE cells apoptosis and cellular senescence, for better understanding the signal transduction involved in dry AMD.

Methods: ARPE-19 tissue culture cells were used to study the role of TAK-1 in the hemostasis of RPE cells. cells were subjected to FACS analysis, immunofluorescence staining, XTT analysis, western blots analysis and real time PCR. Cells were treated with oxidative stress with or without TAK-1 inhibitor (5z-7 oxozeaenol). Cells were harvested and subjected to analysis in the different methods.

Results: Inhibition of the TAK-1 kinase activity reduced the rate of apoptotic RPE cells and shifted the cells to cellular senescence upon oxidative damage. Moreover, TAK-1 inhibition altered the expression of p53, which is the hall-mark of apoptosis, thus affecting the signal-transduction which underlies this process. The aberrant signal transduction led to increase of the senescence phenotype, accompanied by: 1. augmented SA-beta-gal expression 2. RPE pigmentary 3.morphology abnormalities. Finally, the inhibition of TAK-1 affected RPE cells similarly to changes that characterize early AMD

Conclusions: This study demonstrates that TAK-1 is involved in the response of RPE cells to oxidative stress. In RPE cells which TAK-1 was inhibited displayed phenotypes similar to those associated with dry AMD. Furthermore, our results revealed that TAK-1 is essential to the maintenance of healthy RPE cells and prevents cells senescence by regulating their normal morphology and p53. This study may imply a potential novel approach to maintain the RPE cells, thus may halt the progression of dry AMD

TGF-β1 Induced RPE cells transdifferentiation is mediated by TAK-1

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Purpose: Proliferative vitreoretinopathy (PVR) is a scarring process that develops as a complication during retinal detachment (RD), accompanied by formation of fibrotic tissue and it is the most common cause of RD failure. Retinal pigment epithelial (RPE) cells regulate the development of the fibrotic tissue during PVR. RPE cells are quiescent and differentiated cells, however upon RD and the break of the blood-retina barrier, RPE cells are exposed to a variety of cytokines and growth factors. Upon this exposure the RPE cells undergo epithelial-mesenchymal transition (EMT) characterized by enhanced expression of alpha–smooth muscle actin, secretion of chemokines and cytokines, increased cell motility and production of extracellular matrix components. Transforming growth factor-β1 (TGF-β1) plays a key role in EMT of RPE cells. In this study we examined the effect of inhibition of the canonical and non-canonical pathways of TGF-β1 on EMT of RPE cells.

Methods: ARPE-19 Cells were treated with 5Z-7 oxozeaenol [transforming growth factor beta-activated kinase 1 (TAK-1) inhibitor] or SB431542 (TGF-β1 receptor kinase inhibitor) followed by TGF-beta1 (5 ng/ml) stimulation for all experiments. Immunofluorescence assays examined: phospho-p38, alpha-SMA, E-cadherin and stress fiber assembly and subcellular distribution. Cell migration was determined using scratch assay. Cell contractility was examined using collagen contraction assay. Real time PCR assessed the transcription of pro inflammatory factors.

Results: Stimulation of RPE cells with TGF-β1 increases α-SMA expression, cell migration, contractility and the transcription of CTGF (connective tissue growth factor) and collagen type 1, all are EMT features. However, addition of TAK-1 inhibitor abolishes all these processes. Moreover, while TGF-beta1 treatment reduced E-cadherin expression during the EMT process addition of TAK-1 inhibitor halt this process and maintains the naive form of the cells.

Conclusions: This study demonstrates that TAK-1, substrate of TGF-beta1, is a key player in the EMT process of RPE cells. The ability to halt the process of EMT in RPE cells may reduce the severity of the fibrotic response that occurs upon PVR, leading to a better prognosis and increase the probability of success in RD

PI3K and TAK-1 inhibition demonstrate a synergistic effect reducing oxidative damage in RPE cells

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Purpose: Proliferative vitreoretinopathy (PVR) is a scarring process that develops as a complication during retinal detachment (RD), accompanied by formation of fibrotic tissue and it is the most common cause of RD failure. Retinal pigment epithelial (RPE) cells regulate the development of the fibrotic tissue during PVR. RPE cells are quiescent and differentiated cells, however upon RD and the break of the blood-retina barrier, RPE cells are exposed to a variety of cytokines and growth factors. Upon this exposure the RPE cells undergo epithelial-mesenchymal transition (EMT) characterized by enhanced expression of alpha–smooth muscle actin, secretion of chemokines and cytokines, increased cell motility and production of extracellular matrix components. Transforming growth factor-β1 (TGF-β1) plays a key role in EMT of RPE cells. In this study we examined the effect of inhibition of the canonical and non-canonical pathways of TGF-β1 on EMT of RPE cells.

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Conclusions: This study demonstrates that TAK-1, substrate of TGF-beta1, is a key player in the EMT process of RPE cells. The ability to halt the process of EMT in RPE cells may reduce the severity of the fibrotic response that occurs upon PVR, leading to a better prognosis and increase the probability of success in RD.

The role of TAK-1 in autophagy in RPE cells

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Purpose: Proliferative vitreoretinopathy (PVR) is a scarring process that develops as a complication during retinal detachment (RD), accompanied by formation of fibrotic tissue and it is the most common cause of RD failure. Retinal pigment epithelial (RPE) cells regulate the development of the fibrotic tissue during PVR. RPE cells are quiescent and differentiated cells, however upon RD and the break of the blood-retina barrier, RPE cells are exposed to a variety of cytokines and growth factors. Upon this exposure the RPE cells undergo epithelial-mesenchymal transition (EMT) characterized by enhanced expression of alpha–smooth muscle actin, secretion of chemokines and cytokines, increased cell motility and production of extracellular matrix components. Transforming growth factor-β1 (TGF-β1) plays a key role in EMT of RPE cells. In this study we examined the effect of inhibition of the canonical and non-canonical pathways of TGF-β1 on EMT of RPE cells.

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Conclusions: This study demonstrates that TAK-1, substrate of TGF-beta1, is a key player in the EMT process of RPE cells. The ability to halt the process of EMT in RPE cells may reduce the severity of the fibrotic response that occurs upon PVR, leading to a better prognosis and increase the probability of success in RD

Therapeutic potential of adipose tissue derived mesenchymal stem cells for atrophic RPE- Migration, trophic anti-apoptotic effects and differentiation

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Purpose: The pathophysiology of AMD is not fully elucidated; however, it is known that hypoxic stress contributes to RPE dysfunction and leads to the secretion of retinotoxic hypoxic stress factors. Cell therapy aiming to replace non-functional RPE may lead to favorable results. Adipose tissue derived Mesenchymal stem cells (adMSCs) are an attractive cell source for retinal therapeutic applications due to their accessibility and differentiation potential. We aimed to examine the differentiation potential and paracrine activity of adMSCs when exposed to injured RPE cells.

Methods: adMSCs were isolated form sub-cutaneous adipose tissue of patients undergoing abdominoplasty. Cells were characterized by immunostaining and FACS analysis for adMSCs markers. The cells multipotency was proven by induction of differentiation to bone and to adipose cells by accepted protocols. adMSCs and RPE cells were subjected to hypoxia using a hypoxia chamber to simulate the hostile retinal environment of AMD patients. The migratory capacity of adMSCs towards RPE conditioned medium was examined by Transwell Migration Assay. Trophic and anti-apoptotic effect of adMSCs on RPE was examined by culturing RPE cells with adMSCs conditioned medium followed by annexin/PI stain and FACS analysis. adMSCs secretion of growth factors was also studied by qRT-PCR and immunostaining. Finally, the differentiation capacity of adMSCs to RPE was examined by culturing adMSCs with RPE conditioned medium and by qRT-PCR and immunostaining.

Results: Characterized phenotypically for MSCs, and with proven multipotency, adMSCs exhibited enhanced migration towards hypoxic RPE conditioned medium. Under hypoxic conditions RPE cells demonstrated decreased apoptosis once subjected to adMSCs conditioned medium. When cultured with hypoxic RPE conditioned medium, adMSCs upregulated growth factors such as bFGF. Finally adMSCs demonstrated differentiation to RPE by upregulation of RPE markers (best1, tyrosinase etc.).

Conclusions: adMSCs migrate towards hypoxic RPE, decrease RPE's apoptosis rate, and secrete growth factors in response to hypoxic RPE. Moreover, adMSCs exhibited differentiation capacity to RPE. These data imply to a favorable effect of adMSCs in regenerating RPE in a paracrine and a direct manner. This knowledge could serve the development of future cell therapy methods for AMD patients, by using adMSCs for sub-retinal transplantations.

Two-photon in-vivo imaging of retinal micro-structures

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Purpose: Non-invasive fluorescence retinal imaging in small animals is an important requirement in an array of translational vision applications, including the tracking of fluorescently tagged cells and blood vessels over time. Recently, we demonstrated the ability to obtain cellular resolved images in a retina transduced with fluorescent proteins using fluorescence topical endoscopy fundus imaging (TEFI) (Schejter et al,. 2012, TVST). Obtaining these capabilities with two-photon microscopy could have the added advantages of optical sectioning, reduced photodamage and photobleaching, and of being based on infrared light. Here, we demonstrate that two-photon laser scanning microscopy through a mouse's pupil can yield high-quality fundus images of fluorescent retinal micro-structures in-vivo.

Methods: Head-fixed animals, injected intraperitoneally with fluorescein, were imaged using two-photon in-vivo microscopy through the dilated pupil with a 10x water-immersion objective.

Results: These imaging sessions yielded well-resolved fluorescein angiograms which were axially sectioned to individual retinal layers. Comparison of these results with angiograms acquired in the TEFI setup show that while the TEFI system provides wide area images in a single shot, it suffers from low lateral and axial resolution because of its relatively low effective NA. Two-photon imaging thus offers improved lateral resolution and sectioning, in addition to its use of non-visible wavelengths for fluorescent excitation.

Conclusions: These results demonstrate the feasibility of performing two-photon fundus imaging in-vivo, opening new venues for future implementations in retinal structural and functional imaging, such as structural and functional autofluorescence retinal imaging and functional calcium imaging of responses to natural stimuli.

A biological tissue adhesive and dissolvent system for intraocular tumor plaque radiotherapy

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Purpose: To examine the feasibility of a novel technique for plaque radiotherapy placement and removal, using fibrin glue and urokinase, respectively, to explore quantitative variables, and compare these to conventional suturing.

Methods: The feasibility of the surgical technique was tested in 6 enucleated porcine eyes. Plaques without radioactive seeds were placed on the sclera beneath the conjunctiva; fibrin glue was then applied on the plaque, covering it and its immediate environment. The eyes were then submerged in plasma for 3 days. Thereafter, attempts were made to dissolve the glue and release the plaque using urokinase (10,000 units/10cc normal saline (NS)) or NS only, by a surgeon masked as to the nature of the dissolving fluid. In a second group of eyes, adhesion strength was measured using a system constructed of a tension transducer, a pulley, a transmission wire and an electrical winch. The eyes were prepared as described above, after which they were submerged in plasma for 5 days (replaced every 36 hours). Measurements were performed subsequently on 5 glued eyes and 5 eyes in which the plaques were sutured, and the results were recorded and analyzed.

Results: One to 2 ml of fibrin glue was used in order to fix each plaque in place. In all cases the urokinase syringe was identified, as the NS had no effect on the plaque–glue–eye complex, whereas the urokinase dissolved the adhesion between the glue layer and surrounding tissues. The plaques were then delivered out easily, after which a glue \"blanket\" was removed in full. No tissue defects were observed thereafter. The volume of urokinase used per eye was 0.38±0.08 ml. In the second part, the weights needed to detach the plaques were 0.35±0.17 kg and 0.41±0.08 kg for the glue and sutures, respectively (P=0.59).

Conclusions: A novel biological adhesive and dissolvent system using fibrin glue and urokinase was found to be a feasible technique for plaque surgery in an ex-vivo animal model. Fibrin glue was as durable as sutures, but may be preferable to the use of sutures in enabling precise plaque positioning and in the lack of complications, such as globe perforation or plaque displacement. Further in-vivo experiments are warranted.

sIL-2R an immuno-biomarker for prediction of metastases in uveal melanoma

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Purpose: High serum levels of sIL-2R have been reported in acute inflammations and in several types of cancer, especially in the metastatic stage. The aim of the present study was to evaluate the potential of increased sIL-2R levels to predict metastatic uveal melanoma (UM).

Methods: Serum levels of sIL-2R were analyzed by ELISA. The study included a total of 152 subjects: 74 patients with metastasis (Mets), 42 10-year disease-fee (10yDF) patients, and 36 healthy controls (CTRL). Patients were followed up biannually with liver US for the presence of Mets. Blood samples were obtained from the time of primary diagnosis, and on every follow-up visit. Sera from before and after the diagnosis of Mets were assessed by a matched pairs analysis for the 74 Mets patients.

Results: The mean±SE (range) sIL-2R levels for the 3 groups were: 575±41 (107- 1257), 780±60 (313- 1830), and 1401±146 (380- 8969) U/ml for CTRL, 10yDF, and Mets, respectively (p= 0.03).

Conclusions: Significantly higher serum sIL-2R levels were shown in UM pts with metastases. Significant increases in sIL-2R levels on serial evaluations indicate the development of UM metastases, enabling earlier treatment for a better survival of those patients.

The impact of thyroid hormone levels on survival in a uveal melanoma murine model: an experimental study

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Purpose: Uveal melanoma is the most common primary intraocular malignancy in adults. Data suggests that thyroid hormones, mainly free L-thyroxine (FT4), are endocrine modulators of tumor growth. We examined the impact of different levels of FT4 on survival of C57BL/6 mice inoculated with B16F10 mice melanoma cells.

Methods: Two independent in-vivo experiments using C57BL/6 mice were performed. Mice hypothyroid state was induced by adding 1 mg/ml propylthiouracil to drinking water (group A, n=9) and hyperthyroid state was induced by adding 6 µg/ml thyroxin to drinking water (group B, n=11). A third group of mice (group C, n=8) was given plain water. At day 21 the right eye suprachoroidal space of each mouse was inoculated with 102 B16F10 cells / 1 µl PBS. In additional 15 mice, 5 of each group, FT4 levels were measured and these mice were sacrificed thereafter. Further 11 mice (3 of group A and 4 of groups B and C), which were not inoculated with tumor cells (internal control), were given drinking water according to their specified group. Mice were observed on a daily basis for clinical evidence of intraocular tumor growth and followed-up until they died. The time interval between inoculation of tumor cells and death was recorded and the difference in survival time between the groups was analyzed. Tumor bearing eyes of all inoculated mice and lungs of a sample of 2 mice per group were harvested and sent for pathological evaluation, including H&E and immunohistochemical staining for S-100.

Results: At the day of tumor inoculation average FT4 levels were 7.74±0.44 pmol/l, 43.66±1.83 pmol/l and 27.48±2.25 pmol/l for groups A, B and C, respectively (p-value<0.0001). All inoculated mice showed clinical evidence of intraocular tumor growth. Pathological evaluation confirmed the presence of melanoma tumor cells in all enucleated eyes and lung metastasis observed in all sampled cases. The survival time of mice from groups A, B and C were 33.78±3.27 days, 26.45±2.38 days and 29.43±1.13 days, respectively (p-value≤0.02). The internal control group showed no signs of illness at any point and these mice were sacrificed 3 months after initiation of the experiment, suggesting that tumor existence and not the thyroid state was related to survival time.

Conclusions: An in-vivo uveal melanoma hyperthyroid animal model was found to shorten survival time compared to euthyroidism, whereas relative hypothyroidism had a protective role.

MuLV-based replication-competent retroviruses (RCR) target uveal melanoma response to hypoxia in a variety of cell lines

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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. The aim of this work was to evaluate whether the initial findings regarding uveal melanoma (UM) response to hypoxia is general or isolated to the C918 cells line.

Methods: Five UM cell lines (the aggressive primary UM cell line Mel270, and its metastases OMM2.3 and OMM 2.5, along with Mel92.1 and OMM1) were stably infected with Murine leukemia virus (MuLV)-based replication-competent retroviruses (RCR) expressing shRNA targeting CREB, HIF1, and HIF2 separately and all together from a single polycistronic RNA (X3). 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 UM cell lines efficiently albeit, not at the same rate of infection, and knocking down the mRNA and protein levels of CREB, HIF1 and HIF2. However, they all showed a lower sensitivity to hypoxia when compared without previous results from similar experiments with HepG2 as the target of the investigation.

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

Ruthenium-106 plaque brachytherapy in the primary management of ocular medulloepithelioma

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Purpose: To report the outcomes of ruthenium-106 plaque brachytherapy in the primary treatment of medulloepithelioma, a rare intraocular tumour of the non-pigmented ciliary epithelium

Methods: Retrospective interventional case series.

Results: There were 5 eyes treated with primary brachytherapy and 1 eye, with a rapidly enlarging mass and iris neovascularisation, required primary enucleation. Mean age at time of presentation was 58 months and 67% were male. In the brachytherapy group, all 5 eyes had a cystic ciliary body mass with lens changes (sector cataract and notching). The tumour apex dose was a mean of 46 Gy (median 50 Gy, range 40-50 Gy). During a mean follow-up time of 25.6 months, mean elevation of tumour on B scan decreased from 3.62 mm to 2.64 mm. Secondary enucleation was not required in any eyes receiving brachytherapy. Radiation related side effects were observed in two patients following treatment, and included one iris neovascularisation and one non-proliferative retinopathy.

Conclusions: The use of Ruthenium-106 plaque brachytherapy with close monitoring of tumour response is possible in selected eyes with medulloepithelioma.

Mutation analysis of MYB, MYBL1 and FGFR1 in grade I and diffuse pediatric glioma

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Purpose: Gliomas are the most common type of pediatric solid brain tumor. The molecular mechanisms that underlie the development and progression of these tumors are as yet unclear. A better understanding of the molecular mechanisms may improve diagnosis and treatment. In this study, we investigate a pediatric low grade glioma for specific mutations in MYB, MYBL1 and FGFR1.

Methods: 100 LGG was collected according to institutional and national IRB approval. DNA and RNA were extracted. PCR reaction to detect hotspot mutation in IDH1 R132 and IDH2 R172 was performed in 31 and 29 samples respectively. Validation was conducted by direct sequencing. To detect mutations in MYB, MYBL and FGFR1, the streptavidin-coupled Dynabeads method was optimized.

Results: No mutations were detected in IDH1 (0/31), or in IDH2 (0/29). Analysis of the fusion, deletions and mutations of MYB, MYBL and FGFR1 are under investigation.

Conclusions: The lack of IDH 1/2 mutation in this study is supported by the literature. Mutations in MYB, MYBL and FGFR1 genes were recently reported to characterize diffuse gliomas but not grade I. We optimized a method to analyze gene variations and correlated the pathological grade with prognosis. The clear identification of the glioma tumors may provide an improved treatment for the children.

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Periocular Pilomatrixoma: a retrospective analysis of 16 cases

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Purpose: Pilomatrixoma is a benign tumor of the hair follicle, occurring more frequently in the head and neck. There are relatively few published large case series in the ophthalmic literature that report the epidemiological, clinical and histopathological characteristics of the tumor. The purpose of our study was to evaluate additional case series of patients with periocular pilomatrixoma, treated in our institute from 1995 to 2011.

Methods: A retrospective analysis of all cases with periocular pilomatrixoma treated during 16 years was made. Data was collected regarding the age at the time of excision, gender, tumor location, tumor dimensions, suspected clinical diagnosis before biopsy, gross appearance, histopathological features, treatment, recurrence, and other syndromes related and family occurrence.

Results: Only 16 cases with pilomatrixoma were treated during 16 years. Most of the cases (69%) presented in the first two decades of life with female predilection (62.5%). The most common affected site was the upper eyelid (62.5%). All patients were asymptomatic. Various diagnoses were suspected clinically prior to surgical removal and histopathological confirmation of the tumor, and only in 18.75% pilomatrixoma was suspected. Simple resection was carried out in all cases. No recurrence or malignant transformation was reported.

Conclusion: Pilomatrixoma is a relatively infrequent periocular tumor which isn't usually recognized clinically. The findings of the current case series, which is one of the largest published thus far in the ophthalmic literature, are in concordance with the other series of pilomatrixoma, confirming the epidemiological, clinical and histopathological features of this tumor in the periocular region.

Comparison of treatment modalities for circumscribed choroidal hemangioma

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Purpose: To determine the therapeutic outcome for different treatments of circumscribed choroidal hemangioma (CCH)

Methods: Retrospective analysis of CCH cases. Efficacy of treatment was determined by visual acuity (VA), height on B-scan and OCT central retinal thickness change. Photodynamic therapy-treated cases were subcategorized based on laser application settings. Descriptive statistical analysis and Mann-Whitney test were used to evaluate the findings.

Results: There were 52 consecutive cases with CCH. These were managed with external beam radiotherapy (EBRT) (22/52, 41.5%, mean follow-up 40.3 months), photodynamic therapy (PDT) (10/52, 19%, mean follow-up 38 months), plaque radiotherapy (2/52 4%, 61 months) and observation alone (18/52, 34%, 33 months). VA (decimal) was improved by 0.22±0.34 with EBRT and 0.2±0.33 with PDT (p=0.77, Mann-Whitney). Height change (mm) recorded was -1.7±1.5 with EBRT vs -0.9±0.9 with PDT (p=0.1). For different PDT settings (standard vs double-duration) there was no statistically significant difference for VA (0.07±0.32 vs 0.4±0.26, p=1.33), but a significant anatomic effect on height reduction (-0.4±0.7. vs -1.6±0.6, p=0.02).

Conclusions: EBRT appears to be equivalent with PDT in CCH management with regards to post-treatment VA and tumour height. However, double-duration PDT had a more significant therapeutic outcome in comparison to standard settings.

Comparing the incidence of ocular hypertension after penetrating keratoplasty and deep anterior lamellar keratoplasty

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Purpose: The incidence of postoperative glaucoma after corneal transplant procedures varies widely in the literature. The aim of this study was to determine the incidence of ocular hypertension and glaucoma after penetrating keratoplasty (PKP) compared to deep anterior lamellar keratoplasty (DALK), and to assess whether the indication for the keratoplasty or the type of procedure contributes more for developing ocular hypertension.

Methods: Charts of 62 eyes post penetrating keratoplasty or deep anterior lamellar keratoplasty were reviewed retrospectively. Data included: Demographic information, preoperative intraocular pressure (IOP), indication for corneal transplant surgery, type of corneal surgery, postoperative IOP measured at days 1-5, 14-21 and at the last visit. IOP was measured by Goldmann Applanation Tonometer or Tono-Pen XL. Ocular Hyperntesion Post Keratoplasty was defined as the persistence of raised IOP (>21mmHg), one month after the procedure.

Results: PKP was performed in 44 eyes and DALK was performed in 18 eyes. Ocular hypertension developed in 10 (22.7%) of the eyes that underwent PKP and in 0 (0%) eyes in the deep anterior lamellar keratoplasty group, within 10 months of average follow-up. Those who underwent DALK had a significantly lower probability for developing ocular hypertension as compared with those treated with PKP ($P<.0001$, $\chi 2=1606$,,Cox Proportional Hazards model).

Conclusions: The incidence of ocular hypertension following PKP was higher than following DALK. The type of the keratoplasty procedure contributed more than the indication for developing ocular hypertension.

DSPEK - Descemet's stripping pseudo endothelial keratoplasty

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Purpose: Background: Descemet's Stripping Pseudo Endothelial Keratoplasty (DSPEK) is a posterior lamellar surgery in which the recipient's Descemet's membrane is replaced by a silicone implant. This implant acts as an artificial fluid barrier in the posterior surface of the cornea .Purpose**:** To assess the feasibility of DSPEK surgery in an animal model, and to investigate its efficacy.

Methods: 12 rabbits underwent Descemet's stripping in their left eye, in eight rabbits an 8-10.5 mm silicon layer was implanted using an air bubble for its attachment (in a similar way to DSAEK operation). 4 rabbits were left as a control group. Follow up was 1-8 weeks and still ongoing. We used Slit-lamp, pachymetry, histology and anterior segment OCT for the follow up.

Results: The average corneal thickness prior to surgery was 374 microns (+\\- 20), the average corneal thickness of the control eyes was 1650 (+\\- 400) microns. Five out of the 12 eyes tested demonstrated primary failure due to implant detachment, 2 rabbits maintained a clear cornea for a week, followed by the development of corneal edema, 1 rabbit showed a remark recovery of corneal edema following implant exchange, There was no apparent inflammatory reaction during the follow up in the tested eyes.

Conclusions: The preliminary results suggest a possibility of using a fluid barrier as a substitute for endothelium in the treatment of corneal edema: As long as an attached implant was achieved, a positive effect on corneal edema was demonstrated. Larger group samples and longer period of observation is needed.

Objective and subjective assessment of the KBA contact lens for keratoconus.

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Purpose: This prospective clinical study assessed Keratoconic -bi-aspheric (KBA) RGP Hexafilcon A lenses in keratoconus patients (KC) with nipple cones.

Methods: After approval from the ethics committee, patients recruited to the study signed an informed consent. The lenses were fit according to standard protocol. The lenses were dispensed for two weeks with oral and written instructions. Corrected and uncorrected Snellen decimal visual acuity (VA) and L80+ wavefront aberrometer higher order aberration measurements were compared using a paired two tailed t-test with 95% confidence. The Efron scale based physiological assessment and subjective 5-point scale questionnaire were analyzed.

Results: Three male and 4 female subjects (11 eyes; mean age: 34.14 ± 14.11, range: 21-60) were included. Approximately 3 BC modifications from the diagnostic lens were necessary such that 80% (9 eyes) were 0.16 mm steeper, and 27% (3 eyes) were 0.19 mm flatter than the diagnostic lens. Both distance and near VA improved significantly with the lenses (D: 0.04±0.02 and 0.33±0.30; N: 0.66±0.22 and 0.94±0.12; $p<0.001$). 54% (6 eyes) were grade 0, 27% (3 eyes) were grade 1 and 18% (2 eyes) were grade 2. Subjects reported an average of 7.0 ± 2.7 hours of wear, with good scores (>3) in visual stability, satisfaction with VA at three distances, quality of vision in dim light, improvement of mood and quality of life, and low scores (<3) in feeling of foreign body or pain during wear, red eye, eye itch, difficulty with lens removal, and night glare. The total RMS error was reduced significantly with the KBA lenses

Conclusions: KBA lenses can provide up to 7 hours of comfortable wear, significantly improved VA and total RMS aberrations, with subjective satisfaction, alongside minimal staining. The number trial lenses can be reduced by fitting a diagnostic lens 0.8mm steeper than the flattest keratometry reading.

Objective and subjective comparison of three fitting approaches for the Rose K2 lens for keratoconus

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Purpose: The Rose K2 is an aspheric rigid gas permeable contact lens with a standard fit of light apical touch (AT). The Collaborative Longitudinal Evaluation of KC study fit these lenses either flatter or steeper than AT which may result in different pre-corneal tear thicknesses that affect visual quality. In addition, a greater touch may reduce higher order aberrations (HOA). This study systematically compared standard AT with 0.1 mm flatter (FAT) or steeper (SAT) fitting approaches to determine the optimal objective and subjective fit.

Methods: This prospective non-dispensing study was approved by the ethics committee, and subjects with varying degrees of KC signed a statement of informed consent. The base curve of the lens from the trial set was modified until an obtaining an acceptable AT fit. The order of the lens fitting (AT, FAT, SAT) was randomized for each patient and the LogMAR visual acuity, FACT chart peak contrast sensitivity (CS) and peak CS spatial frequency (SF), and L80+ wavefront aberrometer HOA were measured. The parameters were compared using a one-way repeated measures ANOVA with a significance level of 95%.

Results: :Two male and six female KC subjects between the ages of 23-35 (mean age: 28.2± 5) participated in the study. The mean LogMAR VA (AT:0.13 ± 0.03, FAT: 0.16 ± 0.03, SAT: 0.16 ± 0.03) and mean peak CS (AT: 44.8 ± 4.6, FAT: 52.3 ± 7.8, SAT: 48.9 ± 7.3, (%)) were not significantly different (Fdf= 2,12=0.44; P=0.65; Fdf= 2,12=0.43; P=0.65, respectively). However, the SF of the peak CS (AP: 5.1 ±0.4, FAP: 9.2 ±1.5, SAP: 7.7 ±1.5, (cpd)) was significantly different (Fdf= 2,12=6.72; P=0.005) between the AT and FAT (Tukey-Kramer Multiple Comparisons Test). The total RMS, HO RMS, and coma were not significantly different for all fits (p>0.05).

Conclusions: The type of RoseK2 fit does not influence the most parameters of visual quality significantly. However, when debating between the AT and FAT fittings, the AT fit yields better CS performance, which can affect visual quality.

Corneal biomechanical properties in keratoconic, myopic and hyperopic eyes as measured with a Scheimpflug-based tonometer

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Purpose: Background: Keratoconus, a progressive assymetric corneal ectasia, is diagnosed on clinical basis along with additional tests as pachimetry and corneal topography. Current diagnostic methods have high sensitivity for advanced stages, but poor diagnostic value in preliminary stages (i.e "forme-fruste" keratoconus). Past attempts to use the Ocular Response Analyzer to characterize keratoconic corneas in an effort to establish an early diagnostic tool were unsuccessful. The Corvis ST (OCULUS OptikgerÃ¤te GmbH), a novel non-contact tonometer, records the dynamic reaction of the cornea to an air impulse, calculating various parameters, which can presumably help identify early forms of keratoconus. Purpose: To evaluate various corneal biomechanical properties among keraoconus patients in comparison with patients with myopia or hyperopia, and establish parameters that can be used for early diagnosis of keratoconus.

Methods: The corneal biomechanical properties of 36 keratoconic (KCN) eyes, 109 myopic eyes (MY) and 12 hyperopic (HY) eyes, measured using the Corvis ST, were reviewed retrospectively. Statistical analysis was performed on the data in order to control for confounders (IOP, pachymetry, and first applanation time).

Results: In the KCN vs. MY comparison, the first applanation deflection amplitude (0.089±0.017mm vs. 0.099±0.039mm respectively) and the simulated non-contact first applanation time (NTSIM-A1) (7.412±0.331ms vs. 7.66±0.745ms respectively) were significantly different after controlling for confounders. In the KCN vs. HY no significant difference was found in any parameter. No parameter was found significant to differ between the KCN group and the MY & HY groups combined.

Conclusions: Two parameters were found to facilitate early distinction of keratoconus from myopia. However, most parameters overlapped significantly and could not provide proper distinction between keratoconic and non-myopic eyes. Therefore, the findings can only be used as an adjunct to a thorough clinical examination and customary diagnostic tools.

Stiffening of rabbit sclera by bacteriochlorophyll derivative WST11 using near infrared light

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Purpose: To evaluate the efficacy of photochemical stiffening of the sclera by WST11 and near infrared (NIR) on enucleated rabbit eyes for the treatment of progressive myopia.

Methods: Four rabbit eyes were enucleated post mortem and treated topically with WST11 2.5 mg/ml for 30 minutes on the superior or inferior sclera, followed by external illumination with NIR at 10mW/cm2 for 30 minutes by a diode laser at 755nm. The opposite side of the sclera served as control. After the treatment, the eye was dissected to superior and inferior halves. Scleral equatorial strips, 4±0.2mm in width, were cut with a self-constructed double-blade cutter. Stress-strain measurements were performed using a biomaterial tester.

Results: After WST11/NIR the ultimate stress increased by 174% from 2.77±0.99 MPa in the non-treated sclera to 7.6±0.99 MPa after treatment. Young's modulus increased by 200% from 15.2 ±7.5 MPa in the non-treated control sclera to 45.6±3.9 MPa after WST11/NIR treatment.

Conclusions: WST11/NIR treatment significantly increases the biomechanical strength of rabbit sclera and may become a treatment for progressive myopia.

Photorefractive keratotomy for high myopic patients surgery outcomes

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Purpose: :To evaluate the outcome of photorefractive keratotomy for tearting patients with high myopia and myopic astigmatism

Methods: Retrospective analysis of 492 eyes with high myopia (spherical equivalent <=-6D) who underwent photorefractive keratotomy (PRK) without MMC using WaveLight® EX500 Excimer Laser between January 2013 to July 2013. Patient files were analyzed for outcome and complications rate.

Results: Two hundred sixty nine (54.7%) were men. Mean age was 25.7 ± 6.52 years. Mean follow up was 80.34 (4-309) days. Mean Subjective spherical equivalent before and after surgery were -7.3D ± 1.71D and 0.42D ± 0.63D respectively. Pre-operative mean Central Corneal Thickness (CCT) was 523.75 micron and was reduced to 389.41 micron post-operatively (P<0.001). Mean Uncorrected visual acuity (UCVA) Pre-operative and post operative was 1.96 LogMAR ± 0.19 and 0.1 LogMAR ± 0.14 respectively. Mean best corrected visual acuity (BCVA) was 0.07 LogMAR ± 0.07 and 0.06 LogMAR ± 0.07 respectively.

At the last follow up 60.5% of the patients were within ±0.50D from emmetropia and 87.1% were within ±1.00D from emmetropia. Corneal haze was documented in 19 eyes (3.9%).

Conclusions: Photorefractive keratectomy among high myopic patients may be a safe and effective procedure with a low complication rate.

Corneal haze following photorefractive keratectomy- prevalence and risk factors

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Purpose: to investigate the effect of preoperative and intra-operative parameters on the incidence of corneal haze following photorefractive keratectomy (PRK).

Methods: A retrospective case control study included 7535 eyes (3338 patients) that underwent PRK between 2011-12 in Care vision clinic. We reviewed the incidence and severity of postoperative haze and its correlation to various factors such as: preoperative refraction, age and application time of Mitomycin C (MMC) during surgery.

Results: The Incidence of haze grade 1 peaked 2 months following surgery. Average time of haze detection was 68.8±6 days (average±SEM). Haze grade 2 peaked 3 months following surgery on average detection time of 87.1±13 days. Incidence of haze grade 3 peaked 4-6 months following surgery. Average detection time was 115.2±17.4 days. Comparison of average detection time between haze grade 1 and 3 was statistically significant ($p=0.02$).Overall 10.8% of the patients underwent hyperopic PRK developed haze versus 1.3% of myopes ($p=0.0001$). Haze incidence was higher in high myopes(>-6D) than in low-moderate myopes (0D to -6D), ($p=0.002$). Patients with high astigmatism (≥3) had more incidence of mild and moderate haze ($p<0.05$) than patients with low astigmatism. Haze incidence was significantly lower ($p<0.05$) within the moderate myopia group which received longer MMC application time (≥40 sec) than shorter one (<40sec). This trend was similar in hyperopia and high myopia. Eyes that underwent epithelial removal with alcohol developed more haze comparing to eyes that underwent t-PRK ($p=0.01$), specifically mild haze ($p=0.0001$) Multivariate regression analysis showed a significant effect of preoperative spherical equivalent and thick ablation depth ($p<0.0001$) on the severity of haze. However, other factors such as MMC application time, preoperative average k, preoperative cylinder and age were not statistically significant ($p>0.05$). Multivariate regression analysis also revealed that age, size treatment zone, preoperative spherical equivalent and haze had a significant effect on the safety and efficacy indexes of the PRK treatment ($p<0.02$).

Conclusions: Hyperopic correction and large attempts of myopic and astigmatism correction are associated with a higher incidence of haze. Longer MMC application time may assist in preventing haze in moderate myopia.

Simultaneous photorefractive keratectomy and collagen crosslinking for patients with an increased risk profile

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Purpose: Toasses surgical outcomes and complication profile in patients with an increased surgical risk undergoing simultaneous photorefractive keratectomy(PRK) and collagen crosslinking (CXL).

Methods: Eyes of patients classified as having high-risk for corneal ectasia by the surgeon were included. They were treated with photorefractive keratectomy immediately followed by collagen crosslinking with UV/riboflavin. The main outcomes were refractive stability, mean corneal keratometry, mean central pachymetry and the occurrence of postoperative complications such as haze and corneal ectasia.

Results: The study evaluated 136 eyes of 77 patients who were treated with PRK followed immediately by CXL. Mean patient age was 27.69 ± 6.6 years. Mean Follow-up was 367.16 ± 196.5 days (range 96-778). Pre-operative mean spherical equivalent (SE) was -4.49 ± 2.81 Diopter (D), whereas at the last follow-up examination, it was significantly reduced (P<0.001)to-0.02 ± 1.01 D (range 3.13 - -6.13 D). Pre-operative Central Corneal Thickness (CCT) was 495.52 ± 40.85 micron and was significantly reduced to 371.48 ± 47.56 micron post-operatively (P<0.001). Pachymetry remained stable throughout follow up. At the last follow up 69.9% of the patients were within ±0.50D from emmetropia and 88.2% were within ±1.00D from emmetropia. The best corrected visual acuity was 0.06 ± 0.09 LogMAR pre-operatively and 0.07 ± 0.10 LogMAR post-operatively, which was not a statistically significant change (P = 0.28). Pre-operative Uncorrected distance visual acuity (UCDA) was 1.38 ± 0.61 LogMAR and improved significantly (P<0.001)to 0.13 ± 0.21 LogMAR at the last follow up

Conclusions: Simultaneous photorefractive keratectomy and collagen crosslinking in eyes on the lower tier of suitability to refractive surgery may be a safe and effective procedure in this select patient group.

Pain control after excimer laser photorefractive keratectomy: tetracaine 0.3% versus benoxinate 0.15%.

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Purpose: To evaluate the role of diluted benoxinate (localin) 0.15% versus diluted tetracaine 0.3% versus artificial tears in controlling pain after excimer laser PRK.

Methods: 87 consecutive patients that underwent PRK (with laser epithelial removal) were treated with with either Benoxinate 0.15% PRN (up to QID) (n=32), Tetracaine 0.3% PRN (up toQID) (n=32) or Artificial tears PRN for the 5 days following surgery in addition to the regular treatment regime. Daily telephone questionaires were conducted to evaluate the amount of ocular pain, burning sensation, photophobia and epiphora. as well as usage of those drops length of effect.

Results: Ocular pain reports were similar in the 3 groups during the first 3 post-operative days. On day 4 the Benoxinate group reported less ocular pain while on day 5 both Benoxinate and artificial tears had reduced ocular pain. Burning sensation was somewhat higher in patients treated with either Benoxinate or Tetracaine during the first 4 post-op days. On days 5 Tetracaine seemed to do worse that the others. Photophobia and epiphora were similar in all groups on day 1 and 2 while on days 3-5 after surgery Benoxinate had the best results and Tetracaine the worst.

Conclusions: Using Benoxinate 0.15% PRN after PRK might mitigate discomfort while Tetracaine 0.3% might prolong healing time

Pain after excimer laser photorefractive keratectomy: the effect of various epithelium removal techniques

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Purpose: To evaluate the effect of epithelium removal technique on the amount of post-operative pain and discomfort after photorefractive keratectomy(PRK)

Methods: 128 consecutive patients that underwent PRK had their corneal epithelium romoved either by 20% alcohol manual removal (n=39),by trans - epithelial PRK(T-PRK, n=47) or by LASEK with 20% alcohol (n=42).Daily telephone questionnaires were conducted to evaluate the amount of ocular pain , burning sensation, photophobia, and epiphora for the first 5 days after surgery

Results: Ocular pain reports were lower in the LASEK group for the first 3 post-operative days.On day 4 and 5 T-PRK patients seemed to suffer the least ocular pain.Burning sensation and photophobia were somewhat higher in the alcohol PRK group during the first 3 post-op days and lowest in T-PRK on days 4-5.Mean epiphora score was similar in the 3 group on days 1-3(relatively low in LASEK)and lowest in T-PRK on days 4-5.

Conclusions: During the first 1-3 days after PRK the LASEK method had the best scores in all symptoms tested .On days 4 -5 post-op trans epithelial PRK seemed to have the best symptomatology probably to its faster healing.

Laser refractive surgery aimed for monovision correction - success rates and complications

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Purpose: To estimate the success rate of laser refractive surgery in comparison to intended results, when aimed for a mild myopic target refraction versus emmetropic target refraction, as part of monivision laser treatment

Methods: Visual acuity and refraction were recorded in subjects undergoing laser refractive surgery for monovision correction before and following the operation. The resulting visual acuities and refraction were compared with the target values and also between the eyes aimed for myopia and those aimed for emmetropia

Results: :the study evaluated 1009 eyes that underwent laser refractive surgery. Four hundred and forty four (44%) were men. The mean age was 45.36 ± 5.16 (35-59). Four hundred and ninety five (49.1%) eyes were targeted for emmetropia. Subjective spherical equivalence prior to surgery was -3.27 ± 2.53. Post-surgery it was -0.03 ± 0.52 in the emmetropic group and -1.0 ± 0.71 in the myopic group. In the target emmetropic group mean uncorrected visual acuity (UCVA) pre-operative and post-operative was 1.4 LogMAR ± 0.6 and 0.05 LogMAR ± 0.13, respectively. Mean best corrected visual acuity (BCVA) was 0.02 LogMAR ± 0.035 and 0.023 LogMAR ± 0.07, respectively. In the target myopic group the mean uncorrected visual acuity (UCVA) pre-operative and post-operative was 1.43 LogMAR ± 0.6 and 0.38 LogMAR ± 0.3, respectively. The mean best corrected visual acuity (BCVA) was 0.03 LogMAR ± 0.06 and 0.03 LogMAR ± 0.1 respectively. The difference between the spherical equivalence post-surgery and the planned spherical equivalence was -0.13 ± 0.53 in the emmetropic group as opposed to -0.21 ± 0.87 in the myopic group (p=0.166). BCVA prior to surgery compared to post surgery was -0.001 ± 0.066 in the emmetropic group vs 0.006 ± 0.09 in the myopic group (p=0.46).

Conclusions: This study delineates the success rate of refractive surgery in target emmetropic vs. myopic patients. There was a trend towards a bigger error margin in final spherical equivalence when targeting for myopia, yet both groups achieved comparable post-surgical BVCA.

Long term visual outcomes and complications of combined scleral and iris fixation of posterior chamber intraocular lenses

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Purpose: To evaluate the long term visual outcomes and safety of combined scleral and iris fixation of posterior chamber intraocular lenses (PCIOL).

Methods: A retrospective chart review of all patients with irido-scleral PCIOL fixation between 2000-2010.

Results: The charts of 29 patients (38 eyes) were identified. The mean age at surgery was 29.5 years (range 4.5 to 95 years). The mean follow up time was 50.2 months (range 1 to 136 months). Twenty-five eyes (65.8%) required surgery due to crystalline lens dislocation, 11 eyes (29%) due to aphakia and 2 eyes (5.2%) due to PCIOL dislocation. Simultaneous pupiloplasty was needed in 8 eyes (21%). The mean logarithm of the minimum angle of resolution (logMAR) visual acuity was 0.74±0.53 (range 0.1 to hand motion) preoperatively and 0.39±0.39 (range 0 to counting fingers) postoperatively (P=0.0001). Older age and non-traumatic crystalline lens dislocation were associated with greater improvement in visual acuity (P=0.02). Eyes requiring surgical procedures other than lensectomy and/or anterior vitrectomy had less improvement in visual acuity (P=0.005). The most common postoperative complication was iris atrophy (17 eyes, 44.7%). Ocular hypertension was observed in 8 eyes (21%). Retinal detachment occurred in 3 eyes (7.9%) and PCIOL dislocation occurred only in 1 eye (2.6%).

Conclusions: Combined scleral and iris fixation of PCIOL provided favorable visual outcomes in long term follow up. Complications rate was not higher than either procedure alone. Stability of PCIOL was maintained through follow-up.

Lens epithelial cell growth on two different hydrophobic intraocular lenses anterior optical component

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Purpose: To investigate lens epithelial cells (LEC's) proliferation on the anterior aspect of the optical component of two hydrophobic intraocular lenses (IOLs).

Methods: Ten New Zealand white rabbits underwent crystalline lens evacuation and were randomly implanted with an AcrySof® (Alcon) IOL in one eye and a Tecnis® (AMO) IOL in the fellow eye. Biomicroscopy was performed one and two weeks after the surgery and the rabbits were then sacrificed. The eyes were enucleated and the IOLs with the capsules were stained with Hematoxylin and Eosin (H&E) to evaluate LEC's, large cells (macrophages and giant cells) and proteinaceous matrix areas along the edge of the capsulorrhexis on the anterior aspect of the IOLs optical component.

Results: : LECs were found on 10/10 AcrySof ® IOLs and on 0/10 Tecnis® IOLs, $P<0.001$. Areas of proteinaceous matrix deposits at the edge of the capsulorrhexis were found on 8/10 AcrySof ® IOLs and 0/10 Tecnis® IOLs, $P<0.001$. Large cells were found on 10/10 AcrySof ® IOLs and on 9/10 Tecnis® IOLs, $P=1.0$. No difference in the inflammation markers were found between the two groups.

Conclusions: LECs with corresponding proteinaceous matrix deposits were found significantly more on the anterior aspect of the AcrySof ® IOL compared with the Tecnis® IOL. There were no differences in the presence of large cells. Further investigation is required to explain our findings.

MicroRNA-184 is essential for corneal commitment and limbal stem cell homeostasis

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Purpose: Approximately 6 million people worldwide suffer from severe visual impairments or blindness due to corneal diseases. Corneal allogeneic transplantation is often required to restore vision; however, shortage in corneal grafts and immunorejections remain major challenges. In mammals, endogenous, noncoding RNA\'s, designated as microRNAs (miRNAs), specifically inhibit target messenger RNA, thereby silencing protein production or translation. Unfortunately, little consideration has been directed towards characterizing the expression of miRNAs in mammalian ocular tissues. In this study we aimed to identify new miRNAs that are involved in eye morphogenesis, limbal stem cells (LSC) homeostasis and diseases.

Methods: We recapitulated corneal epithelial embryonic commitment by differentiating induced pluripotent stem cells (iPSCs). Differentiated iPSCs were collected at different time points and were subjected to FACS analysis, immunofluorescent staining, and miRNA profiling. The expression profile of selected miRNAs was examined in different tissues and cells by in situ hybridization (ISH) and TaqMan assay, respectively. Knock-down and over-expression of specific miRNAs was further investigated in iPSCs, human limbal cultures to define the contribution of specific miRNA to corneal embryonic commitment and LSC function. Corneal pannus was subjected to ISH to investigate the expression of specific miRNA in pathology.

Results: MiR-184 had the highest hybridization signal in the developing cornea and lens. In adult cornea, miR-184 expression was restricted to progenitors or early differentiated cells in vivo and in vitro but was absent from the compartment of LSC or terminally differentiated cells. We demonstrated that miR-184 represses the stem cell marker cytokeratin 15 (K15), promoted differentiation and attenuated proliferation and clonogenic potential of epithelial stem cells. We thus assessed the possible involvement of miR-184 in LSC deficiency (LSCD). Interestingly, we observed an abnormal increase in miR-184 coupled with a decrease in K15 in patients' tissues. In addition, ectopic expression of miR-184 LSC-enriched culture resulted in a dramatic decrease in LSC clonogenic potential.

Conclusions: Altogether, these data indicate that miR-184 induces an escape from 'stemness' state while abnormal expression of miR-184 may lead to a decline in epithelial stem cell reservoir.

In-Vivo characterization of the ocular surface following transplantation of limbal stem cells on contact lenses: Towards treatment of LSCD

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Purpose: Limbal epithelial sheets are used to promote corneal surface reconstruction following limbal epithelial stem cell deficiency (LSCD). The aim of the present study was to evaluate the potential use of gelatin coated contact lenses (CLs) as a carrier of limbal stem cells (LSC) to the ocular surface focusing on the transition of LSC, phenotype preservation and re-epithelialization

Methods: Biopsies of limbal tissue were taken from naïve rabbit eyes and epithelial cells were isolated and cultured with 3T3 cells on gelatin coated CLs. The preservation of LSC phenotype was determined using p63α and ABCG2 immunostaining. CLs seeded with LSC were labeled with PKH26 and an autologous transplantation was performed following surgical keratectomy. Transition and phenotype of the labeled cells on the corneal surface were evaluated in whole-mount corneas using the SC markers p63α and ABCG2 while epithelial differentiation was evaluated by CK3 and CK19 markers, for corneal and conjunctival cytokeratins, respectively. Slit- lamp microscopy examination with fluorescein eye staining was used for the evaluation of corneal re-epithelialization up to 15 days following transplantation

Results: Proliferation of limbal cells was observed on CLs with a 3T3 feeder-cell layer, showing holoclone formation and retention of viable stem or progenitor cell phenotype. A higher transition of cultivated cells to the ocular surface was observed following a dual 24 hr interval sequential CL transplantation, showing preservation of LSC phenotype in the corneal surface. Finally, an enhanced re-epithelialization was observed in the transplanted animals compared to the sham-transplanted

Conclusions: CLs containing LSC were shown as an ideal carrier for transferring cells to the ocular surface due to SC phenotype preservation, cell transition and friendly user replacement of CLs with no need of sutures. Thus, this novel technique may replace existing methods aimed for reconstruction of the ocular surface in LSCD patients.

Time dependent changes in biomarkers in the tear fluid following ocular chemical injury in rabbits

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Purpose: To monitor changes in tear fluid biomarkers that are involved in corneal inflammation and neovascularization, throughout the dynamic course of a chemical ocular injury in the rabbit model.

Methods: Rabbit eyes were exposed to sulfur mustard (SM) vapor and a clinical follow-up using slit lamp microscope was carried out up to 4 weeks. Tear fluid and corneal samples were collected at different time points post exposure. The levels of various pro-inflammatory cytokines and chemokines, including IL-1α and macrophage chemotactic factor (MCP) -1 were measured by ELISA.

Results: Typical SM-induced ocular injury was developed including a partially healed acute phase in all the exposed eyes, followed by a delayed pathology in 50%-80% of the eyes. The clinical manifestation of the acute injury included corneal erosions and severe inflammation and the delayed injury was characterized mainly by chronic inflammation and corneal neovascularization. Levels of IL-1α and MCP-1 were significantly elevated in the tear fluid following exposure. IL-1α levels were significantly elevated only during the acute injury, and were correlated to the levels in the cornea. MCP-1 levels in the tear fluid were elevated in all of the exposed eyes during the acute phase, but remained high mainly in the eyes in which neovascularization was developed, preceding the clinical manifestation of neovascularization. Interestingly, high levels of corneal MCP-1 were seen only in eyes displaying neovascularization, and could contribute to the elevated levels in the tear fluid at this stage of the injury.

Conclusions: Different profiles of IL-1α and MCP-1 levels were found during the dynamic course of the ocular injury in both the tear fluid and the cornea. The results point out towards different biochemical signaling that is involved in each stage of the injury. Moreover, MCP-1 levels in the tear fluid could be indicative of future neovascularization and the need for a preventive therapy

The effects of Nerve Growth Factor (NGF) on corneal injury associated with LSCD in a chemical burn model in rabbits

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Purpose: We have previously shown damage of corneal nerves following chemical injury that may contribute to development of a delayed-onset Limbal Stem Cell Deficiency (LSCD) clinically expressed by neovascularization (NV) and epithelial defects. The present study aimed to evaluate the therapeutic effects of trophic factors such as Nerve Growth Factor (NGF), on facilitating nerve regeneration and reducing the long-term corneal damage.

Methods: Chemical burn was induced in the right eyes of NZW rabbits, using sulfur mustard (SM) vapor, as previously described. NGF (100µg/ml in PBS), or enriched Fetal Bovine Serum (20% in PBS) were applied topically (x4/day for 12-16 days), starting before appearance of neovascularization (NV). Treatments were given either as a mono-therapy or in combination with Dexamethasone (0.1%, DEX, Dexamycin®, x4/day for the first week). A clinical follow-up was carried out up to 4 weeks. Animals were euthanized, eyes dissected and processed for histology and immunohistochemistry

Results: Treatment with NGF or serum deteriorated the clinical symptoms and increased the incidence of NV, a typical hallmark for LSCD. Moreover, the supplemental growth factors also reduced the improvement seen by DEX, when given as a combined therapy. Histological evaluation confirmed the clinical results. The treated corneas displayed stromal NV, abnormal epithelium, and decreased number of limbal epithelial stem cells (p63 immunohistochemistry). There was no beneficial effect on corneal nerves.

Conclusions: Supplement of trophic factors did not improve the clinical symptoms and the damage in the limbus, in the regime tested hereby. In contrast to our working hypothesis, the growth factors deteriorated the clinical status, thus raising questions regarding their multiple effects in the cornea. Further studies are needed to investigate the role of NGF and other trophic factors in the pathogenesis of delayed-onset LSCD

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Expression of human limbal epithelial stem cell markers and mRNA in long term repeated limbal cultures

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Purpose: To investigate whether repeated primary culturing of fresh and frozen human limbal tissue can give rise to cell colonies containing Limbal epithelial stem cells (LESC).

Methods: Corneo-scleral rings of cadaveric donated corneas were either used fresh or first underwent freezing and thawing. Limbal segments were cultivated under optimal conditions to yield a colony of cells. The limbal segments were then taken and reused in the same manner to grow sequential colonies(Ps). In order to ascertain the existence of LESC in the resultant colonies, expression of the LESC markers p63 and ABCG2 was quantified using immunofluorescent staining and by use of real-time PCR.

Results: Expression of p63 in colonies that grew from freshly cultivated corneoscleral rings as measured by immunofluorescence ranged from 45.57%±12.34% to 0 (P1 to P5, P<0.002). Expression of ABCG2 ranged from 26.28%± 11.29% to 0 (P1 to P6, P<0.002). In colonies that grew from frozen and then thawed corneoscleral rings expression of p63 ranged from 42.60%± 20.54% to 0 (P1 and P2, P<0.012) and that of ABCG2 ranged from 14.76%±4.41%to 0(P1 and P2, P<0.012). When compared to stromal cell cultures containing no epithelial cells,p values remained statistically significant (p<0.007) in all but the last of seven passages for freshly cultivated corneoscleral rings. For frozen and then thawed corneoscleral rings statistically significance (p<0.012) was shown for the first two out of four passages. In freshly cultivated corneo-scleral rings the quantitative expression of mRNA for p63, as calculated using real-time PCR, was 0.17%±0.46% (P<0.001) and 0.089±0.11% (P<0.001) for the P2 and P3, respectively compared to P1(Primary). The quantitative expression of mRNA for ABCG2 was 0.028%±0.01% (P<0.001) and 0.017±0.062% (P<0.001) for P2 and P3, respectively compared to P1.The relative expressions of p63 compared to ABCG2 were 0.691±0.024, 0.7±0.013 and 0.712±0.0138 for P1, P2 and P3, respectively.

Conclusions: Limbal tissue can be successfully subjected to repeated primary culturing, with resultant sequential colonies of cells. Some of the cells in the colonies express LESC characteristics. This process can also be implemented, though with lesser success, to cultivate colonies of cells with LESC properties after freezing and thawing of the limbal tissue.

Efficacy of subconjuctival Aflibercept versus Bevacizumab for corneal neovascularization in a rat model

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Purpose: To compare the Efficacy of subconjuctival Aflibercept (VEGF trap) Versus Bevacizumab for the treatment of corneal neovascularization in a rat model.

Methods: Corneal neovascularization was induced in male Sprague-Dawley rats by application of a mixture of 75% silver nitrate and 25% potassium nitrate to the corneal center of the right eye. Immediately after injury, subconjunctival 0.08ml VEGF trap (25mg/ml) was administered to 11 rats in group1, and subconjunctival 0.05ml Bevacizumab (25mg/ml) was administered to 12 rats in group 2. Corneal newly developed blood vessels were evaluated on days 1,3,7,9,13 by slit lamp biomicroscopy and by digital image capture and analysis (image J,NIH). In the control group, 6 rats were administered with subconjunctival 0.1ml saline solution 0.9% and followed by the same schedule. The presence of corneal new blood vessels was studied Histologicaly and by immunohistochemical staining of vascular endothelial cell.

Results: Corneal neovascularization was first observed clinically on day 3 after injury in the three groups studied. Spontaneous regression was observed on day 13 in all groups as well. In group I the area of neovascularization increased from 11.7% (±7) on day 3 to 12.3% (±9.9) on day 7, 15.5% (±10.2) on day 9 and regressed to 13.3% (±7.8) on day 13. In group II, the area of neovascularization increased from 10.9% (±6.7) on day 3 to 21.3% (±8.2) on day 7, 32.3% (±9.4) on day 9 and regressed to 19.3% (±13.2) on day 13. In the control group the area of neovascularization increased from 15.6% (±7.5) on day 3 to 29.7% (±10) on day 7, 22.5% (±3.2) on day 9 and regressed to 19.4% (±12.6) on day 13. In the rats treated with VEGF trap, the area of neovascularization was significantly lower on day 7 when compared to the control group ($p<0.005$) and on day 7 and day 9 when compared to the Bevacizumab group ($p<0.005$). The clinical findings were compatible with the histologic data and supported by immunohistochemical staining.

Conclusions: Subconjuctival administration of VEGF trap was found to be significantly more effective in inhibiting progressive corneal neovascularization induced by chemical damage in a rat model. These findings may have important therapeutic implications in clinical setting.

The effect of butyroyloxymethyl-diethyl phosphate (AN-7) on corneal neovascularization in a mouse model

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Purpose: Butyroyloxymethyl-diethyl phosphate (AN-7) is a histone deacetylase inhibitor, shown to effectively mediate apoptosis, inhibit tumor growth and induce reduction of vascularization. Our purpose was to examine if AN-7 has an inhibitory effect on corneal neovascularization (NV), induced by a chemical burn of the cornea in a mouse model.

Methods: Corneal neovascularization was induced in the right eye of 30 male C57BL mice, by application of a mixture of 75% silver nitrate and 25% potassium nitrate to the corneal center. Immediately thereafter, 10 mice received intraperitoneal (ip) injection of AN-7, 12 mice received AN-7 eyedrops and 12 mice served as a control. The groups were compared at constant time intervals from the corneal injury using image J analysis of the digital photography taken at each time. In addition, the photographs were graded by two masked examiners to determine the extent, centricity and density of corneal vascularization.

Results: Image J analysis showed that the corneal NV area was significantly reduced in the ip injected group when compared to the control group on day 10 ($p=0.04$) and day 14 ($p=0.03$). No significant difference was observed between the topical AN-7 eyedrops group to the control group at all time intervals. Extent, centricity and density of the corneal NV, did not show statistically significant difference between neither groups at any time interval.

Conclusions: Intra peritoneal injections of AN-7 had a partial inhibitory effect on corneal neovascularization induced by chemical injury in a mouse model. Further studies are warrant to determin the potential clinical significance of ip AN-7 treatment.

Treatment of adenoviral conjunctivitis with a combination of Povidone – Iodine 0.1% and Dexamethasone 0.1% drops

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Purpose: To determine the efficacy of a combination Povidone iodine 0.1% and Dexamethasone 0.1% eyedrops in the treatment of adenoviral conjunctivitis (EKC).

Methods: :In a prospective, randomized, controlled clinical trial, patients with recent adenoviral conjunctivitis (diagnosed clinically and confirmed by PCR) were randomly devided into 3 treatment groups: study group - received povidone – iodine 0.1% and dexamethasone 0.1% four times a day, control 1 group – received dexamethasone 0.1% four times a day and control 2 group – received lubricating eyedrops (Hypromellose 0.3%) four times a day. All patients were examined and filled a questionnaire before treatment and on the 3rd, 5th and 7th day of treatment. On each visit tear specimens were collected for analysis of the viral titer by real time PCR..

Results: We included in the study 78 eyes (26 in each group). Adenovirus type 8 was the most common pathogen (83% of cases). The fastest improvement in patients red eyes, eye itching, foreign body sensation, tearing ,chemosis, petechial subconjunctival hemorrhages, discharge, SPK and pseudomembranes was observed in the study group ($p<0.001$ for all symptoms). Those patients reached a near complete recovery in 5-7 days which was also confirmed by reduction in Adenovirus titers by PCR. The slowest improvement was in the control 2 group. Subepithelial infiltrates were observed in 44% of the control 1 group, 20% of the control 2 group and in 0% of the study group. The rate of reduction in Adenovirus titers was the slowest in the control 1 group (38% vs 46% in the control 2 group vs 92 % in the study group on 5th day of treatment ($p = 0.015$)).

Conclusions: The combination of Povidone iodine 0.1% and Dexamethasone 0.1% four times a day can reduce symptoms and expedite recovery in EKC patients.

Fornix Kenalog injection for thyroid orbitopathy

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Purpose: To compare the effectiveness of fornix Triamcinolone injection with systemic steroid therapy in patients with active thyroid orbitopathy.

Methods: An interventional prospective pilot study was performed on patients diagnosed with active thyroid orbitopathy [Clinical Activity Score (CAS)>or = 3]. Patients included in the study were treated with three upper and lower fornix injections of Triamcinolone acetate 20mg (40 mg/ml) at 4 weeks interval. Each patient underwent full ocular examination, clinical activity assessment, color test, blood sugar, visual field at 1 monthly interval for a period of 6 months. Extraocular muscle thickness was measured by ultrasound examination at entrance to the study and at the last visit. Thyroid antibodies levels were measured for every patient at entrance to the study and after 4 months.

Results: 11 eyes of 7 patients were treated in our study. Initial CAS was 3.81±1.80 [5.00] and fell to 0.63±0.72 [0.50] over 6 months follow up. There was a significant difference in CAS between the baseline and the following visits (according to Friedman test, p-value < 0.0001). The two factors that were significantly influenced by treatment with fornix injection were conjunctival hyperemia and lid retraction (p-value<0.005). Ultrasound examination also showed certain changes. Side effects included a transitory increase in intraocular pressure in one patient which was controlled with topical medication.

Conclusions: A series of three fornix Triamcinolone injection at 4 weeks intervals reduces the inflammatory signs of thyroid- related orbitopathy, as measured by clinical activity score. It has no effect on thyroid antibody levels. It is a simple, effective, safe treatment which eliminates the adverse reactions associated with systemic corticosteroid use.

Cross-talk of ciliary epithelium cells and trabecular meshwork cells: new insights in understanding glaucoma

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Purpose: Human non-pigmented cilliary epithelium (NPCE) includes neuroendocrine and steroidogenic activities. The neuropeptides released by the NPCE in the aqueous humor can serve as messengers to communicate with human trabecular meshwork cells (HTM) and regulate intraocular pressure. The aim of the study is to test the hypothesis that HTM cells are affected via the aqueous humor by unknown factors released by the NPCE. These factors could result in morphological changes, alternations in the balance of protein kinases/phosphatases activities and changes in matrix metalloproteinases (MMPs) expression profile.

Methods: The cellular cross-talk of NPCE and HTM cells were studied by means of direct co-culture system. HTM cells were co-cultured with NPCE cells for 0.25, 0.5, 1, 2, 4 and 8 hr. The effects of NPCE cells on HTM cells were examined, focusing on activation of p38, ERK kinase pathways, phosphatases and MMPs activity. Cellular extracts were analyzed by Western immunoblot using various phospo-specific antibodies. MMPs levels were determined by gelatin zymography. Acid phosphatases and alkaline phosphatases activity were determined by DiFMUP assay.

Results: Applying an in vitro co-culture model of NPCE and HTM cells, we demonstrated that communication between NPCE and HTM cells, appear to promote MMP-9 expression in the HTM cells after 8 hr compared to control. In addition, our results revealed that interaction of HCM and NPCE cells led to activation of MAPKs signal transduction pathways within 5 min of co-culture. Phosphorylation of ERK1/ERK2 peaked at 15 min, then decreased over time and was barely detectable at 4 or 8 hr. Phosphorylation of p38, which was weaker than that of ERK, was maximal by 10 min and diminished by 60 min. Alkaline and acid phosphatases decreased within 10-15 min of co-culture as compared to control.

Conclusions: In this study, it was observed that within 10-15 min of co-culture with NPCE cells, HCM cells revealed increase levels of MAPK kinases, whereas alkaline and acid phosphatases decreased as compared to control. This may support the crosstalk between NPCE and HTM cells. However, more detailed experiments have to be design to determine the relationship between the MMP system, MAPK kinases and phosphatases. Manipulation of this and related HTM signal-transduction pathways may provide targets for developing improved glaucoma treatments.

RPTP- σ over expression in trabecular meshwork cell line as a model for phosphatases role in the ocular drainage system evaluation

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Purpose: :To explore the role of phosphatases in the eye drainage system, by over expression of Tyrosine phosphatase receptor in normal human trabecular meshwork (NTM) cell line.

Methods:Following transfection by PTPR-σ [Protein Tyrosine Phosphatase Receptor-sigma] transfection efficacy was evaluated by flow cytometry. RPTP-sigma activity was evaluated by Western blot, RPTP-σ location was demonstrated by immunocytochemistry and confocal microscopy. Next we examined the differences between NTM and NTM transfected [NTMT] cells. Cells viability was tested by MTT following oxidative stress, MMPs activity was evaluated by zymography. Following oxidative stress differences between phosphatases activity were assessed by the DiMFUP method. NTMT cells and their controls were assayed under the presence of specific RPTP-σ phosphatases inhibitor for RPTP-σ activity by western blot & MMPs activity by zymography.

Results: Transfection efficacy measured along GFP expression, at 48 hrs. post transfection reveled GFP expression is significantly higher (X3.8) in transfected NTM cells than in controls ($P<0.0001$). Western blot analysis showed (X2.25) significant increase in RPTP-σ activity in NTMT cells than in controls ($P<0.01$). No significant differences in cells vitality were found between NTMT and control cells, after oxidative stress. We recognized with high probability, 4 different MMP forms. The MMPs were assigned according to their MWw in NTM cell: Pro form MMP-2, Active form MMP-2, Pro form MMP-9, Active form MMP-9. Pro form MMP-2 and Pro form MMP-9 showed significant higher activity (X2.18,$P<0.01$) and (X1.9,$P<0.05$ respectively) in NTMT cells than in controls. Serine /Threonine phosphatases activity after oxidative stress was significantly higher in NTMT cells than in controls. Phosphatases specific inhibitor (PTP-IV) caused 15% RPTP-σ activity inhibition in NTM cells. In transfected cells significant (31%, $P<0.001$) inhibition in RPTP-σ expression was evaluated. In transfected cells under PTP-IV exposure, a significant inhibition in Pro form MMP-9, Pro form MMP-2, Act form MMP-9 activity was found (48%, 35%,78% respectively). Active form MMP-2 was not affected by RPTP-σ inhibition in NTMT cells. In NTM cells found significant 27% Pro form MMP-9 activity inhibition.

Conclusions: Our findings suggest RPTP-σ activity levels affects NTM cells ability to activate MMPs forms. According to our results, PTRP-σ a is constituently expressed in NTM cells

Ciliary derived exosomes and their roles within the drainage system as a pharmacological intervention target for glaucoma.

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Purpose: Exosomes are microvesicles of endosomal origin that are secreted, and their contents (proteins, lipids, DNA or microRNAs) can alter the physiological states of recipient cells. Based on the hypothesis that signaling does take place within the ocular drainage system, we intend to explore possible signaling communication between human non pigmented ciliary epithelial (NPCE) cells and the human trabecular meshwork (HTM) cells via exosomes as one of the key points for high intraocular pressure (IOP) homeostasis, and the role of IOP homeostasis in the pathogenesis of primary open angel glaucoma.

Methods: Exosomes have been purified from cell culture medium of NPCE cell line by ultracentrifugation. Dynamic light scattering (DLS) and Zeta Potential analysis were performed to determine the size and surface charge of nanoparticles in solution. Transmission electron microscopy (TEM) was used to validate exosomal morphology and integrity. In order to follow up the exosome interaction with HTM cells, NPCE derived exosomes were stained by two dyes with different fluorescent characters. NPCE fluorescently labeled exosomes isolated from NPCE conditioned medium were cultured with HTM cells. After incubation, HTM cells were fixed and stained using DAPI and actin antibody.

Results DLS analysis revealed characteristic exosomes size with 101±13.2 nm radius. Extracted exosomes showed a negative zeta potential of −20.9 ± 6 mV, due to the negatively charged phospholipid membrane. TEM exhibited a cup-shaped morphology with an average 50-100 nm size characteristic of exosomes. We confirmed the ability of HTM cells to uptake exosomes using confocal microscopy. After 2 hours of incubation fluorescently labeled exosomes were up taken by HTM cells**.**

Conclusions: Taken together, these findings suggest that NPCE cells release exosome-like vesicles and that these structures can be transferred into HTM cells, suggestive of a potential role in regulating HTM biology and involving in diverse physiological processes of HTM cells. However, more studies need to be done for exosome characterization; quantification and NPCE derived exosomes content analysis. Exosomal contents vary due to the source of origin and the physiological conditions of cells that secrete exosomes. These variations can provide insights on signaling between the NPCE and HTM cells and may then enable identification of the novel therapeutic pathways for glaucoma treatment.

Signaling between macrophages and trabecular meshwork cells and their potential contribution to glaucoma pathophysiology

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Purpose: In primary open angel glaucoma (POAG) aqueous humor (AH) encounters higher resistance on the drainage system that cause elevated Intraocular Pressure (IOP). Although the eye is considered, immune privilege, numerous studies showed evidence for the presence of lymphocytes and their role in the eye. It has been shown that cytokine and chemokine play a role in regulating AH outflow within the eye immune privilege, through the trabecular meshwork (TM). The immune system cells have an important role in release and recruitment of many cytokines and chemokines as well as immunoregulatory functions. Since the main risk factor for developing of POAG is elevated IOP, immune system factors can plays a role in POAG via cytokines and chemokines modulation. We hypothesis that macrophages growth medium contains various factors that might affects human TM cells changes in-vitro.

Methods: THP-1 monocytes following treated with Phorbol 12-myristate 13-acetate who acquire macrophages ability and are accepted as "Glia like" cells were seeded to 80% confluence. In parallel, NTM cells grown on cover slip to 80% confluence were transferred to the Glia like cells culture for different time points. TM cell lysate was then tested for MMPs activity, MAPK expression and phosphatases activity.

Results: Phosphorylate Erk/ total-Erk ratio and p38/ total-p38 ratio increases significantly in a time dependent manner up to 8hr and to 4hr respectively and decrease at 24hr post co-culture. In both Erk and p38 one may notice in a “bell trend”. Total phosphatases activity exam gives us the same “bell trend” as we seen for Erk & p38, but with no significant effect. The exposure to \"glia like\" macrophages cells increased MMP-9 levels in human TM cells over time up to 2 fold vs. the control. MMP-2 levels stay steady. MMP-9 & MMP-2 that were exposed to the Erk Inhibitor U0126 before their exposure to \"glia like\" macrophages cells showed similar decrease trend in their activity vs. their control.

Conclusions: Based on these results we hypothesize that the MAPK Erk pathway and the MMPs that were examined share a connection between them. These results suggest the involvement of glial cells in the regulation of the TM homeostasis and might be an intervention point for glaucoma treatment.

Digoxin derivatives with selectivity for the α2 isoform of Na,K-ATPase efficiently reduce intra-ocular pressure

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Purpose: Glaucoma is associated with increased pressure, which can be alleviated by reducing inflow or increased outflow of aqueous humour produced in the ciliary epithelium. The pigmented ciliary epithelium express the α1β1 isoform of Na,K-ATPase, and non-pigmented cells mainly express the α2β3 isoform. In principle, an Na,K ATPase inhibitor, with selectivity for α2, that penetrates the cornea could effectively reduce intraocular pressure, with minimal local or systemic toxicity.

Methods: Effects of topically applied cardiac glycosides, glycinamide digoxin (DGlyN) and methylamine digoxin (DMe), on intraocular pressure in rabbits have been assessed by their ability to either prevent or reverse acute intraocular pressure increases induced by 4-aminopyridine or a selective agonist of the A3 adenosine receptor. At zero time one drop of 4AP (40 mg/ml, 30 µl) or IB-MECA (1 µM, 30 µl) was administered to both eyes of each rabbit, and IOP measurements were made at different times as indicated in each experiment. For experiments in which the IOP was elevated for several hours, 4AP was added every 2 hours or IB-MECA every 1.5 hours. IOP (mmHg) was measured using a calibrated Pneumatonometer (Model 30, Reichert technologies).

Results: The basal IOP values for different rabbits are in the range 15-21mmHg. 4AP raised the IOP by 4.18±0.61mmHg (50 eyes). IB-MECA induced a significant but transient increase of 3.92±0.87 mmHg in IOP (12 eyes). Two relatively α2-selective digoxin derivatives, DMe and DGlyN, efficiently normalized the ocular hypertension. ΔIOP = 0.5±0.41 mmHg, 0.5±0.11 mmHg, for 0.5mM and 0.1mM DGlyN, 0 mmHg, 0.38±0.36 mmHg for 0.5mM and 0.1mM DMe respectively. When applied one hour after the first application of 4AP, which was added every two hours, DGlyN and DMe (1mM) reversed the initial rise in IOP within 30 minutes. Similar results were seen when using IB-MECA.

Conclusions: α2-selective digoxin derivatives may be of interest as novel drug leads for treatment of glaucoma.

An Overview of Research Done on Inherited Glaucoma in New Zealand Albino Rabbits

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Purpose: To create a new natural in vivo model for glaucoma research.The majority of animal research models for glaucoma are created by artificial obstruction of the aqueous outflow while creating destruction of the trabecular meshwork, obstruction of aqueous veins, introduction of substances in the iridocorneal angle such as alphachymotripsin,viscoelastic materials and others.The models are creating acute raise of the intra ocular pressure (IOP), fact that is far from the gradual raise of IOP in primary open angle glaucoma (POAG) in human. This methods are creating also inflammatory reaction that is a factor which does not exist in human POAG.

Methods: A number of seven rabbits, which were found suffering of inherited glaucoma,were selected from a normal animal house colony.An in breeding program started and a colony of first , second and third generation of glaucomatous rabbits was created

Results: A colony of 58 rabbits was achieved at the end of 18 months.In the first and second generation the IOP raised gradualy along three to six months following birth.The third generation presented high IOP with the birth and the aspect of the yes was identic to the buphthalmic eyes in human.The values of the IOP presented a range of 22 mm - 40 mm mercury.The IOP was stable on long term up to two years of life in the most extreme cases followed and kept the mentioned period of time.

Conclusions: The inherited glaucoma in rabbits mimic the development of glaucoma in humans.We have done several studies up today while searching the structural,metabolic, physiologic and neural aspect of the presented model.We will present the results of each one of the parameters mentioned above.

Long term results of combined phacoemulsification and express shunt operations

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Purpose: To present our results of combined phacoemulsification and Ex-PRESS shunt operations comparing preoperative vs postoperative visual acuity (VA), intraocular pressure (IOP) and number of anti glaucoma medications.

Methods: Retrospective study of all patients with chronic open angle glaucoma and cataract that underwent combined phacoemulsification and Ex-PRESS shunt implant surgery at Emek Medical Center. All patients were followed up in the Glaucoma clinic for a period of 18 months and more.Surgical success criteria were defined as an IOP greater than 5 mmHG and lower than 18 mmHG without any antiglaucomatic medication.

Results: 46 eyes of 40 patients were included. Mean age 72.34 yrs (range +/- 19.3), F: M 18:22. Period of follow was 18 months. 22 out of 46 eyes had pseudoexfoliation (47.8%). Among those 22 pseudoexfoliation eyes 16 (72.7%) had an IOP less than 18mmHg without antiglaucomatic medication at 18 months.Comparing preoperative to postoperative data: VA improved significantly. Preoperative and postoperative mean VA were 6/15 and 6/9, respectively, $P<0.05$. Mean preoperative and postoperative IOP were 25.6 +/- 19.4mmHg, and 15.56 respectively, ($P<0.05$).The amount of antiglaucoma medications number was reduced from 2.69+/-1.31 per patient preoperatively to 0.26 medications per patient postoperatively ($P<0.05$).Subjected to surgical success criteria of an IOP less than 18mmHg without reintroduction of medication, our cumulative rate success was 76.08%.Complications: We observed three patients who underwent anterior vitrectomy due to a posterior capsular tear and resulted in a good post operative outcome. Two patients had a transient post operative hyphema, and one patient with transient wound leakage.

Conclusions: We found that the Ex-PRESS stent combined with phacoemulsification cataract extraction is clinically safe and effective. Long term follow-up shows a large reduction in IOP and significantly reduces the need for antiglaucomatic medications. Furthermore, among 22 eyes with pseudoexfoliationout, 16 showed an IOP less than 18mmHg without reintroduction of medications

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Contamination of Saflutan ampules after single use - is it safe to use again?

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Purpose: Saflutan is a glaucoma medicine which is potentially advantageous due to its lack of preservative and thus potential for ocular surface toxicity. However, it is relatively expensive, and its single use means that some medicine is wasted. We evaluated the rate of microbial contamination after single use of Saflutan in real-life conditions.

Methods: Glaucoma patients treated with a prostaglandin analogue were provided with preservative free SAFLUTAN for 5 days. After single use, bottles were closed and saved in room temperature (group 1) or in the fridge (group 2). After 2-5 days bottles were collected and the remaining fluid and the tip of the bottle were cultured from 2 bottles of each patient, 24 and 48 hours after use. For the control group ,10 bottles were cultured immediately.

Results: The study group contained 20 patients with an average age of 62 (range 31-78). 14 patients used SAFLUAN in both eyes, and 6 patients in 1 eye only. 29 (76%) of the 38 analyzed bottles were contaminated: 15/19 bottles (79%) after 24 hours of being open and 14/19 bottles (74%) after 48 hours. In group 1 bacteria were recovered from 8/10 bottles (80%), and in group 2 bacteria were recovered from 7/9 bottles (77.7%). 24 hours from opening, bacteria identified were all gram positive organisms. After 48 hours of opening the bottle, 93% were gram positive organisms, and 7% were gram negative organisms. 50% of the bottles showed contamination of both the drop and the tip. Isolated contaminants were mainly normal flora coagulase negative staphylococcus, bacillus and staphylococcus Viridans. Most cultures showed only few bacterial forming colonies. No growth of microorganism was detectedin the control group.

Conclusions: Our data show contamination rate of 79% 24 hours after single use of the preservative free prostaglandin analog SAFLUTAN. This seemingly affirms that re-use of SAFLUTAN is not recommended. However, the practical clinical relevance of the presence of few, non-virulent organism from the patient's own flora may justify further research

When should we measure the IOP change in transition from sitting to lying down?

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Purpose: Intraocular pressure (IOP) is higher when lying down, but has been reported at different intervals after subjects changed body position. To clarify this issue we repeatedly measured IOP at various time points following change in body posture.

Methods: Enrolled were 14 eyes of 14 healthy subjects (aged 36.21 ± 17.98). Baseline sitting IOP was measured with Goldman applanation tonometer (GAT) and pneumatonometer (PT). Then IOP was measured with pneumatonometer after the patient had lied on his back – immediately and after 1,3,5,10,15,30 minutes, then after sitting up again using the same sequence. At 5 and 30 minutes IOP was also measured GAT.

Results: Baseline IOP was 12.61 ± 1.80 (GAT) and 19.86 ± 2.62 (PT). With both tonometers, there was no significant difference in IOP between the various time points. GAT (p=0.062, ANOVA), PT(p=0.734, ANOVA). Average ΔIOP after lying down was 4.76 ± 2.21 (GAT) and 5.46 ± 2.06 (PT) (p=0.407,ANOVA).

Conclusions: In clinical practice, the timing of measuring postural change in IOP is not important in the first 30 minutes. The IOP change is similar when measured with GAT and PT

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Assessment of a combined tropicamide and oxime treatments against miosis and visual dysfunction 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 the beneficial effect of short-acting anti-cholinergic drugs combined with oximes in contradicting the sarin-induced miosis and visual impairments

Methods: Male Pigmented Long-Evans rats were topically exposed to sarin (0-10 µg). Dose response relationship of pupil width was evaluated by an infrared-capable video camera 15 min-72 h following the exposure and for ocular treatments with anti-cholinergic and oximes up to 8 h. Visual function assessment was performed using the “Cued” Morris Water Maze task, 15-35 min, 2 h and 4 h following sarin exposure and 35-50 min following exposure and treatment

Results: Rats showed a dose-dependent miosis, which returned to pre-exposure levels within 24-48 h. Significant reduction in visual function was seen in animals exposed to 0.2 µg sarin and above, 15-35 min following sarin exposure, opposed to animals examined 2 or 4 h following exposure. Short-acting anti-cholinergic or oxime treatments differentially reduced the sarin-induced miosis and the resulting impairment in visual performance. Moreover, the combined treatment presented a rapid beneficial effect on the parameters evaluated

Conclusions: The use of topical combination of short-acting anticholinergic treatment tropicamide with oximes following ocular sarin exposure should be considered.

A new method for subretinal transplantation of human cells as a thin layer in rabbit and porcine eyes

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Purpose: We recently showed that transplantation of human bone marrow mesenchymal stem cells as a thin subretinal layer in Royal College Surgeon (RCS) rats ameliorated retinal degeneration, rescuing photoreceptors along the entire retina. Here we developed a new surgical system for subretinal transplantation of cells in large eye models of rabbits and pigs as a step towards phase I clinical trials.

Methods : DiI-labeled human cells were transplanted into the subretina of New Zealand White rabbits and pigs, using a novel syringe system. In some cases cells were pre-labeled with near infra-red (NIR) ferumoxide nanoparticles. A longitudinal triangular scleral incision starting 4 mm away from the limbus at about 5°axis toward the choroid was formed. An additional tract through the choroid toward the retinal pigmented epithelium (RPE) was created by a bent wire. The cells were injected through the scleral tunnel and its extension. Spectral Domain Optical Coherence Tomography (SD-OCT, Heidelberg) equipped with a NIR camera was used for eye imaging and detection of transplanted cells. Eyes were inoculated for histology analysis shortly after OCT scans and cryopreserved. A fluorescent microscope was used to identify DiI-positive cells.

Results: Transplanted cells were identified shortly after transplantation as a uniform thin sheet of cells distributed along most of the subretina on the basal side of the RPE. These results correlated with OCT scans which detected the transplanted cells in a thin layer in a subretina - basal side of the RPE. No choroidal hemorrhage was observed.

Conclusions: This new surgical system allows therapeutic cells and agents to be in close proximity with the apical and basal side of the RPE in a thin layer with minimal retinal detachment. Furthermore the new surgical system allows introduction of therapeutic agents to the macula without insertion of surgical equipment into the macula. This study is expected to directly lead to phase I clinical trials for mesenchymal stem cell- based therapy in retinal dystrophy patients. Furthermore, implementation of this new transplantation technique may enhance the therapeutic effect of other cell-based therapies and therapeutic agents.

Gene therapy in a sheep model of CNGA3 achromatopsia: long term functional rescue and expression of the vector-delivered CNGA3 mRNA and protein

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Introduction: Achromatopsia (ACHM) is a hereditary vision disorder caused by cone photoreceptor dysfunction, leading to severe impairment of visual acuity, colour blindness and photophobia. In Israel, mutations in CNGA3 gene are the most prevalent cause of disease. We previously reported functional visual improvement following gene therapy in a sheep model of CNGA3 ACHM. The purpose of this study was to provide long term evaluation of visual function in treated eyes and to determine expression of the vector-delivered CNGA3 gene at the mRNA and protein levels.

Methods: AAV5 vectors carrying the intact mouse or human CNGA3 gene (or the GFP marker gene) under control of the red-green opsin promoter were delivered into the subretinal space. Animals were behaviorally assessed (by maze tests) pre- and up to 26 months post-operatively. Passage time and number of collisions were recorded. Eyes were harvested to assess gene expression at the mRNA level by PCR and at the protein level by IHC. Normal (non-affected) and non-treated day-blind sheep served as controls.

Results: Pre-operatively, affected sheep demonstrated marked impairment of photopic visual function. Consistent long-term (over two years) functional rescue was evident in day-blind animals treated by either the human or the mouse CNGA3 gene. Passage time and number of collisions in the photopic maze improved dramatically, approaching the values of normal controls. This improvement did not occur when the treated eye was occluded. PCR (verified by sequencing) demonstrated presence of the appropriate CNGA3 mRNA in treated retinas. Histologically, retinal structure was well preserved in treated eyes. Anti-GFP staining showed strong and cone-specific expression, confirming promoter specificity and efficacy of transfection. Further IHC studies revealed co-localization of CNGA3 protein and red-green opsin in normal and treated eyes, while CNGA3 was not found in non-treated fellow or naive day-blind retinas.

Conclusions: Subretinal AAV5-mediated gene therapy provides long term improvement of cone-mediated visual function in CNGA3 day-blind sheep, with a good safety profile. Treated retinas show CNGA3 mRNA expression and cone-specific localization of the CNGA3 protein. Our hope is to ultimately apply similar treatment in human ACHM patients.

The progressive rod-cone degeneration (PRCD) protein is secreted through the conventional ER/Golgi-dependent pathway

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Purpose: Retinitis pigmentosa (RP) is the most common form of hereditary retinal degeneration. Mutations of the PRCD gene are associated with RP in both dogs and humans. The human PRCD gene encodes for 54 amino acids (aa) of unknown function. The first 20 aa appear to encode for a signal peptide (SP), suggesting that PRCD is a secreted protein. We aimed to test this hypothesis.

Methods: A sporadic RP female patient underwent complete ophthalmological examination and genetic testing for all genes associated with autosomal recessive RP. To study PRCD secretion, C-terminally myc-tagged PRCD was expressed in cultured cells. Cells and conditioned media were analyzed by Western blot and immunostaining. To characterize the secretory pathway of PRCD we studied the effect of various pharmacological agents, which interfere with transport of proteins through the ER and Golgi to the plasma membrane.

Results: The patient was found to be compound heterozygote for two PRCD mutations: the previously reported p.R18X, and a novel variant, p.P25T. Her phenotype resembles that of previously reported patients with PRCD mutations. In transfected cells, PRCD was found in both cell extracts and conditioned cell media. Interestingly, a truncated PRCD protein lacking the first 20 aa was present only in cell extracts and not in media, confirming that PRCD is secreted extracellularly and that its secretion is mediated by its N-terminal SP. PRCD secretion was significantly inhibited by all tested pharmacological agents, confirming that it is secreted through the classic ER/Golgi-dependent secretory pathway. We tested the effect of two mutations on the PRCD protein, and found that p.C2Y, but not p.P25T, affects protein stability, and that neither mutation affects protein secretion.

Conclusions: Our data suggest that PRCD functions as a secreted protein. These findings shed a new light on PRCD function and the etiology of RP.

Chromatic pupillometer-based perimetry in normal eyes and patients with retinitis pigmentosa

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Purpose: To objectively asses visual field defects and retinal functions in patients with retinitis pigmentosa (RP) using a second-generation chromatic multifocal pupillometer device with 76 LEDs in 20 degree visual field with 2.5 mm diameter spots

Methods: Twenty five participants were recruited (16 healthy individuals and 9 RP 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), presented from 2.5 mm-diameter targets at 76 different points in a 20 degree visual field. Stimulus duration was 1 sec. Percentage change in of pupil diameter was 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: All participants easily tolerated the protocol without any discomfort. Significantly reduced pupillary responses were obtained in RP patients under testing conditions that emphasized rod contribution (short-wavelength stimuli) especially in peripheral perimetric locations. By contrast there was no significant difference between pupillary responses of RP patients and normal participants in response to the long-wavelength stimuli. In all patients, minimal pupillary responses were recorded in regions that were non-detected in the Goldmann perimetry.

Conclusions: This study demonstrates the feasibility of using the chromatic multifocal pupillometer for determining the visual field in objective quantitative manner as well as assessing visual field defects in patients with RP. The chromatic pupillometer perimetry results of RP patients were in accordance with patient's pathology of a primary defect in rods followed by loss of cones.

Chromatic pupillometer-based perimetry in patients with Best's vitelliform macular dystrophy

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Purpose: To objectively determine visual field defects in patients with BEST'S vitelliform macular dystrophy using a second-generation chromatic multifocal pupillometer device with 76 LEDs for 20-degree visual field with 2.5mm spot size.

Methods: Nineteen participants were recruited (3 patients with BEST'S vitelliform macular dystrophy and 16 healthy individuals). 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). Target diameter was 2.5mm, duration of stimulus was 1 sec. Stimuli were presented by 76 LEDs in a 20-degree visual field. Percentage change in pupil diameter was calculated. The pupillary responses of patients were compared with their findings on Humphrey's 24-2 perimetry and with the pupillary responses obtained from normal control subjects

Results: All participants easily tolerated the protocol without any discomfort. In all patients, minimal pupillary responses were recorded in regions of decreased sensitivity in the Humphrey's perimetry. A good agreement was observed between the Humphrey's perimetry and the perimetry obtained by pupillary responses to short wave length stimuli. In the patients, larger regions with abnormally reduced pupillary responses were detected in response to the long wave length stimuli as compared with the short-wave length stimuli.

Conclusions: This study demonstrates the potential feasibility of using pupillometer-based chromatic perimetry for objective assessment of visual field defects and retinal function in patients with BEST'S vitelliform macular dystrophy. Our findings also suggest that perimetry testing based on pupillary responses to long wave length stimuli is more sensitive and may enable earlier detection of visual field defects in patients with central macular lesions

Course of sodium iodate-induced retinal degeneration in adult albino and pigmented mice

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Purpose: Sodium Iodate (SI) was shown to induce specific damage to RPE cells, resulting in secondary dysfunction and loss of photoreceptors. The purpose of this study was to establish and characterize the course of SI-induced retinal degeneration in adult albino and pigmented mice.

Methods: Single intraperitoneal injections of SI (25, 50 and 100mg/kg) were performed in 7-8 week old BALB/c and C57Bl/6 mice. Retinal function and structure was assessed at baseline, 24h, 3 days, 1, 2, 3, and 4 weeks following SI administration. Progression of injury was evaluated by ERG, optokinetic tracking (OKT), OCT, histological and immunohistochemical (IHC) techniques.

Results: Dosing studies revealed that 25mg/kg of SI resulted in variable results whereas 100mg/kg was highly lethal. At 50mg/kg, systemic toxicity was not apparent while retinal effects were consistent, and therefore this dose was used. In C57Bl/6 mice, SI injection provoked dramatic decrease in visual acuity within 24h. At 1w, limited recovery was observed but then visual acuity deteriorated further by 4w. Scotopic ERG responses markedly deteriorated in both strains and by 4w were detectable only at highest stimulus intensities. Surprisingly, supernormal photopic cone responses were obtained at 24h (~2.5-fold above baseline), but subsequently significantly deteriorated to less than 15% of baseline at 4w. By 4w, ERG implicit times were significantly prolonged. OCT showed significant thinning of outer retinal layers over time, correlating with histological observations including loss of RPE nuclei within 24h and thinning of ONL to approximately 50% of baseline by 4w. IHC revealed rapid RPE disorganization with loss of tight junctions and markedly reduced expression of RPE65, a crucial visual cycle protein. Rod photoreceptors showed time-dependent decrease of rhodopsin expression. In cones, mislocalization of cone opsins to cell bodies and synaptic terminals occurred.

Conclusions: A single injection of 50mg/kg SI leads to severe RPE injury followed by vision impairment, dysfunction and loss of photoreceptors in both BALB/c and C57Bl/6 mice. Functional, histological and OCT findings were found to correlate in characterizing progression of injury. This easily induced and reproducible non-inherited model may serve as a useful tool for evaluating novel therapeutic modalities for the treatment of retinal degenerations caused by primary failure of the RPE.

Clinical and genetic characteristics of patients with early macular degeneration

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Purpose: To present genetic and clinical characteristics of patients with early onset macular degeneration.

Methods: We interviewed and performed clinical ophthalmic examination, OCT, FAF, FA and genetic analysis in 28 patients with early onset macular degeneration. Blood samples were obtained from the patients and their family members for DNA extraction and mutation screening of the peripherin/RDS gene or the CFH gene.

Results: Two already described peripherin/RDS mutations (c.441delT ,p. R142W) were identified in two macular degeneration families. Genomic sequencing of the coding region of CFH gene revealed a novel p.C357T mutation in a patient with extensive retinal drusen and MPGN.

Conclusions: Genomic heterogeneity underlies early macular degeneration. To the best of our knowledge we report the first descriptions of the C357T mutation in the CFH gene, and its phenotype.

Nonsyndromic retinitis pigmentosa is highly prevalent in the Jerusalem region with a high frequency of founder mutations

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Purpose: To determine the prevalence of nonsyndromic retinitis pigmentosa (RP) in the Jerusalem region with a population size of about one million individuals.

Methods: Medical records of patients with retinal diseases were collected over the last 20 years and included mainly clinical eye exam findings (visual acuity, anterior segment and funduscopy) and electroretinography (ERG). Data was collected on patients who were diagnosed with RP and reside in the vicinity of Jerusalem. Mutation analysis on a subgroup of patients was performed by the candidate gene analysis, homozygosity mapping and whole exome sequencing.

Results: A total of 438 individuals who reside in the vicinity of Jerusalem were diagnosed with RP at our center, according to funduscopic findings and ERG testing. Based on the estimated population size of 945,000 individuals who reside in the vicinity of Jerusalem, the non-corrected estimated prevalence of nonsyndromic RP is 1:2,158. There are two main subpopulations in this area: Jews (65% of the population) and Arab-Muslims (35%). The prevalence of RP was found to be higher among Arab Muslims (1:1,946) compared to Jews (1:2,308), mainly due to consanguineous marriages. To identify the genetic causes of RP in our cohort, we recruited 243 of the patients who belong to 167 families: 61 with autosomal recessive (AR) inheritance, 13 autosomal dominant, 29 isolate cases with consanguinity (indicative of AR inheritance pattern), 51 nonconsanguineous isolate cases, and 13 with X-linked inheritance pattern. In 52 (31%) of the families, we identified the genetic cause of disease, allowing us to revise the inheritance pattern of 13 nonconsanguineous isolate cases to AR pattern, which comprise 44% of families. Interestingly, in 29 (58%) of the solved families, the cause of disease was a founder mutation, identified in the following genes: CRB1, DHDDS, EYS, FAM161A, NR2E3, and RPGR.

Conclusions: Previous studies showed a prevalence of 1:5,663 (on average) for nonsyndromic RP at all ages in the American and European populations. We show here that the prevalence in the vicinity of Jerusalem is about 2.5 times higher than the prevalence reported previously in Maine and Denmark. This high prevalence is likely to be due to a high level of consanguinity in the studied population in association with highly prevalent founder mutations.

Missense mutations in the BBS2 gene can be associated with nonsyndromic retinitis pigmentosa

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Purpose: Bardet-Biedl syndrome (BBS) is known to be caused by mutations in at least 15 genes with an autosomal recessive inheritance pattern and triallelism in a few families. Patients with BBS suffer from a wide spectrum of clinical features including retinitis pigmentosa (RP), polydactyly, renal and gonadal malformations, obesity, and learning disabilities. Mutations in five BBS genes were reported so far to cause nonsyndromic RP, sometimes with only one additional associated clinical feature. The aim of the current study was to identify the cause of disease in families with nonsyndromic RP.

Methods: All participants in the study signed an informed consent that adhered to the tenets of the declaration of Helsinki before drawing a blood sample for molecular analysis. Clinical examination included visual acuity test, funduscopy, and electroretinography (ERG). Genetic analysis included homozygosity mapping and whole exome sequencing.

Results: Aiming to identify the cause of disease in families with nonsyndromic RP, we performed whole exome sequencing in two families followed by Sanger sequencing analysis of the identified mutations in a larger cohort of patients. We identified four BBS2 missense mutations that cause nonsyndromic RP in three siblings of Moroccan Jewish ancestry (compound heterozygotes for p.A33D and p.P134R) and in five patients who belong to three different families of Ashkenazi Jewish ancestry (patients were either homozygous for p.D104A, homozygous for p.R632P, or compound heterozygous for these two mutations). Seven of the eight individuals suffered from the typical features of RP but did not exhibit any of the remaining BBS features, and one patient had RP accompanied by polydactyly and learning difficulties. The mutations perfectly cosegregated with RP in the studied families and the affected amino acids were highly conserved along evolution.

Conclusions: BBS2 mutations can cause nonsyndromic RP or a mild form of BBS.

A yet unrecognized autosomal dominant disorder with predominant ocular manifestations in a Moroccan Jewish family.

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Purpose: Microphthalmia (axial length<21.0 mm) is a developmental defect of the eye. This disorder displays genetic and clinical heterogeneity among which mutations in the ABCB6 gene were recently described in patients with complicated forms of microphthalmia and coloboma. Purpose: To describe a newly recognized syndrome consisting of microphthalmia, early onset cataracts, accompanied by divers ocular and systemic abnormalities.

Methods: Eight members of a Moroccan Jewish family were recruited. All patients underwent a comprehensive ophthalmic examination including; corrected visual acuity, corneal diameter and axial length measurements, corneal topography, and slit lamp examination of the anterior segment, lens and retina.

Blood samples were obtained from participants for DNA extraction. Exclusion of possible candidate loci was made using microsatellite polymorphic markers. Whole exom (WES) analysis was performed in one patient.

Results: The ocular phenotype is characterized by isolated microphthalmia (without coloboma), pre-senile cataract, and corneal abnormalities which include overt keratoconus, high astigmatism and relatively high corneal diameter measurements.Systemic findings include: short stature, variable degrees of mental impairments, and thyroid dysfunction in some patients. Polymorphic markers readings encompassing the "Micro-syndrome" locus [MIM:600118], did not segregate with disease phenotype. WES results followed by bioinformatics analysis identified a missense ABCB6 mutation; c.G328A : p.G110S. Validation studies in order to verify the pathogenicity of this mutation are under process.

Conclusions: We report a yet unrecognized association of microphthalmia, pre-senile cataracts and divers ocular and systemic abnormalities with the identification of a missense mutation in a gene previously related to microphthalmia and coloboma

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A nonsense mutation in CEP250, a mammalian-specific homolog of rootletin, causes a new type of Usher syndrome

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Purpose: Usher syndrome is a heterogeneous group of inherited retinal degenerations with sensorineural hearing loss (SNHL) caused by mutations in at least 12 genes. The aim of this study was to identify the cause of retinal degeneration and SNHL in a family a consanguineous Iranian Jewish family.

Methods: All participants in the study signed an informed consent that adhered to the tenets of the declaration of Helsinki before drawing a blood sample for molecular analysis. Clinical examination included visual acuity test, funduscopy, and ERG. Genetic analysis included homozygosity mapping and whole exome sequencing.

Results: We recruited for the study a family (MOL0028) including six members affected with Usher syndrome. A combination of homozygosity mapping and whole exome sequencing revealed nonsense mutations in two ciliary genes: c.3289C>T (p.Q1097*) in C2orf71 and c.3463C>T (p.R1155*) in centrosome-associated protein CEP250 (C-Nap1). The latter has not been associated thus far with any inherited human disease and the c.3463C>T mutation was absent in 160 ethnicity-matched control chromosomes and in about 13,000 chromosomes (exome variant server database). Patients who were double homozygotes for both mutations had SNHL accompanied by early-onset and severe retinitis pigmentosa, while patients who were homozygous for the CEP250 mutation alone had SNHL with mild retinal degeneration. No ciliary abnormalities in the respiratory system were evident by electron microscopy analysis. C-Nap1 is expressed in photoreceptor cilia and is known to interact with other ciliary proteins, including rootletin and NEK2. Expression analysis revealed the generation of the mutant truncated protein lacking the NEK2-phosphorylation region. By evolutionary analysis we show that C-Nap1 and rootletin are paralogues that arose by genomic duplication about 500 million years ago.

Conclusions: We show here that a nonsense mutation in CEP250 causes a novel form of Usher syndrome, characterized by early-onset SNHL and a mild form of retinal degeneration. The severe retinal involvement in the double homozygotes indicates an additive effect caused by nonsense mutations in genes encoding ciliary proteins.

Isolated foveal hypoplasia is associated with a homozygous SLC38A8 mutation

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Purpose: Foveal hypoplasia is found in various eye disorders such as aniridia, albinism and achromatopsia. However, the molecular basis of isolated autosomal recessive foveal hypoplasia is yet unknown. We ascertained Israeli families of Jewish Indian descent with isolated foveal hypoplasia associated with congenital nystagmus and reduced visual acuity.

Methods: Nine affected individuals (ages 1-65 years) of three unrelated Israeli families of Jewish Indian (Mumbai region) ancestry were studied. We collected clinical data including visual acuity, eye movements, and anterior and posterior segment findings. Full-field electroretinography (ERG), flash visual evoked potentials (VEP) and optical coherence tomography (OCT) were obtained in a subset of patients.Genome-wide linkage analysis was followed by homozygosity by descent analysis, fine mapping and haplotype reconstruction. Whole exome sequencing was done using paired-end protocol at a mean coverage of 30-fold. SLC38A8 expression analysis was performed using PBSX1 pre-perfused C57BL/6 mice.

Results: All patients had nystagmus and reduced vision since infancy. Six patients had strabismus. All patients had normal cutaneous and ocular pigmentation and no iris transillumination. Fundus exam revealed foveal hypoplasia confirmed by the absence of normal foveal pit on OCT. ERG and VEP results were normal.Genome wide homozygosity mapping followed by fine mapping defined 830Kb disease associated locus (LOD score 3.5). Whole exome sequencing identified a single missense mutation in the homozygosity region: c.95T>G, p.(Ile32Ser), in a conserved amino acid within the first predicted transmembrane domain of SLC38A8. The mutation fully segregated with the disease-associated phenotype, demonstrating a ~10% carrier rate in Mumbai Jews. SLC38A8 encodes a putative sodium-dependent amino acid/proton antiporter. Analysis of SLC38A8 expression in mouse tissues demonstrated that it is transcribed solely in the eye.

Conclusions: We showed that a homozygous SLC38A8 mutation underlies isolated foveal hypoplasia. This is a first identification of a gene responsible for autosomal recessive foveal hypoplasia. Following our discovery, others reported additional mutations in SLC38A8 causing foveal hypoplasia in Asian and European families and showed functional role of this gene in the development of the visual pathway.

Advantages and pitfalls of whole exome sequencing

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Purpose: The relatively high rate of consanguineous marriages in the Israeli and Palestinian populations lead to a relatively high proportion of homozygous mutations in genes causing autosomal recessive diseases. The decreasing rate of consanguinity in the latest decades (mainly in the Jewish populations) led to a decrease in homozygosity, and therefore a more limited use of homozygosity mapping (HM). In families with multiple consanguineous marriages, however, the opposite problem takes place in which a large percentage of the genome is homozygous, making identification of a disease-causing loci complex. Our main purpose was to identify additional causes of inherited retinal degenerations using whole exome sequencing (WES), with or without prior HM information, utilizing the strengths while navigating pitfalls.

Methods: Clinical examination included visual acuity test, funduscopy, and electroretinography. WES was performed on 48 patients from 17 families with inherited retinal degeneration and mainly retinitis pigmentosa (RP). Homozygosity mapping using SNP arrays was performed on 5 of the families. WES data analysis was performed by ANNOVAR and array analysis by the Homozygosity Mapper program. Pathogenic sequence variants were validated by Sanger sequencing.

Results: WES analysis, supported by HM in some families, revealed 8 disease-causing mutations (5 of which are novel) in 7 (out of 17) families. All mutated RP genes (except one-USH2A), were not reported so far as causative RP genes in the Israeli and Palestinian populations. Some of the mutations were unlikely to be identified by other methods, highlighting the advantages of WES, including a consanguineous family with nonsyndromic arRP and compound heterozygous USH2A mutations and a family with arRP with a homozygous BBS1 mutation (BBS1 mutations cause of Bardet-Biedl syndrome). Contrary to successes of WES, we encountered some pitfalls of the technique. For example, WES failed to identify mutations in RP gene in a family with adRP. An independent screen of the RHO (rhodopsin) gene revealed a novel heterozygous tandem duplication of 91bp. Since the WES average read size is very similar, WES failed to identify this mutation.

Conclusions: Analysis of WES usually requires processing a large amount of data. Pairing WES with HM allows one to overcome WES pitfalls. In future years, whole genome sequencing, overcoming some of the WES disadvantages, is likely to have a wider use in human genetics.

Identification of genetic defects in cone-rod degeneration by whole exome sequencing

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Purpose: To identify mutations causing cone-rod degeneration (CRD) in the Israeli and Palestinian populations using whole exome sequencing (WES).

Methods: All participants in the study signed an informed consent that adhered to the tenets of the declaration of Helsinki before drawing a blood sample for molecular analysis. Clinical examination included visual acuity test, funduscopy, and electroretinography (ERG). Genetic analysis included WES that was performed on 32 individuals who belong to 10 families with the diagnosis of CRD.

Results: We analyzed a total of 10 families with CRD: three with an autosomal dominant (AD) inheritance pattern, seven with autosomal recessive (AR), and one with X-linked. WES was performed on 1-4 individuals per family. In the XL-CRD family we identified a novel sequence variant (p.GLy479Arg) in the CACNA1F gene. In all three adCRD families, we identifies heterozygous GUCY2D missense mutations affecting the same amino acid (2 families with p.Arg838Cys and one with p.Arg838His). In two AR families, we identified novel homozygous CDHR1 mutations (p.Q461* and c.2087_2090delACAA) and in one family, a known C8orf37 mutation (p.R177W) was identified. The most challenging family was MOL0339 in which two siblings suffered from arCRD and limb girdle. A homozygosity mapping analysis followed by WES revealed three novel mutations in the DYSF gene, known to cause limb girdle, and a novel nonsense mutation (p.R269*) in the ALMS1 gene. While ALMS1 mutations were reported so far to cause alstrom syndrome, the mutation we identified is located in an alternatively spliced region of ALMS1 that does not affect the major ALMS1 transcript.

Conclusion: Using WES we were able to identify the cause of disease in 80% (8 out of 10) of families with CRD and various inheritance patterns. A more comprehensive analysis using whole genome sequencing might be useful in identifying the remaining mutations.

Single nucleotide polymorphic changes in patients with adult onset foveal vitelliform dystrophy

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Purpose: Adult-onset foveomacular vitelliform dystrophy (AOFVD) may accompany other retinal dystrophies, such as Best's disease, age-related macular degeneration (AMD), or others. Findings without familial history are rare, and represent a different dimension of the disease. Our purpose was to investigate patients with AOFVD without familial history to determine a possible genetic basis for the disease.

Methods: Patients with AOFVD (n=52) without familial history were recruited in the retinal clinic of Hadassah-Hebrew University Medical Center. All patients were genotyped for mutations in the peripherin/PRPH2/RDS, IMPG1, IMPG2, and bestrophin genes. Illumina whole genome SNP chip analysis was performed on all patients, including 500,000 SNPs, 250,000 of which were custom variants. Variants were also investigated on 50 AMD patients and 50 age-matched controls, upon which SNP array was also performed.

Results: All patients tested were negative for mutations in the PRPH2, IMPG1, IMPG2 or bestrophin genes. While investigating the PRPH2 gene, in exon 3, a highly polymorphic exon, several polymorphisms were identified that were highly prevalent in the AOFVD patients. Data on those SNPs were compared with HapMap and the Exome Variant Server (EVS) data, to ascertain if these polymorphisms were highly present in our patients. One SNP's minor allele was highly prevalent in our patients (P=0.04), and one SNP showed a trend (P=0.06), compared to EVS data for the European and African-American population (~8600 samples). Both of these SNPs indicate missense variants. Examination of the 241 exomes in the retinal disease exome database from Weizmann Institute did not find a significance allele difference in those two SNPs as compared to the other retinal disease patients.

Conclusions: PRPH2 mutations are uncommon cause of sporadic AOFVD in Israel. Yet, polymorphic variability may play a role in the genetic component of the disease. Further investigation is needed to fully ascertain whether these SNPs can contribute to the pathogenesis of the disease, and whether an additive effect is in play.

Ranibizumab and Bevacizumab decrease macular ganglion cell complex thickness measured with Fournier-domain optical coherence tomography in AMD

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Purpose: To evaluate the effect of multiple intravitreal injections with ranibizumab and bevacizumab on macular GCC thickness in eyes with wet AMD in comparison with age matched controls with dry AMD.

Methods: Retrospective, observational, case control study of consecutive patients.24 eyes treated with either ranibizumab or bevacizumab for newly diagnosed wet AMD were enrolled along with 15 control eyes with dry AMD. All patients were followed by sequential macular RTVueÂ® FD-OCT mappings for six months at least. Macular GCC thickness, defined as the combination of retinal nerve fiber, ganglion cell and inner plexiform layers, was measured and compared between the two groups, at initial and last follow up exams.

Results: Average follow up for all patients was 22.1± 9.0 months. The treatment group received on average 11.5 injections. We found a decrease in the average GCC thickness across the parafoveal region (inner 3 mm) of 9.3±10.7 □m and 1.5±4.3 □m in the treatment and control groups respectively ($p<0.05$). A significant correlation was found between the number of injections and the average amount of GCC thinning in the parafoveal ($r = 0.495$, $p < 0.05$) and the perifoveal ($r = 0.431$, $p < 0.05$) regions, principally in the nasal and temporal quadrants.

Conclusions: Ranibizumab and bevacizumab can lead to substantial GCC thinning, compared to controls, that correlates with the number of injections. This may account for lack of visual improvement in some patients. Further large scale prospective studies are needed to validate these findings.

The effect of posterior vitreouse detachment on intravitreal bevacizumab therapy for neovascular age-related macular degeneration

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Purpose: To investigate the influence of posterior vitreous detachment (PVD) on the short-term functional and anatomic efficacy of intravitreal bevacizumab therapy in patients with neovascular age-related macular degeneration (AMD).

Methods: Retrospective, observational, case control study of consecutive patients. 24 eyes treated with either ranibizumab or bevacizumab for newly diagnosed wet AMD were enrolled along with 15 control eyes with dry AMD. All patients were followed by sequential macular RTVue® FD-OCT mappings for six months at least. Macular GCC thickness, defined as the combination of retinal nerve fiber, ganglion cell and inner plexiform layers, was measured and compared between the two groups, at initial and last follow up exams.

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Conclusions: Ranibizumab and bevacizumab can lead to substantial GCC thinning, compared to controls, that correlates with the number of injections. This may account for lack of visual improvement in some patients. Further large scale prospective studies are needed to validate these findings.

A retrospective cohort study - prognostic factors in Spectralis® OCT for exudative AMD

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Purpose: Therapy of exudative age-related macular degeneration (AMD) with anti-vascular endothelial growth factor (VEGF) substances has evolved to an effective and widespread treatment in the last years, allowing preservation or even improvement of visual acuity in the short and long term.Reliable predictive factors for therapy outcome may enable treating physicians to counsel their patients more efficiently concerning probability of improvement or time point of discontinuation of a certain therapyOur objective in this study was to find out if there are any prognostic criteria in the primary OCT tests of patients with Exudative AMD that could predict the patients' response to Anti-VEGF injections.

Methods: This is a retrospective analysis of 104 naive patients with exudative age-related macular degeneration who received three monthly intravitreal Bevacizumab injections. Visual acuity (VA) before initiation of intravitreal therapy and 4-6 weeks after last intravitreal injection was measured. We divided the patients into 2 groups by their response to treatment, based on VA changes. Stable or improved versus VA deterioration. We then compared the 2 groups to find changes related to various factors in the preoperative OCT tests.The preoperative OCT tests variables were: fluids accumulated inside and below the retina, area and length of the fluids, central retinal thickness and volume, length of discontinuity of Photoreceptors, External Limiting Membrane (ELM) and Retinal Pigment Epithelium (RPE) layers. The locations of the pathologies (Sub/Extra foveal) were also recorded and analyzed.

Results: After comparing the 2 groups, we found out that in the group of people who improved their VA, there was more sub-retinal fluid compared to the group whose VA deteriorated. All other parameters that we checked did not prove to be statistically significant.

Conclusions: When we looked for previous research done in the field, we found only one major study, which had similar results, and showed that Sub-retinal fluid was linked to better prognosis, and Intra-retinal fluid to worse prognosis.This is the first study looking for prognostic criteria in this field in Israel, and is also the largest world-wide, with the previous one having 87 naive patients who received Ranibizumab, compared to Bevacizumab in our study.

Quantifying course of disease in patients with dry AMD and geographic atrophy

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Purpose: To assess the efficacy of different structural and functional techniques in characterizing disease progression in patients with Dry AMD and Geographic Atrophy, in preparation for future interventional clinical trials.

Methods: Patients with dry AMD and GA of 0.5 disc area or more in at least one eye were recruited and are evaluated every six months. Visual function is assessed by best corrected visual acuity (ETDRS), visual fields using the Humphrey Perimeter and the MAIA microperimeter, Color vision (Ishihara and D-15), Reading speed and quality of life questionnaires. Retinal structure and extent of GA was quantified using Fundus Auto Fluorescence (FAF, Heidelberg region finder method), OCT, Infra Red (IR) Photography, Fundus Color Photography, Multi Color Photography, and Fluorescein Angiography.

Results: Eight subjects were thus far recruited (mean age 79.9±8.64). Visual acuity was reduced in all subjects, ranging from 0.06 to 0.8 (decimal ETDRS) (mean average 0.29±0.2). Reading accuracy was reduced in most patients. Tritonopia was a common finding (13 of 14 eyes, 6 of them severe). Microperimetry testing showed that most patients had difficultyin maintaining stable fixation, often preferring an extrafoveal locus. In areas of GA, light sensitivity was markedly reduced. Sensitivity gradually increased across the transition zone, but remained subnormal also beyond the area of GA. After correcting for the shift in fixation, Humphrey perimetery correlated to microperimetry in terms of scotoma size and shape (overlapping the GA). Using the Heidelberg region finder method in FAF images was found to be an efficient way to measure and follow area of GA. Determining GA borders in color and IR images was more difficult, but largely correlatedwith FAF findings. OCT imaging can assist in identifying small spots of GA, but is highly labor intensive. In a subset of patients in which serial imaging is available, gradual, relatively consistent expansion of GA over time was observed.

Conclusions: Microperimetry is an effective way to quantify and correlate retinal function with structure in patients with Dry AMD and GA. FAF analysis, supported by color, IR and OCT imaging allows quantification of GA area and progression. Accurately determining the course of disease will allow to assess the efficacy of future therapeutic interventions, including cell therapy.

Arterial thrombotic events among patients suffering from age-related macular degeneration treated with intra-vitreal injections of Bevacizumab

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Purpose: Introduction: Age-Related Macular Degeneration (AMD) is the leading cause of vision loss among adults in the developed world. Today, Bevacizumab is the most common agent used as treatment for wet AMD. Purpose: To determine the incidence of Arterial Thrombotic Events (ATE's) following intra-vitreal injections of Bevacizumab as treatment for wet AMD at Soroka Medical Center between the years 2009-2011.

Methods: Retrospective case series study. Participants: all patients suffering from AMD and treated with intra-vitreal injections of Bevacizumab between the years 2009-2011. As a control group we included 100 patients suffering from AMD treated with photodynamic therapy (PDT) before the year 2006.

Results: 484 patients, 100 patients in the control group and 384 patients in the Bevacizumab group. During the study period 4160 injections were made, with the average of 10.86 injections per patient. The incidence of ATE was 50 (10.3%) for the entire study population. The incidence of ATE for the Bevacizumab group was 7% (27) compared to 23% (23) in the PDT group (=20.15, pv<0.005). There was a statistically significant difference in the average age of the 2 groups (78.8 in the injection group compared to 82.6 in the PDT group). There was also a statistically significant difference in the average follow up between the 2 groups (30.5 in the injection group compared to 74.3 in the PDT group). The average time interval between intra-vitreal injection and ATE was 4 months. There was no correlation between the number of injections and the risk for ATE (P=0.9).

Conclusions: The incidence of ATE in the injection group was lower than that of the control group, and in accordance to what is known for AMD patients in the literature. Intra-vitreal injection of Bevacizumab is a safe treatment option without increasing the risk of ATE.

Possible anti-inflammatory activity of the cannabinoid system in AMD generated by A2E

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Purpose: Accumulation in the RPE of A2E, a pyridinium bis-retinoid, has the potential to cause RPE cell death and may contribute to the RPE cell atrophy that is observed in AMD. The cannabinoid receptor system is present in human RPE cells and is intimately involved in the oxidative damage process, including that associated with AMD. It has been shown that levels of endocannabinoids are significantly increased in retinal tissue from AMD donors. This study aimed to investigate the effects of pro-inflammatory agents and specific oxidative intracellular signalling related proteins- MAPKs, on the in vitro AMD-A2E model in the presence and absence of cannabinoids (HU-210 and HU-308) and endocannabinoids (anandamide).

Methods: By using A2E-loaded RPE cells exposed to blue light irradiation, we can mimic the oxidative stress taking place in AMD. The presence of pro-inflammatory agents and activation of the signalling pathway were assessed in the presence and absence of cannabinoids and endocannabinoids by Western-blot analysis, flow-cytometry and ELISA.

Results: Experiments were conducted to investigate the ability of cannabinoids to attenuate the effect of A2E on the pro-inflammation agent's secretion. When the RPE cells were exposed to A2E and blue light, anandamide successfully and significantly reduced the amount of the pro-inflammatory chemokine, IL-8. The selective CB1 and CB2 receptor agonists, HU-210 and HU-308, respectively, did not influence IL-8 secretion. A2E alone caused an increase in IL-8 secretion that was attenuated by both HU-210 and HU-308. The ability of irradiated A2E-loaded RPE cells to induce MAPKs pathway activation was also evaluated. A significant decrease in several signals of MAPK was determined following RPE exposure to A2E and blue light irradiation, especially by HU-210 and HU-308.

Conclusions: The above results support our hypothesis that the newly discovered cannabinoid system may attenuate AMD generated by the accumulation of A2E. This study is expected to select candidate therapeutic compounds that may contribute to delaying or arresting A2E-related toxicity to the RPE.

Characterizing the phenotype of differentiated macrophages from patients with age related macular degeneration

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Purpose: Monocytes/macrophages have been implicated in the pathogenesis of age-related macular degeneration (AMD). We previously showed the pro-angiogenic contribution of polarized human macrophages in a rat model of laser-induced choroidal neovascularization (CNV). To gain insight into the pathways underlying this effect, we evaluated the protein and gene expression profile of macrophages from neovascular AMD (NVAMD) patients and controls.

Methods: Monocytes were isolated from six NVAMD patients and six age-matched controls. Cells were matured to macrophages and polarized to M1 and M2 phenotypes using LPS+IFN-γ for M1 and IL-13+IL-4 for M2 polarization. Protein expression was measured using ELISA on cell culture supernatant of non-polarized (M0), M1 and M2 macrophages. Quantitative PCR (QPCR) was performed on cDNA for the same cell type to measure gene expression levels.

Results: In both NVAMD and controls, QPCR demonstrated increased expression level of CCL17 in M2 cells, and IL-12 and TNF-α in M1 cells ($p<0.05$). Elevated VEGF expression was found in M1 as compared to M0 (68.8-fold, $p=0.016$), or M2 (24.3-fold, $p=0.001$) in NVAMD, as well as compared to M2 (11.3-fold, $p=0.004$) in controls. A trend was found in VEGF expression from M1 compared to M0 (47.6-fold, $p=0.07$) of controls. PDGF expression levels were elevated in M1 (10-fold, $p=0.016$) and M2 (6.3-fold, $p=0.04$) as compared to M0 in NVAMD, as well as trends in M1 (12.3-fold, $p=0.07$) and M2 (25.5-fold, $p=0.09$) as compared to M0 of controls. ELISA showed elevated levels of pro-inflammatory cytokines in M1 from NVAMD and controls. Among such cytokines were: TNF-α (799.4±200.9ng/ml), IFN-γ (1990.9±266ng/ml) and IL-6 (2082.6±262.5ng/ml). M2 macrophages secreted higher levels of IL-4, compared to M1 or M0, both in NVAMD (1234.7±237.1ng/ml) and controls (1504.4±328.3ng/ml). MCP-1 levels were higher in NVAMD macrophages compared with controls, regardless of the specific macrophage phenotype ($P<0.0001$). In NVAMD, M2 macrophages secreted higher levels of PDGF (78.7±28.2ng/ml) than M1 or M0, and each phenotype of control macrophages.

Conclusions: This study demonstrated pro-angiogenic/pro-inflammatory gene expression and protein-secretion profile of polarized macrophages from NVAMD patients. Combined with previous findings from the laser-induced CNV model, it is conceivable that activated macrophages have an important role in the pathogenesis of NVAMD, and may be therapeutic targets for AMD.

Analysis of gene expression in monocytes from patients with age-related macular degeneration

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Purpose: We previously showed an inflammatory gene signature in monocytes from patients with age-related macular degeneration (AMD) based on whole genome microarray analysis. In the current study we wished to validate our microarray findings and assess if it can be extended to all stages of the disease.

Methods: QPCR was performed on the blood monocyte population from neovascular AMD (NVAMD; n=17-20), dry AMD (n=6-9), and age-matched controls (n=17-21), not used for microarray analysis. Seven genes were evaluated TMEM176A, TMEM176B, OLR1, FOSB, FAIM3, MS4A1, and NLRP3, chosen based on the magnitude and significance of expression in NVAMD. SAGE data from the National Eye Institute (NEI) was evaluated for expression in control retina tissue.

Results: TMEM176A (P=0.02, FC=2.64) and TMEM176B (P=0.02, FC=2.34) showed increased expression in AMD (dry and neovascular combined) vs. controls. TMEM176A was increased in NVAMD (P=0.03, FC=2.6), and showed a high expression trend in dry AMD (P=0.09, FC=2.7) vs. controls. TMEM176B was increased in dry AMD (P=0.02, FC=2.9), and showed a high expression trend in NVAMD (P=0.05, FC=2.1) vs. controls. OLR1 expression decreased in NVAMD vs. controls (P=0.02, FC=1.8), but increased in dry AMD vs. controls (P=0.008, FC=4.6), as well as higher in dry AMD vs. NVAMD (P=0.004, FC=8.3). FOSB was increased in AMD (P=0.01, FC=3.8), and in dry AMD vs. controls (P<0.0001, FC=6.4), as well as trends of high expression between NVAMD and controls (P=0.1, FC=2.82), and between dry and NVAMD (P=0.1, FC=2.29). NLRP3 showed higher expression between dry AMD and controls (P=0.02, FC=1.8), while showing a high expression trend in dry AMD vs. NVAMD (P=0.12, FC=1.6). SAGE data curated from the NEI showed all genes had a significant presence (>10 tags) in human retina, especially macula, in addition to high expression in the inflammatory system.

Conclusions: The inflammatory signature found via microarray in monocytes from patients with NVAMD has been verified in both NVAMD and dry AMD patients. This data indicates a link between inflammation and both stages of the disease. These genes may underlie the pro-inflammatory involvement of monocytes in AMD. Targeting the expression/function of these genes should be evaluated as targets for treatment of AMD.

Prevalence of CFH Y402H and ARMS2 A69S polymorphism among Israeli intermediate AMD patients towards genotype-directed therapy

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Background: Over the past decade, studies have shown the major influence of polymorphism in two genes (Complement Factor H, CFH; and Age-Related Maculopathy Sensitivity 2, ARMS2) on AMD severity. The Age-Related Eye Disease Study (AREDS) demonstrated decreased progression of moderate-advanced AMD to severe disease in patients receiving antioxidant and zinc supplementation. However, no genetic data was included. Recently, Awh et al. genotyped eleven AMD genetic-risk predictors in 27.3% (995/3640) AREDS participants, and demonstrated that the effect of nutritional supplementation for individuals with intermediate AMD could improve through CFH and ARMS2 genotype-directed therapy. Objective: To describe the prevalence of CFH and ARMS2 polymorphism among Israeli patients with intermediate AMD phenotype, and discuss respective genotype-directed treatment regimens.

Methods: Peripheral blood-derived DNA of 81 patients with intermediate AMD phenotype was examined for known single nucleotide polymorphism (SNP) Y402H in CFH gene and A69S in ARMS2 gene by real-time PCR (DYN Diagnostics LTD). Genotypes were documented alongside with clinical appearance, and statistical analysis of the data was performed.

Results: Among ten (12.35%) non-carriers of the Y402H SNP in CFH gene, four participants (4.94%) carried the wild-type allele of ARMS2 [i.e. C0A0 genotype]; six (7.41%) were heterozygote for A69S SNP [i.e. C0A1 genotype], and none were homozygous for the ARMS2 risk-allele [i.e. C0A2 genotype]. Among 34 (41.98%) participants heterozygote to CFH Y402H, 10 (12.35%) were negative for A69S [i.e. C1A0 genotype], 15 (18.52%) were heterozygote [i.e. C1A1 genotype], and 9 (11.11%) were homozygote [i.e. C1A2 genotype]. Among 37 (45.68%) CFH Y402H homozygotes, 11 (13.58%) were negative for A69S [i.e. C2A0 genotype], 18 (22.22%) were heterozygote [i.e. C2A1 genotype], and 8 (9.88%) were homozygote for both alleles of risk [i.e. C2A2 genotype].

Conclusions: Israeli patients with intermediate AMD could benefit from genotype-directed nutritional supplementation. A significant proportion of our cohort (44.4%), carry genotypes that could benefit from a treatment regimen other than the AREDS formulation. Of them, 25.93% (13.58%+12.35%) carry the C2A0 and C1A0 genotypes respectively, where treatment with antioxidants alone may have the best long term outcome, and 7.41% carry the C0A1 genotype, where treatment with zinc alone is most probably recommended.

BRCA1/2 mutations may play a role in developing neovascular AMD in Ashkenazi Jews

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Purpose: In developed countries age-related macular degeneration (AMD) is the most common cause of visual loss in the elderly population. There are two forms of the disease, exudative and atrophic, and both genetic and environmental risk factors have been identiï¬ ed. Increased expression levels of VEGF and DNA damage with abnormal DNA repair has been linked to the pathophysiology of AMD.BRCA1 and BRCA2 are key proteins in maintaining genome stability and homolog recombinations. They have recently been associated with the increased level of VEGF in tumors harboring mutations in BRCA1/2.In this study, we explored a possible association between exudative AMD and BRCA1/2 mutations. If BRCA mutations are associated with impaired DNA repair and increased VEGF expression, then together with age related damage the mutations may increase the risk of developing AMD with neovascularization.

Methods: The study was approved by the National and Institutional Review Board. Included were 52 patients (26 male/26 females) Ashkenazi Jews diagnosed with wet AMD. Genomic DNA was extracted from peripheral blood leukocytes. All samples were examined for BRCA1 (c.5382insC and 185delAGand) and BRCA2 (c.6174delT) mutations. BRCA mutation analysis was carried out using the High Resolution Melting Curve.

Results: No mutation in BRCA1 185delAG nor BRCA1 5382insC were found. One individual (1.92%) was found to be a carrier of the BRCA2 mutation (c.6174delT).

Conclusions: The prevalence of BRCA1/2 mutations in normal Ashkenazi Jews is 2.5%. In this study we did not find a higher rate of BRCA mutations (1/52) in the wet AMD population. This might exclude the relevance of BRCA1/2 in the neovascular pathophysiology of AMD in the elderly population of Ashkenazi Jews.

Objecive chromatic pupillometer - pupillary responses of healthy subjects to chromatic stimulation from small 2.5-mm-diameter spots

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Purpose: We recently developed a second-generation chromatic multifocal pupillometer with 76 LEDs of 30 degree visual field and a small spot size (2.5 mm diameter) resembling the Humphrey's 30-2 perimetry. Here we determined the pupillary responses of healthy participants to chromatic stimuli at central locations

Methods: 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) presented by 76 LEDs, 2.5 mm target diameter , at increasing light intensities (0.1-10,000 cd/m2). Stimulus duration was 1 sec. The pupillary responses to chromatic stimulus presented at 4 central points of the visual field were tested in 12 normal subjects (ages 24-76).

Results: All participants easily tolerated the protocol without any discomfort. Near exponential increase in pupil contraction was recorded in response to long-wavelength at intensities 0.1-320 cd/m2 and to short- wavelength stimuli at intensities 0.1-430 cd/m2. The pupillary contraction reached a near plateau in response to the long- and short- wavelength stimuli at intensities of 1000 and 1300 cd/m2, respectively.

Conclusions: The chromatic pupillometer enabled the detection of pupillary responses to small spot size chromatic stimuli at a wide range of light intensities. These data will be used for setting an age matched clinical protocol for objective chromatic multifocal visual field testing.

Beyond the eye - behavioral and cortical assessment in posterior cortical atrophy (PCA)

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Background: Posterior cortical atrophy (PCA) is a neurodegenerative syndrome characterized by a progressive and relatively selective decline in higher visual processing. Age of onset is typically 50-65 years old, and the underlying pathology is associated with Alzheimer disease. Even though the syndrome is been recognized for more than two decades, PCA is relatively neglected by clinicians and researchers, and the patients are often referred to recurrent visual evaluation and face considerable delays in diagnosis.

Methods: 6 patients with PCA and 5 age matched controls underwent a comprehensive set of visual and neuropsychological tests, aimed to differentiate between lower and higher visual functions as well as between dorsal and ventral-related cortical functions affected in the syndrome. Functional MRI (fMRI) was performed on 3 patients addressing the neuronal substrate of the visual dysfunctions.

Results: Visual acuity, refractive change, phoria and color perception were within normal limits in all patients. Impaired saccadic eye movements were evident in all patients; and were significantly different from the controls. Stereopsis was impaired in three patients. Addressing visual perception, deficits in the patient's visual perception were mainly seen within dorsal-related functions. These include simultaneous perception, image orientation, figure-from-ground segregation, visual closure, spatial orientation, motion coherence and monocular depth perception. In addition, fine details discrimination was impaired in five patients. Face perception, letter reading and color naming were intact. In accordance with the behavioral findings, fMRI revealed intact activation in ventral visual regions responsible for face and objects perception. Comparing cortical activation during local and global analysis (usingNavon letters) revealed greater activation for local processing in the visual cortex as well as in the Temporo-Parietal junction (TPJ), known to be involved in Geshtalt perception.

Conclusions: The syndrome effects a myriad of both higher and lower visual functions, and can be seen both in behavioral testing and in functional imaging. Greater awareness of the syndrome is needed to improve diagnostic accuracy, clinical management and design of research studies. Based on our findings a therapy program should be instilled, training both ocular motility as well as global perceptual skills.

Near vision improvement in pilots with presbyopia using perceptual learning

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Purpose: Presbyopia results in blurred images and progresses with age, usually starting at ~42-44 years of age. In our earlier studies, near visual acuity (VA) of presbyopes was significantly improved following perceptual learning, persistent for up to 6.2 years (mean 2.5), despite the natural deterioration of ~1.25 Diopters and 2 ETDRS lines expected during this time. Similarly, distance VA in young was improved, with gains in higher visual functions, such as reading, in both age groups. We assume that both improvements in contrast sensitivity and processing speed underlie these gains. Since Israeli Air Force pilots continue combat missions even after the age of onset of presbyopia, they have to deal with the following issues: 1) pilots with perfect distance vision (emmetropes) are required to adapt to flying with glasses in order to enable them to read in the cockpit; 2) pilots with distance glasses prescription (ametropes) need to have a near segment added to the lower part of their lenses. This has a negative influence on the effective field of view of the pilot. Moreover, for pilots flying extensively with night vision goggles (NVGs), flying with glasses means that NVGs must be placed slightly further away from the pilot\'s eyes, also decreasing the size of the visual field. This decrease in visual field may decrease the pilot\'s flying capability. The pilot is faced with a similar problem when flying with a helmet display unit (HDU) that is placed very close to the right eye. Thus, there is an operational need for delaying presbyopia onset or improving near VA in order to avoid the use of optical corrections. Here we aimed to improve near VA of pilots using our perceptual learning method.

Methods: Over 40 pilots (mean age ~47) already started a training protocol for presbyopia (GlassesOff mobile application for iOS devices from 40 cm, 12-15 min/session, 3 times/week).

Results: Based on early post-training results, there was a significant improvement in basic visual functions, such as contrast sensitivity, contrast discrimination and temporal processing, generalized to higher visual functions, such as reading and low-contrast aerial photography interpretation.

Conclusions: We therefore suggest that training based on perceptual learning is effective for overcoming blurred vision in presbyopic pilots with real operational benefits. Once all data is gathered, protocol will be considered for inclusion in IAF standard protocol for correction of presbyopia.

Navigation patterns and spatial perception in visual and vision-deprived navigation with assistive devices

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Purpose: How does lack of vision affect the route one takes in an environment? How does this route change when different assistive devices are used? These questions have significant repercussions as Orientation and Mobility in unknown places pose one of the main challenges facing the blind.Currently, dedicated programs exist for helping the blind learn to navigate using the traditional white-cane. Over the years these programs were improved and have proven to significantly improve mobility. This research has also led to defining unique navigation patterns of white-cane users.Over the past decades many new devices have been developed for the blind. These devices offer different, and often more, information than the traditional white-cane, and may require different patterns of navigation and training for optimal use. Additionally it is unclear how useful some of these parameters, such as increased distance, actually are for non-visual navigation, and if they can be correctly integrated into their spatial perception.

Methods: Here, we use a series of virtual environments to explore the differences in vision-deprived navigation when using the virtual-EyeCane electronic travel aid (which offers increased distance information), when using a virtual version of the traditional white-cane, without using a device at all and when navigating visually.The virtual-EyeCane is based on the Eyecane developed in our lab which augments the traditional whire cane by offering the blind user additional distance information without contact with the user's environment.

Results: We show that the characteristics of navigating with the virtual-EyeCane differ from those of white-cane users and from navigation without an assistive device, and that virtual-EyeCane users complete more levels successfully, taking a shorter path and with less collisions than users of the white-cane or no device. Finally, we demonstrate that virtual navigation with the virtual-EyeCane takes on patterns relatively similar to those of navigating visually.

Conclusions: These results suggest that navigation patterns learned from the white-cane are not necessarily optimal for other devices and that additional distance information is enough to change the spatial perception and navigation patterns from those customarily used in non-visual navigation to patterns more similar to visual navigation. (visual function)

Blind navigation with SSDs in real and virtual mazes

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Purpose: When using sensory substitution devices, blind people can navigate in a simple life-size obstacle course (Maidenbaum et al., 2013, Chebat et al., 2011), and recognize routes (Chebat et al., 2011). Can this be generalized for complex mazes and virtual environments?

Methods: We tested the ability of congenitally blind (CB), low vision and late blind (LvLb), blindfolded control (SbfC) or fully sighted individual (SfvC) to navigate in a real life-size maze using a novel in-house sensory substitution device dubbed the Virtual-Eye-Cane (EC), and then in a virtual computer rendition of the same maze.

Results & Conclusion: Participants improved on training using our device and a virtual rendition of the maze. We show that, within three days of training, participants can learn to use the EC and make fewer errors in the maze, make less collisions, and in less time over three days of training. We also show that congenitally blind participants are able to use the sensory substitution device more efficiently than the blindfolded group, and late blind-low vision group. On the third day of training CB perform as well as sighted participants in the mazes in terms of errors and collisions.

EyeMusic: new approaches to auditory sensory

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Purpose: Sensory-substitution devices (SSDs) provide auditory or tactile representations of visual information. These devices often generate unpleasant sensations and mostly lack color information. We present here a novel SSD aimed at addressing these issues.

Methods: We developed the EyeMusic, a novel visual-to-auditory SSD for the blind, providing visual information while preserving location and color. Our design uses musical notes on a pentatonic scale generated by natural instruments to convey the visual information in a pleasant manner. 12 subjects underwent a short training of 2-3 hours on this device. Training was followed by a shape and color recognition test. Also, subjects completed a survey regarding pleasantness of the device. Additionally, an online comparison of these soundscapes to those of the vOICe was performed among 23 random users.

Results: The subjects achieved a significantly higher score than chance in both color and shape recognition through auditory stimuli. Additionally, the participants found the soundscapes pleasant and potentially tolerable for prolonged use. The resolution obtained, however, remains relatively low compared to vision, as is the case with many SSDs and visual implants. We addressed this problem by enabling perception of the environment through its separate components. In this way, each part is perceived at a higher resolution.

Conclusions: The novel EyeMusic algorithm provides an intuitive and relatively pleasant way for the Blind to extract shape and color information. We showed, also, that in their mind's eye the Blind can create a whole out of its parts. We suggest that this might help in facilitating visual rehabilitation because of the added functionalities and enhanced pleasantness.

Visual learning in ASD - possibilities and limitations

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Purpose: Autism spectrum disorder (ASD) is a neurodevelopmental disorder reflected in social interaction and communication impairments. While the social-related expressions of autism are extensively studied, not much is known about the mechanisms governing sensory plasticity in ASD although there is growing recognition that this is a key component of the disorder. Individuals with ASD commonly undergo highly repetitive training in order to learn. However in non-ASD participants, repeated exposure reduces sensory sensitivity due to adaptation, and results in specificity of learning. Here, we examined the characteristics of visual learning in adults with autism using modulated levels of sensory adaptation.

Methods: Observers with ASD (n=11) were trained with a texture discrimination task (TDT) for 4 days (Harris, Gliksberg, Sagi; Curr. Biol. 2012). Transfer of learning was tested on the 5th day of training by switching the target's location, and the ability to learn the new location was further examined on days 6-8. Half of the observers were trained with standard training ('standard'), while the other half received added task-irrelevant trials ('dummy') in the course of the learning. This latter procedure has been shown to reduce adaptation and lead to transfer of learning in non–ASD subjects.

Results: Our results showed that in ASD, similar to non–ASD observers, dummy trials effectively reduced adaptation and lead to generalization of learning. In addition, for both groups learning following 'standard' training was specific. Interestingly, while non-ASD observers learn at the new location (days 6-8), ASD observers performance at the new location was comparable to the initial performance level (over-specific).

Conclusions: These finding suggest that ASD observer's visual learning share commonalities with the learning of non-ASD observers. Effectiveness of dummy trials in reducing adaptation, further resulting in transfer of learning, was demonstrated for both groups. However, ASD learning was over-specific when a new target location was introduced. Together, these findings elucidate key properties of perceptual learning in ASD and offer guidance for future intervention.

Shape identification using auditory colors in the blind

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Purpose: To explore the ability of blind and sighted subjects to use the EyeMusic SSD for shape and color identification.

Methods: A new visual to auditory sensory substitution device, the EyeMusic, was used to teach congenitally blind individuals the identification and differentiations of shapes. The visual to auditory sensory substitution device EyeMusic uses different musical timbres to represent color, a feature of the visual modality that up until now was inaccessible to the blind.

Results & Conclusions: While congenitally blind cannot perceive the physical properties of color, here we show that by binding color to timbre they can utilize the information carried by color in order to discriminate shapes and visual features that would not have been distinguishable otherwise.

Actions guided by the EyeMusic sensory substitution device

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Purpose: A key property of a sensory substitution device – where one sense is used to convey information usually conveyed using another sense – is that it would enable users to successfully move within their environment.

Methods: I will present results from our studies exploring movement guided by the visual-to-auditory EyeMusic SSD developed in the Amedi lab.

Results: I will present a quantitative comparison between visually guided movements and movements guided by the EyeMusic SSD, and discuss how information flowing through the action-perception loop transfers across senses. I will argue that sensory-motor learning is not sensory-modality-specific, but rather novel sensorimotor information can be transferred between sensory modalities**.**

Conclusions: I will conclude by outlining the important implications of these findings for visual rehabilitation, and for the visually impaired.

The brain as a task machine – implications for combining invasive and non-invasive approaches

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Purpose: Sensory substitution devices (SSDs) have come a long way since first developed for visual rehabilitation. They have produced exciting experimental results, and have furthered our understanding of the human brain. Unfortunately, they have still not evolved into practical visual rehabilitation, and are currently considered as reserved primarily for experiments in controlled settings. However, over the past decade, our understanding of the neural mechanisms behind visual restoration has changed as a result of converging evidence, much of which was gathered with SSDs. This evidence suggests that the brain is more than a pure sensory-machine but rather is a highly flexible task-machine. i.e., brain regions can maintain or regain their function in vision even with input from other senses. This complements a set of more promising behavioral achievements using SSDs and new promising technologies and tools.

Methods: We developed 2 new SSDs based on this theory, the EyeCane substituting depth with auditory and tactile cues, and the EyeMusic substituting color location and shape with auditory waveforms, and used them in a battery of behavioral tests.

Results: The devices were successfully used for a range of tasks ranging from finding an object and successfully reaching for it to navigation in real and virtual worlds.

Conclusion: Our new results, combined with all these changes strongly suggest that the time has come to revive the focus on practical visual rehabilitation with SSDs and we chart several key steps in this direction such as training protocols and active sensing.

The time course of ocular parameters in ADHD during a continuous performance task (CPT) and the effect of medication

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Purpose: To show that ADHD subjects fail to suppress microsaccades and eye blinks while anticipating a visual stimulus. We investigated the time-course of these ocular parameters along sessions and the effect of medication on it.

Methods: 22 subjects diagnosed with ADHD and 20 control subjects performed 2 sessions of t.o.v.a. while their eye movements were tracked. ADHD subjects performed the second session after taking medication (MPH). We measured the average rates of eye blinks and microsaccades during the entire trial duration (2 seconds) and during the peri-stimulus interval (-100 to 150 milliseconds around stimulus onset) and investigated their time course along the 20 min sessions.

Results: Microsaccade and blink rates increased monotonically over time during the session for both groups, and more so in the peri-stimulus interval. This increase was significantly faster and reached higher levels in the un-medicated ADHD group. With medication, the level and time-course of the microsaccade rate fully normalized to control level, regardless of the time interval (peri or post stimulus) within trials.

Conclusions: ADHD subjects fail to maintain sufficient level of arousal during a simple and prolonged task, which limits their ability to dynamically allocate attention during anticipated stimuli and suppress involuntary eye movements. This impairment normalizes with medication and its oculomotor quantification over time could potentially be used for differential diagnosis.

Improving visual functions in TBI patients by perceptual learning

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Purpose: Accumulating evidence suggests that the adult visual cortex retains significant potential for experience-dependent plasticity. A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. It is widely acknowledged that neuronal interactions in visual processing are robustly affected by changes in the balance between excitations and inhibitions. We had previously developed a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations under the conditions of spatial and temporal maskingIn our earlier studies, our paradigm induced significant improvements in amblyopia (Polat, Ma-Naim, Belkin and Sagi (2004) Improving vision in adult amblyopia by perceptual learning. Proc Natl Acad Sci U S A 101(17): 6692-6697) and presbyopia (Polat, Schor, Tong, Zomet, Lev, Yehezkel, Sterkin and Levi (2012). Training the brain to overcome the effect of aging on the human eye. Scientific Reports, 2: 278). Severe traumatic brain injuries (TBI) are sometimes associated with visual dysfunction which has no effective treatment. Here we applied perceptual training paradigm to patients suffering from visual dysfunction following TBI.

Methods: Patients were trained on contrast detection of foveal and peripheral Gabor targets under spatial and temporal masking conditions, targeting the improvement of both collinear facilitation and temporal processing. Patients were trained on a PC computer from a distance of 1.5 meters, once or twice a week.

Results: Training improved lateral interactions, measured as an increase in facilitation and a decrease in suppression, if existed. These gains were generalized into improvements in the basic visual functions, such as contrast sensitivity, visual acuity, crowding, reaction time, and Vernier acuity, as well as in higher visual functions, such as reading. There was also improvement in the oculomotor parameters, both in the pattern of eye movements and during fixation. Moreover, in several patients, training caused improvements in eye fixation, thus significantly increasing the reliability of visual field testing.

Conclusions: The results allow us to conclude that the visual improvements are not due to the development of a compensational eye movement or fixation strategy to overcome the visual deficiencies, but rather due to improvements of the neural networks involved in the basic visual processing in the brain..

Grating acuity is reduced in children with acute papilledema

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Purpose: To assess visual function in children with acute papilledema using sweep visual evoked potentials (sVEP).

Methods: Contrast sensitivity and grating acuity were prospectively measured by using sweep visual evoked potential (VEP) testing in nine children with mild or moderate acute papilledema, aged 9-16 years. Five children were tested longitudinally before and after treatment. The data of patients was compared with 11 age matched controls utizing the Mann-Whitney U Test.

Results: Control group's log MAR (mean 0.10, range -0.06 to 0.25) was better than the papilledema group (mean 0.33, range 0.19 to 0.48). Five patients showed recovery of contrast sensitivity following treatment of their raised intra-cranial pressure (ICP) between first and last visit (log peak contrast sensitivity, p= 0.024; grating acuity in logMAR units, p=0.059).

Conclusions: In children undergoing treatment for raised ICP, sVEP may be a useful adjunct to monitor treatment. SVEP was able to detect improvement in contrast sensitivity despite absence of apparent clinical change in disc edema.

Simultaneous monocular tracking of two targets in the Common Chameleon (Chamaeleo Chameleon)

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Purpose: Chameleons are arboreal lizards that forage visually for insect prey. Their eyes are highly mobile and perform large amplitude, independent, saccadic movements. Once prey is detected, eyes converge, the tongue shows an "initial protrusion", distance is visually estimated and the tongue is struck. Chameleons are here used as a model for visually guided behavior. We ask: (1) Can chameleons track two targets simultaneously and monocularly (i.e., one with each eye)? (2) Are there distinct tracking patterns? (3) Are tracking responses lateralized?

Methods: Common chameleons (C. chameleon) were trained to respond to computerized prey models on a computer screen. Then, in each test, the chameleon was presented with a single target at the centre of the screen. Once it showed eye convergence and an Initial Protrusion of the tongue, indicating that both eyes view the same area the target diverged into two targets, moved in opposite directions at the same velocity. Head and eye movements were video filmed and analyzed.

Results: (1) Chameleons showed a clear capacity to visually tracking two moving targets, simultaneously & monocularly, (2) Monocular tracking of diverging targets, comprised “smooth” phases interspersed with brief and rapid “steps”, (3) For the \"smooth\" phases: The mean duration and frequency, per test, were similar over all tests, (4) For the \"steps\": The mean frequency, per test, was similar over all tests, (5) The patterns of “smooth” and “steps” differed between monocular tracking of two targets and binocular tracking of a single target, (6) There was no evidence for lateralization in eye movements..

Conclusions: To our knowledge, this is the first report of a capacity of simultaneous and monocular tracking in a vertebrate. In ectotherms, the optic nerves are fully decussated and inter-tectal connections are not developed to the level of mammals'. We suggest that eye movements in chameleons are not "independent" and are under a higher neural control that allows independence in scanning, yet is coordinated / dependent in binocular or monocular tracking movements, depending on the context.

Visual acuity in the Common Chameleon (Chamaeleo Chameleon)

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Background: Common chameleons use vision to catch prey and avoid predators. They show large amplitude, "independent" eye movements to scan the environment. Once a target is sighted they switch to binocular fixation following which the tongue is struck at the prey. They are unique in their precise estimation of prey distance, using monocular lens accommodation effort and in having the only known negatively powered lens. Questions: (i) What is the visual acuity of chameleons? (ii) Is visual acuity related to eye size? (iii) What is the effect of the direction of stimulus motion on acuity?

Methods: Acuity of chameleons was tested by their optokinetic response (OKR), in a rotating drum (radius 46cm or 68cm; Angular velocity ~6deg/sec) lined with vertical, high contrast, black and white bars. Bar widths (2, 1, 0.5mm) provided respective frequencies of 2.9, 5.9, 8.3&11.7 c/deg. The drum rotated clockwise (CW) or counter clockwise (CCW). Chameleons' external eye diameter was 10.8mm (Â±SE=0.55, n=8), 7.3mm (Â±SE=0.25, n=4) and 3.3mm (Â±SE=0.13, n=10). Acuity of chameleons was tested by their optokinetic response (OKR), in a rotating drum (radius 46cm or 68cm; Angular velocity ~6deg/sec) lined with vertical, high contrast, black and white bars. Bar widths (2, 1, 0.5mm) provided respective frequencies of 2.9, 5.9, 8.3 & 11.7 c/deg. The drum rotated clockwise (CW) or counter clockwise (CCW). Chameleons\' external eye diameter was 10.8mm (±SE=0.55, n=8), 7.3mm (±SE=0.25, n=4) and 3.3mm (±SE=0.13, n=10).

Results: The visual acuity of the chameleons was ca. 10 CPD and was not positively correlated with eye size. Temporal to nasal (TN) stimulus motion elicited a higher OKR response compared with the respective naso to temporal (NT) motion direction.

Conclusions: Behavioral visual acuity in the common chameleon is higher than in other lizards of similar axial length (e.g., sleepy lizard Tiliqua rugosa; New&Bull, 2011), or reptiles with larger eyes (e.g. Loggerhead Caretta caretta; Bartol et.al, 2002 and Midland banded water snake Nerodia sipedon pleuralis; Baker et.al, 2007).The greater sensitivity of the common chameleon to motion in the TN direction is similar to other vertebrates (e.g. frogs, chicks, fishes), yet differs from the African chameleon in which the responses to TN and to NT directions were similar (Tauber&Atkin 1967).

Retinal function and structure in the Chinchilla

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Purpose: Few mammalian species have a pure rod retina. Yet Detwiler (1949) claimed that the chinchilla retina is "cone free", and Duke-Elder (1958) stated that "it is presumed that chinchillas have a pure rod retina". Our aim was to characterize retinal function and morphology, using electroretinography (ERG), immunohistochemistry (IHC) and Optical Coherence Tomography (OCT) in order to test these statements.

Methods: Rod and mixed rod-cone function was recorded after overnight dark adaptation (5 steps, 0.0096-30cd*sec/m2), while transient and flicker cone responses were recorded after 10 minutes light adaptation (13 pigmented eyes). Retinas were imaged using OCT. Retinal sections were immunostained with the cone marker peanut agglutinin, anti-rhodopsin, anti-blue opsin, and anti-red/green antibodies to determine the presence of cones and their subpopulations.

Results: We were able to record both rod and cone responses. Preliminary ERG analysis reveals that rod a-wave amplitude increased with intensity, but surprisingly, so did implicit times. Unexpectedly, rod b-wave amplitude did not increase with intensity. A- and b-wave amplitudes of both rods and cones were only 10-25% of respective values in pigmented mice. Preliminary IHC revealed presence of rods and red/green cones, but in some areas only very few blue cones were seen.

Conclusions: Contrary to historic statements, the chinchilla retina contains functional cones. There are additional unexpected findings in our study, including the low amplitudes, and lack of change in dark adapted b-wave amplitude as a function of intensity. These results may be due to saturation of photoreceptor function in relatively low intensity, a low functional bipolar/ photoreceptor ratio, and / or due to low numbers of functioning cones. Additional IHC studies, and OCT imaging, may reveal the basis for some of our findings.

Chromaticity underwater: colorful fish may not be more conspicuous to Great Cormorants

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Purpose: Water acts on light as a chromatic filter so that chromaticity of underwater targets undergoes differential attenuation, and thus affects visual resolution. Colors are frequently used in shallow water fishes as part of their signals social communication (aggression, courtship). Frequently their patterns comprise black and color bars. Theory predicts that color will render its bearers more conspicuous to predators. Great cormorants are pursuit divers and major predators of fish. Is underwater visual resolution of cormorants to chromatic and achromatic targets higher than to achromatic targets?

Methods: Hand-reared Great cormorants (N=6) were 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). Grating frequencies ranged from 1.4 to 12 cpd. Illumination was diffuse daylight and water turbidity ranged 0.3-5.6 NTU. 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: Maximal underwater visual resolution for achromatic and chromatic gratings was ca. 8cpd. Resolution for achromatic gratings was higher than for chromatic gratings but not significantly so. Chromatic components did not have a significant effect while the effects of gratings frequency and of individual differences on resolution were significant. The significant individual differences in resolution were stable over a period of several years.

Conclusions: Because chromaticity of targets did not affect visual resolution, we suggest that colorful individuals are not more conspicuous to their predators underwater. A venue to follow is the combination of chromaticity and motion. Long term individual differences in visual capacities lend support to the need to study individuals and not "statistical averages".

A bio-inspired stereo compound-eye imaging device based on the visual system of the praying mantis

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Purpose: Introducing a scheme for the geometric design of an active vision system. The system is based on principles of the optical structure of the compound eye of the praying mantis, combining a wide field of view for detecting objects with a high resolution for smooth pursuit.

Methods: We introduce (i) A mathematical method to characterize a single compound eye imaging device by its caustics, (ii) A mathematical model for the design and characterization of a stereo compound eye system, using two mathematical tools: iso-disparity curves and OCPs (Ommatidial optical axes Cross Points). Finally, we offer a depth from self motion algorithm.

Results: We produce an omnidirectional system, designed to identify targets over a wide field of view and to produce sufficient visual information to estimate distance to selected targets without a zoom mechanism. Furthermore, our imaging device is designed to be small and simple. We comply with these requirements using three principles (i) Single compound-eye camera geometry : an efficient geometric shape for each compound eye-like imaging device, (ii) Design of stereo configuration, i.e. the correct placement of the two eyes on the head, based on the analysis of the stereo performance requirements. (iii) A mechanism for self-motion to improve depth estimation.We also provide mathematical tools suitable for the demands our stereo biologically inspired omnidirectional vision system design.

Conclusions: We achieved a biomimetic geometric design of an active vision system that is stereo omnidirectional and cope with the contradictory tasks of a wide field of view and distance estimating without a zoom mechanism.

Cone function in normal and day blind sheep. A large animal model for CNGA3 achromatopsia patients

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Purpose: Recently we reported on day blindness in sheep caused by a mutation in CNGA3 gene, thus making affected sheep a naturally-occurring large animal model to study therapeutic intervention in CNGA3 achromatopsia patients. The purpose of this study was to characterize cone function in normal and day blind sheep, with the aim of generating baseline data for ongoing gene therapy studies.

Methods: Cone function was recorded with full-field electroretinography (ERG) in 10 normal control animals, 6 heterozygous carriers of the CNGA3 mutation and 36 day blind sheep, homozygous for the CNGA3 mutation. Following light adaptation (10 min., 30 cd/m2), responses were recorded using 36 steps at four increasing intensities (1, 2.5, 5 and 10 cd*s/m2). At each intensity, the single photopic flash response and 8 cone flicker responses (10Hz-80Hz to determine the critical flicker fusion frequency, CFF), were recorded, resulting in a total of nine steps at each light intensity.

Results: The normal sheep ERG wave is bipartite in nature, with CFF>80 Hz. There was no effect of gender or age on cone function in any of the groups, except an age-related decline in a-wave amplitude of the day blind animals. There were no significant differences in cone function between normal control and heterozygous carriers. In all four flash intensities, the single photopic flash a-wave and b-wave amplitudes were significantly lower ($P<0.005$), and implicit times significantly delayed ($P<0.0001$), in day blind animals. In all four flash intensities, representative 20 Hz b-wave amplitudes of day blind sheep were significantly lower in day blind animals ($P<0.05$). In addition, CFF values were significantly lower ($P<0.0001$) in day blind sheep at all intensities.

Conclusions: CFF of normal sheep is significantly higher than that of humans or rodents. The lack of differences between carriers and normal controls implies that a single alpha3 subunit is sufficient for normal function of the CNGA channel. Cone function is severely depressed in day blind sheep, similar to findings in achromatopsia patients. Our results will provide baseline data for ongoing gene therapy studies.

Polarization vision - why animals and not humans?

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Purpose: Except of detecting a fade yellow-blue "bowtie" pattern known as the Haidinger's brush, when gazing at a polarized white surface (such as LCD computer screens), humans are incapable of detecting polarized light, and do not make use of this channel of information in their vision. Unlike humans, terrestrial and aquatic animals, both vertebrates and invertebrates are highly sensitive to light polarization abundant in the sky and underwater, and utilize it for various visual tasks such as sun-compass for navigation, orientation, contrast enhancement, habitat selection, and signaling and communication. The basis for the difference in sensitivity to polarized light between vertebrates and invertebrates lies in the directionality of the retinal molecules that absorb the light. While in invertebrates, the retinal molecules are highly directional; in vertebrates they are completely disoriented. This directionality allows for the differential absorption of light according to the electric (e-) vector orientation of the incoming light and consequently for the detection of polarized light.

Methods: Response to polarized light was checked behaviorally in the silverside fish Atherinomorus forskali, a small (~5cm) pelagic planktivor. Using an optomotor response apparatus, fish were presented with rotating polarized stripes that polarization insensitive visual system such as the human eye could not detect. This method evokes tracking movement of sensitive animals which aim to stabilize the visual scene

Results: Positive respond was documented as the fish swam with the rotating polarized stripes. the respond depended on the spectrum of the light as the fish swam under illumination that included ultraviolet (UV) light only.

Conclusions: It is concluded that A. forskali is sensitive to polarized light. This is the first convincing behavioral evidence of any vertebrate sensitive to polarized light. As the fish retinal molecules are disoriented in similar to that of humans, the mechanism for polarization detection in fish remains a mystery.

The sealing effect of external diathermy on leaking sclerotomies after small gauge vitrectomy surgery - a clinico-pathological report

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Purpose: To evaluate local histological and wound architecture changes in scleral wounds of varying sizes following the application of external diathermy.

Methods: A 3-port pars plana vitrectomy was performed on fresh porcine eyes to remove the vitreous gel. The sclera was penetrated 3.0 mm from the limbus in a beveled manner using trocars of various sizes: 20-, 23-, 25-, and 27-gauge. At the end of the surgical procedure external bipolar diathermy with a power of 44 Watts was applied to the sclerotomy sites for 5 seconds and compared to a nondiathermized control. This experiment was repeated three times in three different eyes for every gauge tested. Eyes were then placed in 4% formaldehyde and embedded in paraffin. Histological sections through the sclerotomies sites were stained with hematoxylin, eosin and Masson's trichrome collagen stains. Sites were microscopically examined for histological changes, with particular attention to collagen changes sealing the wounds and for adhesion of conjunctiva to the sclerotomies.

Results: Sixty percent of the small gauge (27, 25 G) sclerotomies were closed without diathermy, in comparison to none of the larger gauge sclerotomies. Histological sections of all sclerotomies for which diathermy was not applied showed sclerotomies with homogenous collagen architecture throughout the thickness of the sclera. Large gauge sclerotomies (20 G) for which diathermy was applied demonstrated partial thickness outer scleral melting and denaturation of scleral collagen. Fusion of tissue over the sclerotomies sealing the outer portion of the sclerotomies was noted in all the small gauge sclerotomoies.

Conclusions: Applying external diathermy on a leaking sclerotomy is an effective way to seal leaking sclerotomies in small gauge sutureless vitrectomy surgeries.

New application of hydrogel-sealant to close 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 treat retinal breaks; as laser, freezing, sclera 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 hydrogel implant to the retina with the aim to close retinal tears. DuraSeal is a biocompatible and biodegradable hydrogel with high compatibility to the environment of the eye and was therefore chosen for these studies.

Methods: 12 Male New Zealand rabbits were divided into 2 groups (n=6/group); 1) Retinal detachment (RD) with no treatment and 2) RD with treatment. Retinal detachment was created in the right eye of each animal while left eyes were left as internal controls. For the detachment; a 25G vitrectomy was performed upon which the inferior retina was detached by intravitreal infusion of 0.1ml balanced salt solution using a soft-tip needle between the neural retina and RPE, a small tear was created by the needle. After the detachment was confirmed, the treated group received trans-scleral injection of 0.1ml hydrogel into the subretinal space, whereas the RD group received sham injection of saline. Eyes were clinically evaluated using indirect ophthalmoscope prior to the surgery and on 1, 3, 7 and 14 postoperative day, ERG was performed before and 14 days post-surgery and sealants toxicity was evaluated on enucleated eyes using H&E histological staining.

Results: The DuraSeal hydrogel was easily injected into the sub-retinal space of the detached retina with no major complications. The hydrogel was found to absorb water from its surrounding as it swell. Retinal reattachment was seen two weeks upon hydrogel injection with minimal toxicity to the sensory retina.

Conclusions: Use of sealant hydrogels was proved to be a feasible method to seal retinal breaks and may open a new avenue for retinal detachment surgeries. Future long-term clinical, functional and toxicological studies are set to evaluate its full potential for clinical applications.

Seasonal airsoft gun-related ocular injuries and macular OCT follow up of one case with macular edema

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Purpose: To describe the ocular injuries related to Airsoft gun bullets in children over one month in 2008 during a Middle Eastern Festive holiday ("Elfeter") and to present one case with OCT follow up of macular edema.

Methods: Retrospective case series. All consecutive cases of patients with Airsoft gun-related ocular injuries during 9-10/2008 (Elfeter Holiday) were included in this study.All patients were treated in the Department of Ophthalmology at Haemeq Medical Center, Afula, Israel.The main outcome measure was ocular injuries of the patients from Airsoft Guns during one holiday.

Results: Twelve patients with a mean age of 13.3±11.7years (5 - 49) were examined; 11 were males. 8 patients were hospitalized and 4 treated in the outpatient clinic. The ocular injuries included hyphema 11, corneal erosion and edema 10, traumatic mydriasis 3 and retinal edema 3. The range of the Visual Acuity on presentation was 1 to HM and last follow up range of the visual acuity 1 to 0.25.

Conclusions: Airsoft Gun ocular injuries are common in children due to the availability of seemingly harmless toy guns which in fact are very dangerous. These injuries occur especially during the festive holiday season and could be prevented by increasing awareness among the public

Computerized analysis of OCT images: segmentation and measurement of retinal layers thickness

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Purpose: Optical Coherence Tomography (OCT) has rapidly become a leading imaging modality in both clinical practice and research. As resolution and quality improved, the need for accurate segmentation and measurement of the retinal layers within OCT images increased. Currently most centers employ manual measurement, a method prone to significant observational and experimenter biases. We aim to develop a software tool that will allow objective, consistent measurement of total retinal thickness and of specific retinal layers in OCT images, with emphasis on the Outer Nuclear Layer (ONL).

Methods: Background noise was removed and the location of the inner and the outer retinal borders were determined separately. We first isolated the brightest elements of the scan by the Otsu method. The Retinal Pigment Epithelium (RPE) was identified by isolating the largest component of the scan's connectivity map. Remaining noise was removed using an adaptive Wiener filter. To identify the Inner Limiting Membrane (ILM), we constructed a difference array of the image intensity. A Sobel filter emphasized the edges of composite structures. Another connectivity map was constructed, with the uppermost largest component comprising the ILM. The distance between the RPE and the ILM was denoted as full retinal thickness. The intraretinal layers were identified applying a clustering algorithm by pixel intensity. Correct classification of the pixels into clusters was ascertained by verifying layer connectivity.

Results: Our preliminary results include the application of the algorithm to 15 scans of healthy and 10 scans of Leber Congenital Amaurosis patients with an identified RPE65 mutation. The segmentation of the software was in agreement with manual segmentation performed by a retina specialist. The mean thickness of the ONL was 81.4 (7.1 SEM) in healthy vs. 39.5 (8.5 SEM) in RPE65 patients ($p<0.01$). Full retinal thickness measurements were 270.1 (16.9 SEM) in healthy vs. 198.5 (22.4 SEM) in patients ($p<0.05$). Measurements in microns, one-way ANOVA.

Conclusions: This prototype software tool provides the framework for objective, semi-automated estimation of retinal layer thickness. Further improvements and large scale validation of the algorithm are currently being performed. This may enhance monitoring and quantification of disease progression in patients with retinal disease, as well as guide future therapeutic interventions including gene and cell therapy.

Quantifying metamorphopsia in patients with various types of macular abnormalities

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Purpose: To quantify subjective visual deformity in patients suffering from macular abnormalities using the M-CHARTS

Methods: Newly diagnosed patients with subfoveal CNV secondary to AMD, diabetic retinopathy or retinal venous occlusion were recruited. All patients were tested with the M-CHARTS which isa set of 19distorted dotted lines diagrams. The dot intervals range between 0.2° to 2.0° visual angles. Metamorphopsia is scored according to the minimum visual angle of the dotted line needed to null the distortion.

Results: Twenty-nine patients included in this study. 14 patients had AMD-CNV, 10 had DM-CME and 5 had a retinal vein occlusion. In 85.7% of patients with AMD-CNV, there was a positive metamorphopsia score (mean 0.75), average central macular thickness by OCT was 390±113µ. Only 60.0% of patients with DN-CME had a positive metamorphopsia score (mean 0.4) ,average central macular thickness was 460±95µ. However, 80.0% of patients with retinal vein occlusion had a positive metamorphopsia score (mean 1.40) with central macular thickness of 533±115µ.

Conclusion: In the majority of patients with maculopathy, it was possible to quantify the visual distortion using the M-CHART. It may serve as an easy self-follow-up and early detection tool in those patients.

Non-mydriatic fundus camera for diabetic retinopathy screening in a safety net hospital: Assessment of effectiveness, prevalence and risk factors

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Purpose: To evaluate diabetic retinopathy (DR) prevalence, risk factors and the effectiveness of non-mydriatic fundus camera as a screening tool for the detection of DR.

Methods: A retrospective, population based, cross sectional study. Diabetic patients, referred by their primary care physicians to a DR community screening program, were included. 45 degree digital color fundus images were obtained using a Topcon TRC NW-6S camera. Images were interpreted by retina specialists using a quality rating system. Patients with retinal findings or unreadable photos were referred for a complete examination. Outcome measures were attendance rates, photograph quality, DR prevalence and associated risk factors.

Results: 948 diabetic patients were sent for camera screening, with an attendance rate of 65.6% that increased during the study period. The mean age was 55.8±11.6 years , the majority (56.9%) were Hispanic and 43.5% were uninsured. Overall photo quality rating was relatively high, 81.7% graded as good or fair. 30 photos (2.9 %) were completely unreadable. The prevalence of newly diagnosed DR was 11.1%. Independent DR associated risk factors included: Hispanic race (OR=2.29), lack of health insurance (OR=2.49), longer duration of diabetes (OR=1.07), higher HbA1c levels (OR=1.19), presence of diabetic complications (OR=2.93) and lack of previous eye examination (OR=13.22).

Conclusions: Non-mydriatic fundus camera is an effective and feasible screening tool for the early detection of DR. It should be considered, in areas with limited access to health care to improve quality of care and potentially reduce vision loss rates.

Assessment of retinal perfusion using ultra wide filed imaging in patients with diabetic retinopathy treated with intravitreal bevacizumab

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Purpose: To evaluate retinal perfusion in diabetic retinopathy (DR) before and after treatment with monthly intravitreal bevacizumab (IVB) injections over a medium term follow up, using ultra wide field (UWF) retinal imaging.

Methods: A retrospective, interventional, non comparative case series. Diabetic patients with newly diagnosed proliferative diabetic retinopathy (PDR) and/or macular edema (ME) were included. All were treated with IVB 1.25 mg/ 0.05cc injections every 4-6 weeks, if pan retinal photocoagulation (PRP) could be deferred for at least four weeks at physician discretion. Patients with previous treatment with laser and/or anti angiogenic therapy, media opacity or PDR complications were excluded. Follow up included fluorescein angiography (FA) using UWF laser scanning ophthalmoscope technology (Optomap panoramic 200TxTM, Optos®) that allowed for high resolution visualization of the retina up to 200 degrees in one frame. The main outcome measure was the extent of retinal perfusion . Secondary outcomes were regression of neovascularization (NV), macular ischemia, BCVA and need for additional PRP or vitrectomy.

Results: Twelve eyes of six patients (five males and one female) were enrolled in the study. Mean age was 54.8± 8.1 years. 50% were treated with insulin with an average HbA1c of 8.45%. 50% had hypertension and 66.7% had hyperlipidemia. Eleven eyes were diagnosed with PDR and eight eyes with ME. Patients received on average 3 injections (range 2-4) and followed for an average of 16.5± 3.2 weeks. IVB allowed for regression of NV in eleven eyes, demonstrated on FA a month after the first injection. The average ischemic area decreased significantly from 86.2%± 4.9% to 77.2%± 10.7% and the average perfused area increased significantly by 66.5% during the follow up period (P=0.0024) . Two eyes showed minimal reduction in ischemic area after treatment and one of them developed mild persistent vitreous hemorrhage without evidence of active NV. Macular ischemia didn't evolve in any of the study eyes. None of the eyes developed DR complications that required rescue with PRP or vitrectomy. Average visual acuity improved significantly from 0.48 log MAR before to 0.26 log MAR after treatment (p=0.0036).

Conclusions: IVB injections improved retinal perfusion in a small series of patients with DR over a medium term follow up. Further prospective large scale studies are needed to determine the role of IVB in PDR.

Blood vessel pattern in the fundus of subjects with albinism

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Purpose: To Assess the spatial configuration of the main arteries and veins of the temporal arcade in genetically diagnosed subjects with albinism and normal subjects and to assess its relationship to visual acuity and spherical equivalent. Assessment of the angle with which the vessels leave the optic nerve has been used in evaluation of macular structure.

Methods: Fundus photographs of the posterior pole (30° field of view) including the main retinal blood vessels were taken using a Topcon fundus camera (TRCNW65) in subjects with albinism (n=16) and age similar controls (n=18). Measurements of the angle between the main inferior and superior artery were made using a custom vessel segmentation program at a number of eccentricities extending for two disc diameters from the center of the optic nerve head. Visual acuity and spherical equivalent was determined for each subject.

Results: For the arteries, angle varied significantly with group ($F=8.79$; df 1,524, $p<0.01$) and eccentricity ($F=38.1$; df 15,524, $p<0.01$). For the veins, angle also varied significantly with group ($F=10.4$; df 1,532, $p<0.01$) and eccentricity ($F=15.5$, df 15,532, $p<0.01$). The angle between superior and inferior veins was significantly larger in controls than in subjects with albinism. Separation of artery/vein pairs was larger in controls than in albino subjects (14° vs 3°). Visual acuity was significantly poorer in the albino subjects ($p<0.001$). Spherical equivalent of albino and control subjects was similar. Neither visual acuity nor spherical equivalent was significantly related to blood vessel angle.

Conclusions: Differences in spatial configuration of retinal arteries and veins may be a consequence of the altered retinal development that leads to abnormal foveal pit formation in albinism.

Hyperbaric oxygen treatment reduced stroke damage and improved vision in a child and perfusion after middle cerebral artery occlusion in mice

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Purpose: In previous studies we have investigated the therapeutic effect of hyperbaric oxygen treatment (HBOT) on rAION, ONC and CRAO models in rodents. Recently, HBO therapeutic potential has been put to advantage for purposes of cellular tolerance and neuroprotection following stroke in human. A 3 years old girl, preterm 29 weeks at 934 gr, who was diagnosed for VP shunt malfunction was urgently operated when developed brain herniation. Post operative exam revealed no respond to light. MRI showed bilateral occipital stroke. The child was sent for HBO treatment. Following the 10th treatment, the mother reported significant improvement. Repeated MRI showed improvement. The purpose here to examine the effects of HBOT in the treatment of experimental middle cerebral artery occlusion (MCAO) in rodents.

Methods: Temporary MCAO was performed on anesthetized male C57Bl/6 mice using a filament method. After either 30 or 90 minutes of occlusion, the filament was removed, and mice were given either no treatment or 60 minutes of hyperbaric 100% oxygen treatment at 2.5 atmospheres pressure. Brains were collected 24 hours after MCAO and the infarct area was examined using 2,3,5-triphenyltetrazolium chloride (TTC) staining

Results: Twenty four hours post-MCAO, TTC staining showed a large lesion volume (120±13 mm3 for 30' MCAO; 173±23 mm3 for 90' MCAO) and a significant reduction in lesion volume of HBOT mice for both occlusion periods (66.5±36.7 mm3 for 30' MCAO; 53.2±17.2 mm3 for 90' MCAO). Lesion volume significantly increased from 30' to 90' MCAO. Brain edema was also significantly reducedby HBOT with 90' but not 30' MCAO due to the smaller edema produced by the 30' MCAO. TTC staining revealed a relatively larger ischemic penumbra relative to core lesion with HBOT treatment.

Conclusion; Our results also show that reduced brain edema can be produced by a single HBO treatment and that this is associated with improved perfusion of damaged areas.

Long-term outcome of intravitreal dexamethasone implant for the treatment of noninfectious uveitic macular edema

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Purpose: To report the long-term outcome of intravitreal dexamethasone drug delivery system (DEX-DDS) injection for noninfectious uveitic macular edema.

Methods: Retrospective study of eyes with noninfectious uveitic macular edema treated with DEX-DDS injection with at least 6 months follow-up time. Macular edema was diagnosed by clinical examination, fluorescein angiography and Heidelberg Spectralis spectral domain optical coherence tomography (SD-OCT). Patients' data were collected and included details of uveitis, ocular inflammation, best corrected visual acuity (BCVA) and SD-OCT at baseline and each visit during follow-up. Number of injections and potential complications were recorded.

Results: 8 eyes (7 patients) were included. One eye with anterior uveitis, six eyes with intermediate uveitis and one eye with panuveitis. Mean follow-up time was 17.3 months. In 1 eye the injection was given as adjunctive treatment. Macular edema resolved in all eyes, 3.9 weeks (range, 1–6.9) post injection. The mean BCVA improvement was 0.25 logMAR ($p < 0.05$), 3.9 weeks (range, 1–6.9) post injection. Central point thickness improved from 612 ±143 µ to 250 ±55 µ ($p < 0.05$). In 5 eyes macular edema did not recur after a mean follow-up of 14.5 months. Macular edema relapsed in 3 eyes (2 patients) after a mean time of 4.7 months (range, 3.6–6.3). These patients had repeated injections; 1 patient had 2 injections and 1 patient had 4 injections with macular edema resolution. Two eyes had intraocular pressure elevation which was well controlled under topical treatment.

Conclusions: Intravitreal DEX-DDS injections resulted in resolution of macular edema and visual acuity improvement. Some eyes required repeated injections, but most eyes achieved long-term resolution. No significant complications were notice**.**