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

הכנס השנתי ה-43, 2023

הפקולטה לרפואה ע"ש רפפורט, טכניון, חיפה

תכנית הכנס

יו"ר: פרופ' שחר פרנקל

גזבר: פרופ' חיים לוי

חברי ועד: פרופ' יוסי מנדל, ד"ר שירי סודרי, ד"ר סאמר חטיב, ד"ר אביגיל בריוזקין, פרופ' רובי שלום פוירשטיין, פרופ' דינה צור, ד"ר הדס בן אלי

בחסות:

ISVER 2023		
Ruth Auditorium		
9.00-100.45	**Retina** Moderators: Ori Segal & Dinah Zur **Anterior segment** Moderators: Irit Bahar & David Smadja	
10.45-11.00	**ISVER Business Meeting**	
11.00-11.30	Break	
	Blue room	**Green Room**
11.30-13.00	**Genetics, Retinal degeneration and Therapy** Moderators: Eran Pras & Tamar Ben-Yosef	**Onco Plastics Glaucoma Neuro Pediatrics** Moderators: Ofira Zloto & Nitza Goldenberg-Cohen
13.00-14.00	Break	
14.00-15.30	**Visual function + Rapid fire: visual function+ anterior segment** Moderators: Hadas Ben-Eli & Eitan Livny	**Animal model + rapid fire animal model** Moderators: Dror Sharon & Ruby Shalom-Feuerstein
15.30-15.45	Break	
15.45-17.00	**Rapid fire Neuro Onco Plastics Pediatrics Glaucoma** Moderators: Nur Khatib & Daphna Landau	**Rapid fire Retina, retinal degeneration and therapy, genetics** Moderators: Miri Ehrenberg & Liran Tiosano

Retina			Ori Segal & Dinah Zur	Ruth Auditorium	9:00
76	Ben Ari	Hadas	**Neuro-retinal function biomarkers for diagnosis and monitoring disease progression in patients with Parkinson's disease**	Ruth Auditorium 9:00	5 minutes
67	Kramer	Adi	**Unbiased Proteome Analysis of Aqueous Humor from Patients with Age-related Macular Degeneration**	Ruth Auditorium 9:05	5 minutes
109	Segal	Ori	**Optic Density Ratio of Sub Retinal Pigment Epithelium Fluid is Associated with Improvement of BCVA after 12 and 36 Months of Follow Up**	Ruth Auditorium 9:10	5 minutes
64	Sharon	Yael	**Specific MicroRNAs as Biomarkers for Uveitis in Juvenile Idiopathic Arthritis**	Ruth Auditorium 9:15	5 minutes
11	Shmueli	Or	**Measuring geographic atrophy area using spectral-domain optical coherence tomography versus fundus autofluorescence**	Ruth Auditorium 9:20	5 minutes
46	Shwartz	Yahel	**Age-related Macular Degeneration (AMD) Staging from Routine Clinical OCT Scans using Deep Learning (DL)**	Ruth Auditorium 9:25	5 minutes
74	Zur	Dinah	**Automated Quantitative Volumetric OCT Analysis and Clinical Characteristics of 4485 Neovascular AMD Eyes with Long-Term Follow-Up in Real World Settings**	Ruth Auditorium 9:30	5 minutes
	Discussion			9:35	

Anterior segment			**Irit Bahar & David Smadja**	**Ruth Auditorium**	**09:50**
97	Altshuler	Anna	**Discovery of discrete limbal epithelial stem cell populations, their function and niche**	Ruth Auditorium 09:50	5 minutes
52	Cohen-Tayar	Yamit	**Predicting keratoconus progression by early tomography data using machine learning algorithms**	Ruth Auditorium 09:55	5 minutes
94	Hadad-Porat	Shira	**Immune cells serve as niche cells for limbal epithelial stem cells**	Ruth Auditorium 10:00	5 minutes
19	Malichy Farber	Idan	**Corneal injury repair is enhanced by clinical-grade alpha1-antitrypsin in vivo**	Ruth Auditorium 10:05	5 minutes
117	Ramia	Jose	**Repeatability of Corneal Mapping Measured Using a Hybrid Optical Coherence Tomographer with Placido Topography Versus a Scheimpflug Tomography**	Ruth Auditorium 10:10	5 minutes
22	Safir	Margarita	**Psychiatric Comorbidities as risk factors for Keratoconus**	Ruth Auditorium 10:15	5 minutes
110	Tiosano	Alon	**Preoperative assessment of eyes at risk of developing Intraoperative floppy iris syndrome (IFIS), Using Artificial Intelligence (AI)**	Ruth Auditorium 10:20	5 minutes
	Discussion			10:25 – 10:45	
	ISVER business meeting			Ruth Auditorium 10:45	
	Coffee Break			11:00 - 11:30	

Genetics, Retinal Degeneration and Therapy			**Eran Pras & Tamar Ben-Yosef**	Blue room	11:30
57	Jaskoll	Shlomit	**Sodium Iodate Induced Retinal Degeneration in BALB/C Mice**	Blue room 11:30	5 minutes
68	Markus	Amos	**Hybrid Retinal Implant Concept: Optimization of photoreceptor cell seeding in micro-wells array implant**	Blue room 11:35	5 minutes
133	Matsevich	Chen	**Gene Augmentation Therapy Attenuates Retinal Degeneration in a Knock-Out Mouse Model of *Fam161a* Retinitis Pigmentosa**	Blue room 11:40	5 minutes
103	Ofri	Ron	**Immune response to intravitreal AAV vector injection in a sheep model of CNGA3 achromatopsia. A serological and clinical survey.**	Blue room 11:45	5 minutes
62	Solomon	Arieh	**Inhibition of Sema-3A promotes cell migration, axonal growth, and retinal ganglion cells survival**	Blue room 11:50	5 minutes
29	Ben-Yosef	Tamar	**Identification of Ceramide Kinase-Like (CERKL) protein-protein interactions in the mammalian retina**	Blue room 11:55	5 minutes
77	Dallasheh	Shada	**Disease modeling and treatment development for RNA splicing factor retinitis pigmentosa using iPSC-derived retinal pigment epithelium cell models**	Blue room 12:00	5 minutes
75	elsana	baker	**Aplasia of lacrimal and salivary glands (ALSG) caused by a partially penetrant novel FGF10 donor splice-site mutation**	Blue room 12:05	5 minutes
47	Grunin	Michelle	**Identifying X-chromosome variants associated with age-related macular degeneration**	Blue room 12:10	5 minutes
36	Schneider	Nina	**Site-Directed RNA editing using Endogenous ADAR of Inherited Retinal Disease-causing Variants within Splice Site Regions**	Blue room 12:15	5 minutes
	Discussion			12:20 - 13:00	

Onco, Plastics, Glaucoma, Neuro, Pediatrics			Ofira Zloto & Nitza Goldenberg-Cohen	Green room	11:30
5	Ben Simon	Guy	**New Evidence of Müller's Muscle as a Sensory Proprioceptive Organ**	Green Room 11:30	5 minutes
125	Eiger-Moscovich	Maya	**Treatment of conjunctival palpebral lesions using Ruthenium plaque brachytherapy "sandwich technique"**	Green Room 11:35	5 minutes
142	Khatib	Nur	**Lacrimal gland volume measurements in normal and thyroid orbitopathy patients using Magnetic Resonance Imaging**	Green Room 11:40	5 minutes
85	Kubovsky	Shoham	**Ru-106 plaque brachytherapy for retinoblastoma at Hadassah - 28 years of experience**	Green Room 11:45	5 minutes
107	Marcovich	Arie	**A rat model of human choroidal melanoma**	Green Room 11:50	5 minutes
53	Nitzan	Itay	**Blepharoptosis and Cognitive Function in 1.4 Million Adolescents: More than Meets the Eye**	Green Room 11:55	5 minutes
69	Bar-Or	Alon	**Identification of structural changes in the macula and optic nerve head as early biomarkers of Alzheimer's' Disease**	Green Room 12:00	5 minutes
131	Ben-Arzi	Assaf	**Early characteristics of Thalassemia & Sickle cell in OCTA in the pediatric population**	Green Room 12:05	5 minutes
118	Kramarz Dadon	Judith	**Intraocular injection of various hydrogels did not induce glaucoma in mice**	Green Room 12:10	5 minutes
119	Lavy	Itay	**Rebound Effect in Gradual vs. Prompt Cessation of Atropine 0.01% treatment for Childhood Myopia**	Green Room 12:15	5 minutes
38	Shemesh	Rachel	**Longitudinal Optical Coherence Tomography Indices in Idiopathic Intracranial Hypertension**	Green Room 12:20	5 minutes
28	Wygnanski-Jaffe	Tamara	**An eye-tracking based dichoptic amblyopia home treatment is comparable to standard occlusion for amblyopia: a multicenter randomized clinical trial (RCT)**	Green Room 12:25	5 minutes
	Discussion			12:30-13:00	

Visual function & Rapid fire: visual function and Anterior segment			Hadas Ben -Eli & Eitan Livny	Blue room	14:00
128	Barayev	Edward	**Color vision deficiency is associated with increased prevalence of amblyopia, strabismus and ametropia: A large population study**	Blue room 14:00	5 minutes
42	Blique	Hadas	**The effect of reading direction on the Development Eye Movement (DEM) test results in Hebrew speaking children**	Blue room 14:05	5 minutes
24	Shneor	Einat	**Baseline Characteristics in the iREAD Study: Israel Refraction, Environment, and Devices Study**	Blue room 14:10	5 minutes
44	Ben-Eli	Hadas	**Development and Validation of Self-Administrate Visual Acuity Near Chart**	Blue room 14:15	2 minutes
25	Doron	Ravid	**Objective Quantification of Viewing Behaviours During Printed and Electronic Tasks in Emmetropic and Myopic Ultra-Orthodox Jewish Men**	Blue room 14:17	2 minutes
83	Rotenstreich	Ygal	**Pediatric refraction measurement with Inverse Shack-Hartmann device without cycloplegia**	Blue room 14:19	2 minutes
80	Achiron	Asaf	**The Antibacterial Efficacy of High-Fluence PACK Cross-Linking can be Accelerated**	Blue room 14:21	2 minutes
27	Dotan	Assaf	**The effect of mydriatics on posterior synechia formation after combined pars plana vitrectomy, phacoemulsification, and intraocular lens implantation**	Blue room 14:23	2 minutes
78	Gal	Eyal	**Short Term Evaluation Two Types of Specialty Soft Contact Lenses for Keratoconus**	Blue room 14:25	2 minutes
122	Gunz	Stav	**Complications of Scleral Lens Wear Amongst Keratoconus Patients**	Blue room 14:27	2 minutes
32	Ifrah	Reut	**Meibomian gland dysfunction in Fitted and Over the Counter Contact Lens Wearers compared with non-Contact Lens Wearing Controls**	Blue room 14:29	2 minutes
40	Livny	Eitan	**Protective shield placed on the optical cylinder in patients after Osteo/odonto-keratoprosthesis (O/OKP): A case series**	Blue room 14:31	2 minutes

132	Luski	Shahar	**Scleral Contact Lens Designed to Reduce Ptosis**	Blue room 14:33	2 minutes
16	Nahum	Yoav	**Finite element modelling of geometrical factors affecting Descemet's membrane endothelial keratoplasty (DMEK) graft adherence**	Blue room 14:35	2 minutes
124	Omar	Lua	**Efficacy and Possible Advantage of Mini-scleral and Scleral Contact Lenses Over a Period of Twenty-four Months in Severe Dry Eye**	Blue room 14:37	2 minutes
114	Reitblat	Olga	**Evaluation of IOL Power Calculation with the Kane Formula for Pediatric Cataract Surgery**	Blue room 14:39	2 minutes
45	Rozanes	Eliane	**CEMENT OCCULAR INJURY LEADING TO ISOLATED CORNEAL ENDOTHELIAL DYSFUNCTION: A CASE SERIES OF A RARE ENTITY**	Blue room 14:41	2 minutes
123	Smadja	David	**Relationship between Corneal Topographic Asymmetry and Epithelial Thickness Profile Map Patterns in Laser Vision Correction (LVC) Candidates**	Blue room 14:43	2 minutes
14	Wattad	Muhamad	**Corneal injury: Expedited healing by alpha1-antitrypsin**	Blue room 14:45	2 minutes
43	Wunch	Inbar	**Refractive Results Following Implantation of Multifocal, Monofocal and Monofocal with Increased Depth of Focus Intraocular Lenses After Cataract Surgery**	Blue room 14:47	2 minutes
95	Yassen	Gharam	**MicroRNA-184 regulates corneal tissue turnover and active stem cell population**	Blue room 14:49	2 minutes
129	Zlatkin	Rita	**Accuracy of Belin/Ambrósio Enhanced Ectasia display map prediction of corneal ectasias in patients with spherical corneas**	Blue room 14:51	2 minutes
	Discussion			14:53 - 15:30	

Animal Models			**Dror Sharon & Ruby Shalom Feuerstein**	**Green room**	**14:00**
100	Dimri-Wagh	Shalini	**Reprogramming to rescue total stem cell loss**	Green room 14:00	5 minutes
102	Dolgin	Vadim	**Coloboma-microphthalmia-anophthalmia in Iranian Jews: from human genetics to mouse studies**	Green room 14:05	5 minutes
37	Kapelushnik	Noa	**The Use of Acoustic Manipulation of Intraocular Particles-In vitro and Ex vivo trial**	Green room 14:10	5 minutes
63	Obied	Basel	**Cobalt affiliation to the optic nerve**	Green room 14:15	5 minutes
48	Palevski	Dahlia	**3K3A-Activated Protein C prevents microglia activation, inflammasome formation and tightens the blood retinal barrier in ocular inflammation**	Green room 14:20	5 minutes
136	Slotky	Aviad	**Characterization of neurite extension in rat photoreceptors precursors (rPRP) – in vitro model**	Green room 14:25	5 minutes
99	Azrad Leibovitch	Tamar	**A new rat model for retinal degeneration: The GCaMP6f+\-RCS-\- Rat**	Green room 14:30	2 minutes
115	Ben Zvi Elimelech	Rony	**The retinal pathways triggered by Amyloid-β42: RNA-sequencing and pathway analysis in rats**	Green room 14:32	2 minutes
93	Bilu	Carmel	**Glucose intolerance and subsequent ocular pathology - Effects of photoperiod and food: evidence from a study in a diurnal rodent**	Green room 14:34	2 minutes
98	Farah	Nairouz	**Retina resuscitation following death**	Green room 14:36	2 minutes
35	Horwitz	Vered	**Using Random Forest Classifier for predicting the clinical outcome of chemical induced ocular injury**	Green room 14:38	2 minutes
96	Misherki	Rabea	**Point mutation in P63 leads to limbal stem cell deficiency that is rescued by a small molecular weight compound**	Green room 14:40	2 minutes

108	Richard	Stephen	**Imaging optic nerves following crush damage in mice**	Green room 14:42	2 minutes
106	Shalom-Feuerstein	Ruby	**Limbal stem cell regulation by biomechanical cues**	Green room 14:44	2 minutes
51	Weinberger	Yehonatan	**3K3A-Activated Protein C treatment exerts anti-inflammatory effects and inhibits choroidal neovascularization in a murine model**	Green room 14:46	2 minutes
23	Zuk-Bar	Nitay	**Study on the BAF (SWI/SNF complex) subunits BAF155 and BAF170 activities in the development and maintenance of pigmented eye lineages in mammals.**	Green room 14:48	2 minutes
	Discussion			14:50-15:30	
	Break			15:30-15:45	

Rapid fire: Neuro, Onco, Plastics, Pediatrics, Glaucoma			Nur Khatib & Daphna Landau	Blue room	15:45
144	Balilty	Lena	**Unusual Agressive Orbital Infection: 4 cases.**	Blue room 15:45	2 minutes
143	Ben-David	Geulah	**Orbital Dermoids with spillage. 3 cases**	Blue room 15:47	2 minutes
86	Darawshe	Mohammed	**Calcium levels in tears and association with nasolacrimal duct obstruction**	Blue room 15:49	2 minutes
65	David	Daniel	**Quality of Life After Eyelid Ptosis Repair Surgeries**	Blue room 15:51	2 minutes
6	Landau	Daphna	**Orbital Fat Density as a Diagnostic Tool in Pre-septal and Orbital Cellulitis**	Blue room 15:53	2 minutes
9	Madgar	Shiran	**Cryptophthalmos: Associated Syndromes and Genetic Disorders**	Blue room 15:55	2 minutes
7	Shalev	Dafna	**Magnetic Resonance Diffusion-Weighted Imaging in Differentiating Lacrimal Gland Lymphoma**	Blue room 15:57	2 minutes
91	Shapira	Yinon	**Magnetic resonance dacryocystography may provide enhanced spatial and temporal resolution in the assessment of functional epiphora**	Blue room 15:59	2 minutes
141	Shyriaiev	Hana	**Basosquamous carcinoma an increasingly important entity: Immuno-stains contributing to its pathological diagnosis**	Blue room 16:01	2 minutes
8	Smadar	Lital	**Outcome of Silicone Sling Frontalis Suspension in Isolated Uncomplicated Congenital Ptosis vs. Complicated Ptosis**	Blue room 16:03	2 minutes
54	Vorobichik berar	Ofri	**Re-surgery for Congenital Ptosis: Characteristics, Success Rates and Predicting Factors**	Blue room 16:05	2 minutes
2	Zloto	Ofira	**The surgical management and outcomes of kissing nevi of the eyelids**	Blue room 16:07	2 minutes
84	Arazi	Mattan	**Eyelid-Light Reflex in Patients with Unilateral Horner's Syndrome**	Blue room 16:09	2 minutes

137	Badir	Nayrouz	**Pre and post operative excyclotorsion in fundus photos**	Blue room 16:11	2 minutes
33	Coster	Dan	**The effect of body mass index reduction on intraocular pressure in a large prospective cohort of apparently healthy individuals in Israel**	Blue room 16:13	2 minutes
12	Goldenfeld	Modi	**Direct selective laser trabeculoplasty in open angle glaucoma study design: a multicentre, randomised, controlled, investigator-masked trial (GLAUrious)**	Blue room 16:15	2 minutes
116	Hen	Shira	**Addition of MiSight 1 day Contact Lensess with Combination of Low-concentration Atropine in for Myopia Control Treatment**	Blue room 16:17	2 minutes
105	Khury	Leem	**Fundus photos of Optic disc pallor in line with optical coherence tomography and support clinician diagnosis.**	Blue room 16:19	2 minutes
39	Pesoa	Yair	**Incidental Unilateral Macular findings in Children**	Blue room 16:21	2 minutes
121	Ramia	Farid	**Combination Low-Concentration Atropine and Contact Lenses for Myopia Control**	Blue room 16:23	2 minutes
	Discussion			16:25 - 17:00	

Rapid fire: Retina, Retinal deg, Therapy & Genetics			Miri Ehrenberg & Liran Tiosano	Green room	15:45
92	Altmann	Gali	**Alga-derived 9-Cis-β-Carotene rescues cones and reduces retinal microglial cell activation**	Green room 15:45	2 minutes
66	Shimonovich	Roy	**Prediction of Progression to Scar in Age Related Macular Degeneration**	Green room 15:47	2 minutes
126	Ben-David	Gil	**Cannabinoids receptors and inflammatory markers characterization in experimental autoimmune uveitis (EAU)**	Green room 15:49	2 minutes
70	Cnaany	Yaacov	**A Simple Automated Process for Bulk Download of Optical Coherence Tomography Scans**	Green room 15:51	2 minutes
135	Dor	Omer	**A fully automatic AI doctor assistant tool for explainable detection and staging of age-related macular degeneration in 3D macular SD-OCT scans**	Green room 15:53	2 minutes
41	Goldstein	Ayelet	**Machine learning for classification Proliferative Diabetic Retinopathy in Latino and African American Cohorts**	Green room 15:55	2 minutes
34	Hilely	Assaf	**Pachyvitelliform Maculopathy: Optical Coherence Tomography Analysis of a Novel Entity**	Green room 15:57	2 minutes
31	Kanaan	Areej	**Endophthalmitis in patients receiving Anti-VEGF injections for retinal pathologies: clinical outcome and disease quiescence.**	Green room 15:59	2 minutes
134	Stanescu	Nir	**Long-term outcomes of anti-vascular endothelial growth factor treatment in peripapillary subretinal neovascular membrane due to age-related macular degeneration**	Green room 16:01	2 minutes
30	Vofo	Brice	**Prospective evaluation of vitreous traction on retinal lattice degeneration and atrophic holes by swept-source optical coherence tomography.**	Green room 16:03	2 minutes
81	Wattad	Aya	**Topographic correlation between anatomical and functional macular measures in patients treated with hydroxychloroquine**	Green room 16:05	2 minutes
71	Abu Elasal	Maria	**Genetic analysis of 250 index cases with inherited retinal diseases using a panel of 351 retinal genes**	Green room 16:07	2 minutes

104	Freund	Ofek	**A novel HPS5 acceptor splice-site mutation causing Hermansky Pudlak Syndrome type 5**	Green room 16:09	2 minutes
79	Gazit	Inbal	**Variants in the WDR45 gene within the OPA-2 locus associate with isolated X-linked optic atrophy**	Green room 16:11	2 minutes
72	Salameh	Manar	**An intronic REEP6 variant causes autosomal recessive retinitis pigmentosa in Arab-Muslim patients**	Green room 16:13	2 minutes
17	Sharon	Dror	**An In-Depth Single-Gene Worldwide Carrier Frequency and Genetic Prevalence Analysis of CYP4V2 as the cause of Bietti Crystalline Dystrophy**	Green room 16:15	2 minutes
90	Sher	Ifat	**Genotype-phenotype associations in Israeli PRPF31 retinitis pigmentosa patients**	Green room 16:17	2 minutes
111	Valensi	Johanna	**RNA Editing of relatively common worldwide Mutations causing inherited retinal diseases using the endogenous Adenosine Deaminase Acting on RNA enzyme**	Green room 16:19	2 minutes
	Discussion			16:21-17:00	

ABSTRACTS

Neuro-retinal function biomarkers for diagnosis and monitoring disease progression in patients with Parkinson's disease

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Purpose: To investigate the relationships of rod- cone- and melanopsin-mediated pupil light reflex (PLR), changes in SD-OCT peripapillary RNFL thickness, sleep quality and Parkinson's disease (PD) duration and severity.

Methods: 21 PD patients (mean age ± standard deviation: 61.29 ± 11.54 years) and 35 age-similar healthy controls (65.07 ± 11.22 years, p=0.29) were enrolled. All participants underwent: (1) A neurological assessment of PD stage and progression according to the MDS Clinical Diagnostic Criteria for PD; (2) PDSS sleep questionnaire; (3) MOCA cognitive test; (4) Ophthalmic evaluation by a senior ophthalmologist; (5) Spectral Domain Optical Coherence Tomography (SD-OCT) imaging; (6) Visual acuity test; (7) Color vision test (D15); (8) Chromatic Pupilloperimeter under mesopic light adaptation conditions to assess the PLR for small (0.43°) red and blue light stimuli presented at central (4.2°) and peripheral (21°) visual field locations. Patients were tested in two visits, two years apart.

Results: Nine patients presented with aberrant color vision (7 were defined as small changes, one protanope and one Tritan). The rod-mediated maximal percentage of pupil contraction (PPC) was significantly lower at central and peripheral retinal locations in PD patients compared with controls (14.04% vs 7.7% p<0.02). Maximal contraction velocity (MCV) was significantly lower at central and peripheral compared with controls (p<0.028). Cone-mediated PPC and MCV were less affected. Impaired melanopsin-mediated PLR was recorded in the central and peripheral retina, with faster pupil recovery in the PD patients compared to controls (74% vs 84%, p< 0.00049). Those changes in PLR were more prominent in the inferior and central visual file locations. A preliminary analysis of the changes between the two visits suggested deterioration of the melanopsin-mediated PLR in the central and peripheral retina. Rod and cone mediated PPC and MCV did not significantly differ between the two visits.

Conclusions: In PD patients, the intrinsic and extrinsic light responses in ipRGCs are diminished compared to controls. The intrinsic responses are affected at central and superior peripheral retinal locations. Monitoring melanopsin-mediated PLR may prove useful for PD diagnosis and monitoring disease progression.

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

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

Methods: AH was collected during cataract surgery from 34 neovascular AMD (nAMD) patients (mean age 79±6.6 years, Female/ Male=16/17), 14 samples from 13 atrophic AMD (aAMD) patients (mean age 79.6±6.4, Female/ Male=7/7 and 30 controls (mean age 69.1±8.7, Female/ Male=16/14) in Hadassah-Hebrew University Medical Center. LC-MS/MS analysis was performed using a Q Exactive Plus mass spectrometer. Ultimate 3000 Dionex. Mass spectra data were processed using the MaxQuant computational platform, version 2.0.3.0. Statistical analysis was performed using the Perseus statistical package. Only proteins for which at least eight non-zero LFQ values were obtained in at least one sample group were accepted for statistical analysis by t-test and volcano plot. Functional Analysis on significant P-value (FDR corrected) proteins was performed via DAVID 6.8.

Results: A total of 642 proteins were identified in AH by LC-MS/MS via appropriate filtering of which only 380 proteins were used for the statistical analysis as per the above. Twenty-one proteins were upregulated in nAMD (nAMD/Control>2, peptide tags>2). 38 proteins were upregulated in control (nAMD/Control<0.5, peptide tags>2). Functional analysis demonstrated enrichment for 7 groups upregulated in nAMD including blood coagulation (enrichment score (ES): 4.77, KW-0094), protease inhibitor (enrichment score (ES): 4.37, KW-0646), HDL (enrichment score (ES): 4.12,KW-0345), fibrinogen complex (enrichment score (ES): 3.53 GO:0005577), proteoglycan (enrichment score (ES): 3.53, KW-0654), lipoprotein metabolic process (enrichment score (ES): 3.32, GO:0042157), lipid transport (enrichment score (ES): 2.4, KW-0445). Lysosomal lumen (enrichment score (ES): 2.7, GO: 0043202) was down regulated in nAMD. There was no functional class that was differentially expressed between nAMD and aAMD samples and between control and aAMD samples.

Conclusions: Unbiased AH proteomic profiles of AMD patients identified functional classes of proteins that show altered expression in association with the disease. Further research may identify potential clinical biomarkers for AMD in the AH.

Optic Density Ratio of Sub Retinal Pigment Epithelium Fluid is Associated with Improvement of BCVA after 12 and 36 Months of Follow Up

Ori Segal (2), Nir Stanescu(1), Khaled Khalifa(2), Roee Arnon(1), Gilad Rabina(4), Arie Y. Nemet (2), Noa Geffen (3),
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Purpose: The purpose of this study was to investigate the prognostic significance of optical density ratio (ODR) on best corrected visual acuity (BCVA) in patients with treatment-naive neovascular age-related macular degeneration (nAMD) treated with anti-vascular endothelial growth factor (VEGF) agents.

Methods: This study was a retrospective review of clinical records from January 2011 to November 2020. The study included consecutive patients with AMD treated with at least three anti-VEGF injections, macular optical coherence tomography (OCT) images before and after treatment, and at least 12 months of follow-up. Exclusion criteria included myopia, visual impairment due to ocular comorbidities, intraocular surgery within three months before or during follow-up, and unreadable OCT imaging. ODR was calculated using flexible and strict methods in each OCT image.

Results: We used correlation analysis and regression models to investigate the relationship between baseline OCT parameters and deltaBCVA. We found that ODR of the sub-RPE compartment, calculated with the strict method, had a statistically significant effect on deltaBCVA at 12 and 36 months of follow-up ($p < 0.05$).

Conclusion: This is the largest study on ODR in nAMD patients to date and suggests that ODR calculated using the strict method may be a useful predictor of visual outcomes in nAMD patients treated with anti-VEGF agents.

Specific MicroRNAs as Biomarkers for Uveitis in Juvenile Idiopathic Arthritis

Yael Sharon,(1,2) Gil Ben-David, (1,2) Guy Shapira, (2,6) Yael Nisgav, (1,4) Shani Pillar, (3) Nir Pillar, (2) Gil Amarilyo, (2,5) Liora Harel, (2,5) Noam Shomron, (2,6) Michal Kramer (1,2,4)
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Purpose: Juvenile idiopathic arthritis-associated uveitis (JIA-U) is a silent vision-robing disease. Favorable visual outcome depends largely upon early diagnosis and aggressive treatment to control inflammation. This study was aimed to investigate specific microRNA's (miRNA) expression in JIA-U compared to JIA without uveitis as well as active versus non-active disease and explore a possible role as predictive biomarkers of the disease.

Methods: miRNA expression profiling was performed on peripheral blood mononuclear cells (PBMCs) of 44 pediatric patients with JIA-U, with both active (n=7) and non-active (n=15) disease, and patients with JIA without ocular involvement (n=10). Patients with other types of uveitis served as controls including active (n=6) and non-active (n=6) disease. We have previously used nanostring panels, and added the high-throughput small-RNASeq for subsets of samples to be analyzed accordingly.

Results: Significant differential expression was found for several miRNAs in JIA with and without uveitis (all following FDR<0.05). miR-204-3p and miR-6124 increased in the JIA-U groups (active and non-active) vs the control. Conversely, miR-579-3p and miR-3912-5p were decreased for JIA-U patients vs. controls. Also noteworthy, miR-493-3p and hsa-miR-4454 were increased in active vs. non-active uveitis and in active vs. control, thus indicating presence of active uveitis.

Conclusions: This study is the first to demonstrate different expression profiles of miRNAs in JIA patients with and without uveitis, as well as active and non-active ocular disease. If verified in larger studies, these findings may enable to identify JIA patients prone to develop uveitis and detect activity of the disease."

Measuring geographic atrophy area using spectral-domain optical coherence tomography versus fundus autofluorescence

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Purpose: To compare geographic atrophy (GA) area and shape descriptors in dry age-related macular degeneration (AMD) measured using fundus autofluorescence (FAF) annotation versus optical coherence tomography (OCT) annotation with the cRORA (complete retinal pigment epithelium and outer retinal atrophy) criteria.
Design: Observational cross-sectional study.

Methods: GA findings on FAF and OCT were annotated at a single time point in 36 pairs of FAF and OCT scans obtained from 36 eyes in 24 patients with dry AMD. The primary outcomes were GA area, focality, perimeter, circularity, minimum and maximum Feret diameter, and minimum distance from the center. These primary outcomes were then compared between FAF and OCT. We also applied univariate and multivariate regression in order to analyze the putative correlation between the primary outcomes measured on OCT and the difference in GA area measured between FAF and OCT.

Results: Total GA area measured on OCT was 5.07±3.76 mm2; in contrast, total GA measured on FAF was 13.47±8.64 mm2 ($P<0.0001$), a mean difference of 8.40±6.40 mm2. Multivariate regression analysis revealed a significant correlation between the difference in area between OCT and FAF and the total baseline lesion perimeter measured on OCT (adjusted r2: 0.38; $P<0.0001$).

Conclusions: We report that GA area measured on FAF differs significantly from GA area measured on OCT; moreover, this difference is correlated with the baseline lesion perimeter measured on OCT. Further research is warranted in order to determine the clinical relevance of these findings.

Age-related Macular Degeneration (AMD) Staging from Routine Clinical OCT Scans using Deep Learning (DL)

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Purpose: Optical coherence tomography (OCT) is a common imaging tool to identify and follow AMD. Artificial intelligence studies often use color fundus images or OCT scans from standardized clinical trials protocols to classify AMD. We aim to evaluate the accuracy of classifying AMD using spatio-volumetric DL models with clinical setting OCT volume scans having different imaging quality and density.

Methods: OCT and infrared (IR) scans of a consecutive real-world cohort of 1011 AMD patients over 13 years were analyzed. Baseline and last visits of 1953 eyes were annotated for the stage of the disease, biomarkers and additional pathologies. For the DL training, annotations of eyes at the non- neovascular stage at baseline were included. Five sub-groups were classified: No AMD, non-nvAMD stages (early, intermediate, and late) and nvAMD. The OCT scans+IR were converted to videos and automatically manipulated to achieve best accuracy. We used Timesformer, Motionformer and Video-MAE models that were originally developed for video classification and adapted to fit classifying OCT+IR. Training of the models included 2067 annotated eyes. To assess annotation reliability and expert agreement, 104 randomly selected OCT scans were given to additional three experts for evaluation. OCT scans variations were measured by number of frames, resolution, retina rotation, and grayscale variance.

Results: The DL models reached test accuracy of 75.9% for five classes, and 90.3% and 95.3% for nvAMD vs. non-nvAMD and No-AMD vs. AMD respectively. AUC-ROC (OvR) was 0.92, 0.94 and 0.92 respectively. The Fleiss' Kappa coefficient for the three experts and original annotation was 0.65, 0.73 and 0.73 for five classes, nvAMD vs. non-nvAMD and no-AMD vs. AMD respectively. The average expert-annotation pair Cohen's-kappa coefficient was 0.61, 0.68 and 0.6 respectively, while the model-to-annotation agreement was 0.76, 0.85 and 0.8. OCT scans number of frames were 19-100 with average of 37. Retinal rotations range was 41-146 degrees.

Conclusions: Our AI algorithms can accurately classify AMD stages using routine, volume OCT and IR scans. These DL models were proven to be stable across the scans variations and might be a useful step into development of a tool to support the clinical management of patients with AMD and to improve the database for further research.

Automated Quantitative Volumetric OCT Analysis and Clinical Characteristics of 4485 Neovascular AMD Eyes with Long-Term Follow-Up in Real World Settings

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Purpose: Applying an automated deep learning optical coherence tomography (OCT) image recognition algorithm in a large real-world clinical dataset of neovascular age-related macular degeneration (nAMD) patients with long-term clinical follow-up from two tertiary Retina centers. The BI-AMD project aims to provide measurable indicators to enable models for personalized treatment approaches in nAMD. Here we describe the dataset with its demographics, clinical characteristics, and algorithm output volumetric retinal fluid information in naïve nAMD eyes starting anti-VEGF therapy

Methods: This retrospective study at Tel Aviv Medical Center and Queens University Belfast includes 2 cohorts of consecutive naïve nAMD patients, treated with anti-VEGF injections. Demographic and clinical data were extracted from EMR systems, organized according to a pre-specified common data dictionary. Imaging data were extracted into E2E and DICOM files and analyzed using the NOA algorithm (Notal Vision, LTD), which provides automated segmented volumetric topographic OCT fluid analysis.

Results: The current dataset contains 4,485 eyes from 3,637 patients, who received 59,575 intravitreal injections and performed 71,497 OCT scans over a median follow-up of 4.54 years (0.3-11.1).
At baseline, 950 eyes (21.2%) had subretinal fluid (SRF), 673 (15%) had intraretinal fluid (IRF), and 2634 eyes (58.7%) had both.
Mean baseline visual acuity (VA; logMAR) was 0.55 (0-2.7); 23.7% (n=1061) had good VA (<0.3) and 15.1% (n=677) had low VA (≥1.0).
Within eyes with SRF, a significantly greater proportion had good baseline VA (43.7%), compared to those with IRF (25.3%), or both SRF and IRF (15.4%).
Eyes with both SRF and IRF had a significantly greater proportion with low VA (21.2%), compared to those with IRF (9.4%) or SRF (3.2%).
IRF volumes were increasing with age, while total retinal and SRF volumes were similar between different age groups (range 50-104 years).
Females and males had similar distribution of IRF (73.5% vs. 74.1%) and SRF (78.7% vs. 82.1%), with no evidence for a systematic difference in mean fluid volumes.

Conclusions: To our best knowledge, the BI-AMD dataset contains the largest real-world cohort of naïve nAMD patients integrating segmented volumetric topographic retinal fluid data with clinical information and up to 10 years follow-up. This enables us to develop, train, and validate the framework for predicting personalized treatment need and outcomes in nAMD real-world care.

Discovery of discrete limbal epithelial stem cell populations, their function and niche

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Purpose: To discover new limbal stem cell (LSC) populations, their genetic signature, cycling properties and niche.

Methods: We combined single-cell RNA sequencing, lineage tracing and mathematical analysis of LSCs and their niche. Limbal and stromal cell populations were identified in silico and validated by in situ hybridization and immunofluorescent staining. Quantitative lineage tracing was performed to follow clonal growth and pattern over time, proliferation analysis and niche immune cell function were explored using immunodeficient mouse models and topical immune repressors.

Results: We report the identification of previously undescribed two LSC populations localized in separate sub-compartments that we termed the “outer” and “inner” limbus. Lineage tracing data suggests that quiescent outer LSCs (qLSCs) participate in wound healing and boundary formation while inner limbus hosts active LSCs (aLSCs) that maintain corneal epithelial homeostasis. Notably, T cells serve as niche cells for qLSCs, regulating quiescence and wound response. In addition, limbal niche fibroblast cell population, their markers and secreted factors. Immunostaining reveals a very organized compartmentalization of stromal cell types that reside in well-segregated compartments. We propose that the new LSC populations are abundant, follow stochastic rules and neutral drift dynamics maintained by unique niche cells.

Conclusion: This study provides a useful atlas that uncovers the main corneal epithelial cell populations, capturing the signature and the niche of quiescent and activated LSC states. These data open new research avenues for studying the mechanisms of cell proliferation and differentiation as well as the applications of LSCs in regenerative medicine.

Predicting keratoconus progression by early tomography data using machine learning algorithms

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Purpose: To identify early indicators of keratoconus progression in pentacam tomography data using machine learning (ML) techniques. This will allow early referral of patients for cross-linking (CXL) treatment before irreversible deterioration.

Methods: A retrospective study of pentacam tomography tabular dataset including 11,760 tests in Beilinson medical center. Data was organized initially by retrieval of patients who received keratoconus diagnosis in chameleon diagnosis field or CXL ATD code. We excluded tomographies performed after CXL or corneal transplant, pachymetry under 370 microns which cannot be considered for CXL, and errored tests from our analysis. We also manually validated the data included in chameleon. A boosted decision tree (BDT) was trained on the final dataset using cross-validation method.

Results: The final dataset included 935 tomography tests of stable group not referred for treatment, and 283 tests in the deterioration group. Our results demonstrate ML training of tomography data in keratoconus patients based on their referral for CXL was unable to predict progression, as indicated by a mean receiver operating characteristic area under the curve (ROC-AUC) of 0.51±0.18, mean precision of 0.27, mean recall 0.26, and mean F1 score of 0.21. Further algorithmic manipulation of the data using unsupervised methods such as dimensionality reduction and clustering were explored. These methods demonstrated a similar distribution of CXL in the data, and did not yield any significant insight of parameters which may assist to predict progression by a single test.

Conclusions: Our ML analyses showed that keratoconus patients referred for CXL did not have early predictor markers of deterioration in their tomography data compared to a stable, untreated group of keratoconus patients. Hence, referral for CXL using ML algorithms did not demonstrate superiority to the current clinical practice of human referral, and it was still not possible to predict disease progression with a single test. Future research will attempt to identify predictors for early CXL treatment by training on multiple tests, compared to our current referral methods."

Immune cells serve as niche cells for limbal epithelial stem cells

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Purpose: The limbal stem cell (LSC) microenvironment, “the niche”, is believed to influence LSC function. However, our knowledge on limbal niche components and mechanisms of niche – LSC regulation is poor. Here, we aimed to characterize the sub-populations of immune cell in the limbus niche and to uncover their potential function as niche cells.

Methods: Immunostaining of limbal/corneal wholemount and tissue sections was performed using antibodies against LSC and immune cell specific markers. LSC proliferation, marker expression and wound healing response was examined following inhibition of the immune cell activity and in immunodeficient mice.

Results: We identified significant numbers of dendritic cells and T cell populations including γδ and regulatory T cells in the outer LSC niche. Expression of outer LSC markers (GPHA2/CD63) was significantly affected by inhibition or absence of immune cells. LSC proliferation was extensively higher following immune cell inhibition or ablation. Delayed corneal regeneration was observed in immunodeficient mice.

Conclusion: This study uncovers a new role for immune cells as LSC niche cells. Future studies are required in order to identify the mechanisms by which specific immune cell populations influence LSC function.

Corneal injury repair is enhanced by clinical-grade alpha1-antitrypsin in vivo

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Background: Corneal epithelial injury typically heals without complications. However, more extensive and deeper epithelial damage that is more centrally located, might form a scar and impair visual acuity. Alpha1-antitrypsin (AAT) is a circulating protein that modulates inflammation towards resolution; it is physiologically elevated under inflammatory conditions. According to in vitro and in vivo studies, AAT-rich conditions promote human epithelial gap repair and improve wound healing.

Aim: To investigate the impact of AAT treatment on the healing process of corneal erosion in mice.

Methods: Corneal abrasions of 2 mm diameter were performed in wild-type (WT) mice using an ocular burr. Topical AAT (0.007 mg per abrasion, n=12) or saline (n=16) was applied directly onto the injured site at the time of injury and every 4 hours later until complete wound closure was achieved. At various time points, re-epithelialization rates were measured, and histology and gene expression profiles were performed.

Results. AAT-treated mice exhibited significantly higher closure rates across all time points. For example, at 10 hours from injury, the area of the remaining wound in saline-treated wounds was twice that of the treatment group (42.83±19.56% vs. 25.79±11.49%, area of the exposed wound, percent from time 0, respectively; p=0.012), and at 16 hours the differences continued to grow (14.67±9.94% vs 4.04±4.89%, respectively; p=0.002).

Conclusion. These results suggest that treatment with topical clinical-grade AAT accelerates corneal wound repair in mice. Being a remarkably safe agent for other clinical indications, the data support the future application of AAT in human corneal abrasion and other diseases of the eye surface.

Repeatability of Corneal Mapping Measured Using a Hybrid Optical Coherence Tomographer with Placido Topography Versus a Scheimpflug Tomography

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Purpose: To assess the repeatability of corneal mapping measured using a hybrid optical coherence tomographer with Placido based topography versus a Scheimpflug based tomography.

Methods: This study included 38 eyes of 19 keratoconus patients. Their average age was 27±6.8 and 57% were male. The keratoconus was categorized according to Belin staging system in group one as stage 2 or 3 (ten patients) or group two as stage 4 (nine patients). They were measured using a Scheimpflug based tomography system (Pentacam, Oculus GmBH, Wetzlar, Germany) and with a hybrid OCT and Placido based system (MS-39, Costruzione Strumenti Oftalmici,CSO, Florence, Italy). The patients were all measured at the same time of day in identical environments. None of the patients had undergone any previous procedures or surgeries including cross linking or intra-stromal rings. They instilled no topical medications including artificial tears. The CSO measurements were acquired after a blink and stabilization of the tear film. Five measurements were performed on each instrument and the highest quality measurement as defined by the QS index in the Pentacam and the acquisition quality index in the MS-39 were used for analysis. Repeatability was assessed using coefficient of variation (CoV).

Results: In the keratoconus group one, the CoV was less than 1.63% in both instruments when analyzing central 3 mm keratometry, maximum K, Q value, posterior elevation, pachymetry at the thinnest point and anterior chamber depth. In the keratoconus group two, data from the same measurements was acquired, showing a greater CoV, but still below 2.13%. The repeatability results were lower in both instruments with regard to astigmatism in the severe keratoconus group.

Conclusions: The repeatability of maximum K, Q value, posterior elevation, pachymetry at the thinnest point and anterior chamber depth measurements was high in both the Scheimpflug based tomography and the hybrid OCT and placido based instruments. The repeatability was slightly higher in the keratoconus group one than the keratoconus group two.

Psychiatric Comorbidities as risk factors for Keratoconus

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PURPOSE: To assess the risk for keratoconus in young adults with various psychiatric comorbidities.

METHODS: In this population-based cross-sectional study 940,763 medical records of Israeli adolescents and young adults in military service aged 16-45 years were reviewed. The occurrence of anxiety, obsessive compulsive disorder (OCD), autism and attention deficit hyperactivity disorder (ADHD) was evaluated in cases with and without keratoconus. Association between keratoconus and psychiatric comorbidities was tested using uni- and multivariant analyses.

RESULTS: Overall 940,763 adolescents and adults were included. Mean age was 17.56±1.47 years, and 40.70% were female. Keratoconus was documented in 1,533 cases, with a prevalence of 0.20%. Patients with keratoconus were 1.58 times more likely to be diagnosed with ADHD compared to the general population (OR=1.58, CI 1.38-1.81, $p<0.00001$). After adjusting for age, gender, intellectual status, height and weight- the results remained significant (hazard ratio=1.46, CI 1.27-1.67, $p<0.00001$). Anxiety disorder, OCD and autism demonstrated comparable prevalence among cases with and without keratoconus ($p>0.05$ for all).

CONCLUSIONS: In a large cohort of young adults, ADHD was significantly associated with a diagnosis of keratoconus, even after adjusting for possible confounders. These results suggest the need for screening of patients with ADHD for early signs of corneal ectasia, with emphasis on patients with active eye rubbing.

Preoperative assessment of eyes at risk of developing Intraoperative floppy iris syndrome (IFIS), Using Artificial Intelligence (AI)

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Purpose: To develop an AI algorithm capable of identifying eyes with a risk of developing Intraoperative floppy iris syndrome (IFIS)

Methods:
Preoperative infra-red images of the anterior segment were labeled according to the presence or absence of IFIS as recorded in their surgical charts and reviewed retrospectively.
The data was allocated by a ratio of 75% for training, 15% for validation, and 10% for testing.
A convolutional-neural-network-based model was proposed to classify to probability for IFIS based on the binary image label.
The model's performance was internally validated, and the evaluation indicators included accuracy, specificity, and negative predictive value.

Results:
Five thousand thirty patients were identified, with 5,013 eyes of 3,458 patients included for analysis.
The patients' mean age was 73.58±9.98, with 1,826 females (52.8%).
The AI test algorithm achieved an accuracy of 90% with a negative predictive value of 95% and a specificity of 90%.

Conclusion
A novel AI algorithm can identify in a reliable way patients safe from developing IFIS. This insight encourages the integration of AI tools into clinical practice and may contribute to the safe planning of cataract surgery by minimizing the risk of intraoperative complications."

Sodium Iodate Induced Retinal Degeneration in BALB/C Mice

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Purpose:
The study aimed to provide a detailed view of NaIO_3 (Sodium Iodate - SI) induced retinal degeneration in 6-8 weeks old male BALB/c mice and characterize a dose appropriate for experimental needs. SI administration has been shown to cause rapid and selective necrotic cell death of the retinal pigment epithelium (RPE) and suspected apoptotic death of photoreceptors. It has been reported that albino rats are more sensitive to the compound as compared to pigmented rats. The appropriate concentration of SI in intraperitoneal injections to mice is highly variable in the literature and controversial. In this project, we aimed to find the optimal concentration to create an experimental window with enough damage to be detectable and measurable and with a limited level of toxicity.

Methods:
SI in three different concentrations (20 mg/kg (n=3), 30 mg/kg (n=4), or 40 mg/kg (n=8)) was administered intraperitoneally to BALB/C mice. Retinal damage was evaluated by fundus auto fluorescence (FAF) images (excitation wavelength: 488 nm). Thickness of the RPE and the outer nuclear layer (ONL) was evaluated by optical coherence tomography (OCT, Spectralis, Heidelberg Engineering) and immunohistochemistry. Retinal structure was assessed before SI injection (baseline - day 0) and then at 3, 5, and 7 days post-injection.10-mm thick retinal sections were stained with DAPI (4′,6-diamidino-2-phenylindole). Measurements were standardized, using a section crossing the optic nerve in all specimens. In addition, six positions in a interval of 300 mm starting from the optic nerve were highlighted for ONL retinal thickness measurements.

Results:
OCT and FAF images demonstrated a barley detectable impairment of retinal structure following 20 mg/kg SI administration, and mild impairment in following administration of the 30 mg/kg dosage.Treatment with 40 mg/kg resulted in substantial damage, manifesting on in ONL thinning (fold change range 0.5-1.125 at the various distances from the optic disc, p-value range 0.034-0.867), as well as in altered outer retina structure in OCT and altered FAF pattern. Systemic toxicity was not observed.

Conclusions:
The study identified 40 mg/kg as the minimal SI concentration sufficient to induce measurable retina damage in BALB/C mice to recapitulate features or retinal and macular degeneration. This model can then be utilized to assess potential therapies and gain insight to mechanisms underlying retinal damage.

Hybrid Retinal Implant Concept: Optimization of photoreceptor cell seeding in micro-wells array implant

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Purpose – Our group is developing a novel Hybrid retinal implant for vision restoration in patients with degenerative diseases, whereby, cells are seeded on a scaffold microwells structures at the bottom of which are electrodes. Sealing of the cells in the microwells is a major component in this implant. In this study we investigated the effect of microwell diameter and various cell and surface treatments on cell adhesion and sealing.

Methods – hPRPs were differentiated from hESC and seeded on SU8 devices fabricated by lithography with 20, 15 and 10 μm wells in diameter. SU8 surfaces were treated with N2-plasma and polylysine/Laminin. To render the cells more amenable to entering and adhering to the wells, they were treated with magnetic particles and attracted by magnet positioned below the implant and underwent centrifugation. Cell morphology and adhesion to the micro-well walls were imaged using confocal microscopy and the Imaris software 24 hours after seeding.

Results – Our results reveal effect of the well size on the number of cells that were successfully sealed within a well with the optimal well size being 10 μm with one cell per well, whereas in larger there are more than a single cell per well. Moreover, surface treatment with centrifuge and magnets particles enhanced cell adhesion and cell entrance to the depth of the well.

Conclusion – This work highlights the biocompatibility of the SU8 scaffold, and the feasibility of sealing PRP cells within the microwell, a crucial requirement for the realization of our novel concept.

Gene Augmentation Therapy Attenuates Retinal Degeneration in a Knock-Out Mouse Model of Fam161a Retinitis Pigmentosa

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Purpose:
Retinal degenerations diseases have become the “testing ground” for novel therapeutic modalities including gene and cell-based therapies. Mutations in FAM161A are the most common cause for recessive retinitis pigmentosa (RP) in the Israeli society. Recently, we reported a new Fam161atm1b/tm1b Knock-Out (KO) mouse model that was generated by deletion of the major exon (#3). In this study we describe the effects of AAV-mediated gene augmentation in Fam161atm1b/tm1b KO mice.

Methods:
2 µl of viral vector suspension (5*1010 vg/µl) of AAV2/8-IRBP-hGRK1-FLAG-mFam161a Long isoform was injected into the sub-retinal space of P24-P29 Fam161atm1b/tm1b KO mice to characterize the safety and efficacy of gene augmentation treatment. In-vivo retinal examinations at three, six and eight months of age were performed using OKT, FFERG, Fundus Auto-Fluorescent (FAF) and Heidelberg-SPECTRALIS Optical coherence tomography (OCT) imaging. Ex-vivo retinal morphometry was performed using hematoxylin-eosin (H&E) staining. Viral transduction and FAM161A expression were validated by immunohistochemical (IHC) staining.

Results:
OKT revealed preservation of visual acuity (VA) at the age of eight months with an average score of ~0.35 c/d in the treated eyes compared to 0 c/d in the untreated fellow eyes. Scotopic a-wave and b-wave responses were significantly higher (p-value<0.05) in treated eyes compared to untreated fellow eyes at the age of three months, six- and eight-months. Retinal assessments in-vivo using FAF and OCT revealed safety of viral vector administration and a significant rescue of the ONL and inner\outer (IS\OS) photoreceptor segments in the treated eyes compared to the untreated fellow-eyes. Histological analysis manifested significant preservation of ONL thickness at 8 months of age maintained up to 7-8 rows of ONL nuclei, while untreated retinas showed practically a complete loss of photoreceptors. Immunohistochemical staining demonstrated a robust expression of the normal FAM161A protein in photoreceptors as well as intact IS\OS photoreceptor segments in treated areas.

Conclusions:
To conclude, this is the first example of successful gene augmentation therapy using AAV-mFam161a Long isoform viral vector in Fam161atm1b/tm1b KO mouse model which manifests retinal degeneration course of disease between the age of one month to eight months. The results of this study may serve as an important step towards future application of gene augmentation therapy in FAM161A-RP patients by identifying a promising isoform to rescue photoreceptors and their function.

Immune response to intravitreal AAV vector injection in a sheep model of CNGA3 achromatopsia. A serological and clinical survey.

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Purpose. Intravitreal (IVT) gene therapy is being developed as a safe, effective and cheap alternative to subretinal (SR) gene therapy. However, IVT injection of a viral vector may trigger an immune response, especially in patients pre-exposed to the specific virus. The problem is potentially significant as adeno virus is ubiquitous, and most gene therapies use Adeno Associated Viral (AAV) vectors. Following successful SR gene therapy in a sheep model of CNGA3 achromatopsia, our group is currently developing alternative IVT therapy in this naturally occurring large animal model. Our aim was to compare the immune response to IVT injection of AAV2 in naïve sheep and in animals with pre-existing antibodies.

Methods. Neutralizing antibody titers were determined pre-operatively and 12 weeks post-injection using a serum neutralization assay. AAV2 vector encoding the luciferase gene was incubated with a series of sheep serum dilutions and HEK293T cells. Cell transduction was determined by luciferase activity, detected in lysed cells by luminescence readings. AAV2 was injected IVT in nine seronegative sheep and in six sheep with pre-existing antibodies. An uninjected, seronegative sheep and a SR-treated sheep served as controls. Animals underwent post-injection ophthalmic examination.

Results. Twelve weeks post IVT injection, 2/9 seronegative sheep remained seronegative, while 7/9 sheep had titers of 1:40 - 1:2560. In animals with pre-exiting antibodies, titers rose in 3/6 sheep, were unchanged in 2/6 sheep and decreased in one sheep. The uninjected sheep remained seronegative and antibody titer in the SR-treated sheep increased following treatment. Vitreous haze and hemorrhage was seen following injection in 3/6 animals with pre-existing antibodies, but not in any seronegative animals.

Conclusions. IVT viral vector injections in patients pre-exposed to AAV may result in local inflammation. However, there is no difference in the serological response of the two groups, and IVT injections will trigger antibody production in pre-exposed patients, as well as in patients who had not been pre-exposed to the virus.

Inhibition of Sema-3A promotes cell migration, axonal growth, and retinal ganglion cells survival

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Purpose: Semaphorin 3A (Sema-3A) is asecreted protein that deflects axons from inappropriate regions and induces neuronal cell death. Intravitreal application of polyclonal antibodies against Sema-3A prevents loss of retinal ganglion cells ensuing from axotomy of optic nerves.This suggested a therapeutic approach for neuroprotection via inhibition of the Sema-3A pathway.

Methods: To develop potent and specific Sema-3A antagonists,we isolated monoclonal anti -Sema-3A antibodies from a human antibody phage display library and optimized loe-molecular weight Sema-3A signaling inhibitors. The best inhibitors were identified using in vitro scratch assays and semiquantitative repulsion assay.

Results: A therapeutic approach for neuroprotection must have a long duration of action. Therefore, antibodies and low molecular weight inhibitors were formulated inextruded implants to allow controled and prolonged release. Following release from the implants, Sema-3A inhibitors antagonized Sema-3A effects in scratch and repulsion assays and protected retinal ganglion cells in animal models in rats and rabbits. The models were of optic nerve injury, retinal detachment, acute glaucoma and NAION .

Conclusion: Collectively, our findings indicate that the identified Sema-3A inhibitors should be further evaluated as therapeutic candidates for the treatment of Sema-3A-driven central nervous system degeneratrive process.

Identification of Ceramide Kinase-Like (CERKL) protein-protein interactions in the mammalian retina

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Purpose: Mutations in the Ceramide Kinase-Like (CERKL) gene are associated with severe retinal degeneration. Several different functions have been proposed for CERKL, including mRNA-binding, association with microtubules, autophagy and mitochondrial biology. However, despite these findings, the pathways by which it exerts these roles and the direct connection to retinal disease are not fully understood. The purpose of this work was to identify and characterize CERKL-binding proteins in the mammalian retina.

Methods: CERKL protein-protein interactions were identified implementing the Ras Recruitment System (RRS), a cytoplasmic-based yeast two-hybrid system, on a bovine retina cDNA library. Identified interactions were confirmed by co-immunoprecipitation. Immunostaining was used to test for co-localization of CERKL and its putative interactors in the retina.

Results: We identified an interaction of CERKL with fumarylacetoacetate hydrolase domain containing 1 (FAHD1), a mitochondrial enzyme that serves as a regulator of mitochondrial function and senescence. This interaction was confirmed by co-immunoprecipitation. Immunostaining demonstrated that in the mouse retina CERKL and FAHD1 both localize to the cytoplasm of retinal ganglion cells, and may co-localize in amacrine and photoreceptor cells as well. In addition to FAHD1, we identified tumor protein translationally-controlled 1 (TPT1) as another putative CERKL interactor. TPT1 is involved in multiple biological processes, including stress response and autophagy.

Conclusions: We identified putative interactions between CERKL and two retinal proteins, FAHD1 and TPT1. Both proteins are promising CERKL-interactors, given recent findings on CERKL's involvement in autophagy and mitochondrial biology in the retina. These findings enhance our understanding of CERKL's role in the normal retina and the pathophysiology of CERKL-related retinal degeneration.

Disease modeling and treatment development for RNA splicing factor retinitis pigmentosa using iPSC-derived retinal pigment epithelium cell models

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Purpose: Mutations in the pre-mRNA processing factor 31 (PRPF31) are the second most common cause of autosomal dominant retinitis pigmentosa (RP). Interestingly, although RNA splicing is required for the normal function of all cells, mutations in these genes lead specifically to retinal degeneration. Moreover, disease progression varies significantly between patients, and some carriers are totally symptomatic. Animal models do not mimic the human disease further limiting treatment development. The aim of this research is to study the role of PRPF31 in patient-derived retinal pigment epithelium (RPE) models and to use these models to develop treatment for PRPF31-RP.

Methods: Induce pluripotent stem cells (iPSC)-RPE models were established from skin biopsies of two PRPF31-RP patients and a control healthy subject. RPE cell phenotype was assessed by staining with antibodies directed against RPE cell markers including Ezrin (marker of cell polarity), ARL13B (cilia marker), and MERTK (receptor mediating photoreceptor phagocytosis). The effect of the EMA-approved Ataluren, that selectively induces ribosomal read-through of premature but not normal termination codons, was tested in RPE cells of a patient with a nonsense mutation.

Results: After 119 days of differentiation, control RPE cells formed confluent pigmented cell monolayers with the classical honeycomb organization. By contrast, small cell-free areas were observed in the RPE cultures of the PRPF31-RP patients. Interestingly, PRPF31 expression level was similar in skin fibroblast of patients and controls. However, patients' RPE cells expressed substantially lower levels of PRPF31 compared with control cells, but the protein maintained a nuclear localization. Immunostaining with the cilia marker ARL13B indicated significantly reduced percentage of cilia-positive cells in patients' RPE cells ($p<0.005$). Ataluren treatment elevated PRPF31 protein expression, improved the RPE cell polarity, and increased the number of cilia-positive cells in the patient's cells.

Conclusions: RPE models were successfully established for a healthy donor and two PRPF31 RP patients. Ataluren treatment rescued RPE phenotype in the PRPF31 nonsense mutation RPE model. The iPSC-derived RPE models are expected to enhance our understanding of genotype/phenotype relationships and may lead to the discovery of personalized treatments for PRPF31 RP patients.

Aplasia of lacrimal and salivary glands (ALSG) caused by a partially penetrant novel FGF10 donor splice-site mutation

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Purpose: Twelve individuals from 6 generations of single Bedouin kindred presented with epiphora from early age. We aimed to delineate the clinical phenotype of the disease and to identify the underlying genetic defect.

Methods: Clinical phenotyping was determined by senior ophthalmologists and geneticists following informed consent and IRB approval. Patients underwent a comprehensive eye exam, including Schirmer test and slit lamp examination and annotation of other systemic findings. Genetic studies combined linkage analysis and whole exome sequencing, followed by filtration of candidate variants through standard pipelines and segregation analysis using Sanger sequencing. Aberrant splicing of the mutant FGF10 exon 2 sequence was assayed in HEK-293 cells transfected with plasmids constructed to harbor the wildtype or mutant sequences, followed by PCR using primers from exon 1 and 3.

Results: Ophthalmologic examination of the affected individuals revealed tear deficiency and congenital punctal atresia. Multiple caries with no concomitant abnormalities of the ears or digits were also noted, determining a diagnosis of aplasia of the lacrimal and salivary glands (ALSG). Genetic analysis identified a disease-causing novel heterozygous splice-site mutation in intron 2 of FGF10, segregating through the kindred as expected for dominant heredity with incomplete penetrance. Transfection of HEK-293 cells with plasmids expressing wildtype or mutant FGF10 sequences proved that the mutation results in absence of exon 2 in the mutant RNA.

Conclusions: We report a novel dominant splice-site mutation in FGF10, eliminating transcription of exon 2 and causing ALSG with epiphora from a young age, with variable expression and incomplete penetrance.

Identifying X-chromosome variants associated with age-related macular degeneration

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Purpose: In genome-wide association studies(GWAS), X chromosome(ChrX) variants were not fully investigated. Sex-specific effects and ChrX-specific quality control(QC) are needed to examine these effects. Previous work identified 52 autosomal variants associated with age-related macular degeneration(AMD) via the International AMD Genomics Consortium(IAMDGC), but did not analyze ChrX. Therefore, we aim to investigate ChrX variants for AMD association.

Methods:
We genotyped 29,269 European individuals (M/F:10,404/18,865;AMD:12,087/14,273) via custom chip and imputed after ChrX-specific QC(XWAS 3.0) using the Michigan Imputation Server. Imputation generated 1,221,623 variants on ChrX. Another imputation included non Europeans (total:52,189 individuals) via the TOPMed Imputation server, generating 5,869,633 ChrX variants. Age, informative PCs,and subphenotypes were covariates for logistic association analyses with Fishers correction. Gene/pathway analyses were performed with VEGAS,GSEASNP,ICSNPathway,DAVID,and mirPath.

Results: Via logistic association on Europeans with sex correction, variants in/near the genes SLITRK4,ARHGAP6,FGF13 and DMD were nominally associated with AMD($P<1x10-6$,Fishers combined-corrected). Via association testing of subphenotypes of choroidal neovascularization and geographic atrophy(GA), variants in DMD associated with GA($P<1x10-6$,Fishers combined-corrected). Via gene-based analysis with VEGAS, several genes were AMD-associated($P<0.05$, both truncated tail strength/truncated product P) including SLITRK4 and BHLHB9. Pathway analysis using GSEASNP and DAVID showed genes associated with nervous system development(FDR: P:0.02), and blood coagulation(FDR: P:0.03). Variants in the region of a microRNA(miR) were AMD-associated($P<0.05$, truncated tail strength/truncated product P). Via DIANA mirPath analysis, downstream targets of miRs show association with brain disorders and fatty acid elongation($P<0.05$). A long-non coding RNA on ChrX near the DMD locus was also AMD-associated(4x10-7). Epistatic analysis testing a t-statistic for a quantitative trait found an association that was different between cases/controls in the XG gene.

Conclusions: ChrX variants may show an association with AMD pathogenesis, and these variants may be linked to novel pathways. Further analysis is needed to confirm results and to understand their biological significance and relationship with AMD development in worldwide populations

Site-Directed RNA editing using Endogenous ADAR of Inherited Retinal Disease-causing Variants within Splice Site Regions

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PURPOSE: Site-directed RNA editing (SDRE) utilizing the endogenous human adenosine deaminase acting on RNA (ADAR) enzyme, also expressed in the eye, is a possible new genetic therapy for inherited retinal diseases (IRDs). Introduction of guideRNAs (gRNAs) to recruit the endogenous ADAR to a mutated RNA, facilitating the deaminization of A>i (read as G), allows for editing. Certain IRD mutations are in close proximity to or in a splice-site, but little is known about effective design of gRNAs for editing in such regions and the effect of gRNA introduction on proper splicing. Our aim is to design and introduce gRNAs for the exonic TRPM1-p.K294* mutation close to an exon boundary and the CERKL-c.238+1G>A intronic mutation, into a cellular system with a splicing assay, and to measure the effect on editing and splicing.

METHODS: Chemically modified gRNAs artificially produced, some validated within a yeast model and others independently designed, were introduced into ADAR1/2 overexpressing HeLa cells transfected with a plasmid harboring the relevant mutations. Splicing efficiency is measured by gel electrophoresis of PCR products as well as next generation sequencing (NGS) analysis and editing efficiency is measured by Sanger sequencing and NGS.

RESULTS: Two gRNAs were designed to edit the TRPM1-p.K294* mutation, an exon-exon and an exon-intron gRNA targeting the mRNA and pre-mRNA molecules and yielded editing levels of 37% and 32% respectively. Our results show that the exon-intron gRNA does not prevent proper splicing. NGS showed that pre-mRNA transcripts were quite rare (~2.5%) at 48h but showed higher editing levels when treated by exon-intron gRNA compared with exon-exon gRNA. Though this was the case, no significant advantage was seen when introducing a mixture of the two gRNAs showing that a mixture of gRNAs may not be necessary for this type of exonic mutation. Experimental design of an ADAR editing experiment for the CERKL-c.238+1G>A mutation has been initialized and the experiment is currently being performed.

CONCLUSIONS: No studies have been reported so far in which the interplay between splicing and RNA editing of disease-causing mutations was examined and therefore the current study will shed light on editing efficiency and effect on splicing when performing ADAR-mediated SDRE on areas close to or within splice sites. Our results indicate that even gRNA that hybridize to splice-site regions might not interfere with natural splicing and therefore even splice-site mutations, and not only exonic ones, can be targets for RNA editing experiments."

New Evidence of Müller's Muscle as a Sensory Proprioceptive Organ Guy Ben Simon [1], Chen Mayer,[1] Nir Gomel,[2] Mattan Arazi,[1] Ofira Zloto,[1] Amir Dori,[1] Daphna Landau-Prat,[1]
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Purpose: to determine whether proprioceptive nerves are present in Müller's muscle.

Methods: This was a prospective cohort study in which histologic and immunohistochemical analyses of excised Müller's muscle specimens were performed. Twenty fresh Müller's muscle's specimens from patients undergoing posterior approach ptosis surgery in one center between 2017-2018 were evaluated by histologic and immunohistochemical analysis. Axonal types were determined by measuring diameter in methylene blue stained plastic sections and by immunofluorescence of frozen sections.

Results: We identified large (greater than 10 micros) and small myelinated fibers in the Müller's muscle, with 6.4% of these fibers being large. Immunostaining with choline acetyltransferase showed no evidence of motor axons in the samples, identifying large axons as sensory A-beta fibers, likely proprioceptive. In addition, we identified C-fibers using double labeling with peripherin and neural cell adhesion molecule.

Conclusion: Overall, large myelinated sensory fibers are present in the Müller's muscle, likely serving proprioceptive innervation. This therefore suggests that proprioception may have a role in non-voluntary eyelid spatial positioning, in addition to visual deprivation, as a stimulus to retractor activation, and sheds new light on our understating of this complex mechanism.

Treatment of conjunctival palpebral lesions using Ruthenium plaque brachytherapy ""sandwich technique""

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Purpose: Treatment of palpebral conjunctival lesions is problematic due to late diagnosis, difficult surgical approach, and the need to preserve eyelid integrity. We aim to describe our experience in the treatment of those lesions using Ruthenium plaque brachytherapy as an alternative for a wide excision which sometimes mandates an exenteration.

Methods: The medical records of all the patients treated by Ruthenium plaque brachytherapy for conjunctival lesions at the Hadassah Medical Center from 1/1/2010 to 31/12/2022 were reviewed. Patients treated for lesions in the palpebral conjunctiva were included in the analysis.

Results: Four patients were included in the analysis, two males and two females, at a median age of 70.2 (range 59.8-79.7) at the date first seen. Two of the patients were treated for conjunctival melanoma, one for sebaceous carcinoma, and one for squamous cell carcinoma. All the lesions were located in the left upper eyelid. A ruthenium plaque was sutured to the palpebral conjunctiva in all the patients. The matching non-radioactive ""dummy"" plaque was sutured to the external eyelid to prevent exposure of the surroundings to radiation. Mean follow-up was 31 months (range 16.3-61.2 months) from the date first seen and 24.7 months (range 5.9-48.9 months) from plaque brachytherapy. One patient had local recurrence during follow-up, which was treated by repeated plaque brachytherapy. This patient refused sentinel lymph nods biopsy. He later developed a metastatic disease which led to his expiry. The other three patients had no local residual disease or metastatic disease at the end of the follow-up. All patients suffered from madarosis and conjunctival scars. Two patients also experienced repeat corneal erosions.

Conclusions: Treatment of palpebral conjunctival lesions using ""sandwich"" Ruthenium plaque brachytherapy is a relatively safe and effective treatment method, using available resources in an Ocular Oncology service. To the best of our knowledge, this treatment was never described before.

Lacrimal gland volume measurements in normal and thyroid orbitopathy patients using Magnetic Resonance Imaging

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Purpose: To formulate reference values for evaluation of lacrimal gland volumes using Magnetic Resonance Imaging in normal and thyroid orbitopathy patients.
Introduction: In different orbital diseases such as thyroid orbitopathy, structural and inflammatory changes occur in the lacrimal gland. Previous studies using computed tomography imaging have demonstrated that the lacrimal gland volume is larger among patients with thyroid orbitopathy.

Methods: This is a retrospective case series of 22 lacrimal glands in 11 normal patients and 28 lacrimal glands in 14 thyroid orbitopathy patients from July 2015 to November 2021. This research was performed according to the institutional declaration of Helsinki. Normal patients were recruited from a subset of patients hospitalized in the Ophthalmology department with optic neuritis, optic neuropathy, or other neurological cause of visual disturbance unrelated to the lacrimal gland. Patients with thyroid orbitopathy were diagnosed in the Oculoplastic Clinic at Emek Medical Center. All patients underwent a Magentic Resonance Imaging of the brain and orbit. All patients with thyroid orbitopathy underwent endocrinological evaluation, ocular evaluation and orbital MRI examination. Lacrimal glands were evaluated on T2-weighted images using a simple method of volume measurement with Siemens' Synovis imaging software.

Results: The mean volumes for normal and thyroid orbitopathy patients were 0.62 ± 0.11 cm3 and 0.70 ± 0.13 cm3, respectively. Mean lacrimal gland volumes in normal female vs. male patients were 0.66 ± 0.10 vs. 0.58 ± 0.11, whereas in the thyroid group female vs. male patients had volumes of 0.71 ± 0.09 cm3 vs. 0.69 ± 0.15 cm3. Female predominance in the normal group was 45% (5/11) vs. 57% (8/14) in the thyroid orbitopathy group.

Conclusion: Mean lacrimal gland volumes are larger in patients with thyroid orbitopathy compared to normal patients."

Ru-106 plaque brachytherapy for retinoblastoma at Hadassah - 28 years of experience Kubovsky Shoham, Saban Ori, Eiger-Moscovich Maya, Pe'er Jacob, Frenkel Shahar
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Retinoblastoma is a radiosensitive tumor. However, treatment veered from EBRT due to increased secondary tumors. Nevertheless, brachytherapy remains an effective therapeutic tool for primary and recurrent retinoblastoma tumors. Here we describe our 28 years of experience with this treatment modality.

Methods:
A retrospective review of the medical records of children treated for retinoblastoma at the Hadassah Ocular Oncology Service.

Results:
From 1994 to 2022, we treated 78 eyes of 74 children with Ru-106 plaque brachytherapy. 34 (46%) were girls , and 40 (54%) were boys. The mean age was 2.2 years (range from 3.5 months to 12.5 years, with a Standard Deviation of 2 years). 36 (46%) treatments were given to the right eye, and 42 (54%) treatments were given to the left eye. The most used plaque was CCA (62%). The average irradiation dose was 4,548 cGy to the apex and 23,930 cGy to the base. None of the treatments left a retinal scar at these low irradiation doses, as opposed to the retinal scarring after a total dose for uveal melanoma. In two of the children, the plaque was moved to cover more than one site in tandem. 37 (74%) were secondary treatments, and 20 (26%) of the treatments were primary. The local recurrence rates were 27% for the secondary and 20% for the primary treatments after a mean of 5.8 months in both groups.

Conclusion:
Ru-106 plaque brachytherapy is effective and safe for both primary and recurrent retinoblastoma.

A rat model of human choroidal melanoma

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Purpose: Research models that allow to investigate choroidal melanoma are key towards the development of new therapeutic modalities for this devastating disease. Implantation of human choroidal melanoma cells in animal models best reflects the physiological properties of this malignancy. Such models have been successfully described in immunosuppressed rabbits and immunodeficient rats. Here, we established an experimental model for the study of human choroidal melanoma by implanting a human choroidal melanoma cell line in the choroid of Sprague Dawley rats under administration of systemic immunosuppressors.

Methods: Sprague Dawley rats were injected intraperitonially with 1mg/kg Tacrolimus daily for seven days prior to tumor cell inoculation, and thereafter daily until termination of the experiment. 92.1 human choroidal melanoma cells were injected into the choroidal space of a Sprague Dawley rat eye. Tumor growth was evaluated by Phoenix MicronIVTM image-guided Optical Coherence Tomography (OCT) imaging, which included a real-time camera view and OCT scan of the retina, and by histopathological examination of eye sections.

Results: Initial tumor growth was observed in the choroid two weeks following injection of 92.1 cells using the MicronIVTM imaging system camera and OCT scans. Histology of eye sections confirmed the presence of melanoma tissue. Measurement of choroidal tumor size revealed that on average, tumors reached 1mm diameter in 3-5 weeks.

Conclusion: We established an experimental model for investigating human choroidal melanoma using rats under administration of Tacrolimus as systemic immunosuppression. This model provides the advantage of using rats as smaller and less expansive models compared to rabbits. Further, this model allows to utilize WT, rather than knockout immunodeficient, rats by injecting immunosuppressors. Together, we describe an accessible, cost-effective, rat model of human choroidal melanoma which may advance research in this field.

Blepharoptosis and Cognitive Function in 1.4 Million Adolescents: More than Meets the Eye

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Purpose: To examine the association of blepharoptosis with cognitive function in late adolescence.

Methods: This population-based cross-sectional study included 1,411,570 Israeli-born adolescents (791,463 men, 56.1%) aged 16-19 years, who were examined in preparation for compulsory military service between 1993 through 2017. The diagnosis of blepharoptosis was verified by an ophthalmologist. Cognitive function was evaluated using a validated four-domain assessment (problem-solving, verbal abstraction and categorization, verbal comprehension, and mathematical abilities). Cognitive Z-scores were categorized as high (≥1 standard deviation (SD)), medium (−1 to <1 SD), and low (<−1 SD). Relationships were analyzed using regression models adjusted for sociodemographic variables.

Results: Overall 577 (41 per 100,000) participants were diagnosed with blepharoptosis, most of them were men (67.8%). The proportion of unilateral and bilateral visual impairment among participants with blepharoptosis was 13.0% and 3.5%, respectively. The diagnosis of blepharoptosis was associated with a 0.18 SD decrease in cognitive Z-score (95% CI -0.254, -0.099). The adjusted odds ratios for low and high cognitive Z-scores among participants with blepharoptosis were 1.54 (95% CI 1.25, 1.89) and 0.80 (95% CI 0.62, 1.04), respectively. This relationship persisted when the analysis included only participants with normal visual acuity or unimpaired health status.

Conclusions: This study demonstrates an association between blepharoptosis and cognitive function in late adolescence. Our results stress the importance of timely and appropriate treatment for this multilayered condition. Future prospective studies should investigate the causal properties of this link and aim public health policies at its prevention.

Identification of structural changes in the macula and optic nerve head as early biomarkers of Alzheimer's' Disease

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Purpose: To characterize early structural changes in the macula and optic nerve head in asymptomatic offspring of Alzheimer disease (AD) patients.

Methods: 204 offspring of AD patients (Family History positive, FH+) and 87 age-similar subjects with no family history of AD (FH-) were enrolled. All subjects underwent complete ophthalmic examination and multicolor spectral domain optic coherence tomography (SD-OCT) imaging. Cognitive assessment included executive function and episodic memory tests. MRI brain imaging was performed in 216 of the subjects (FH+=165; FH-=51) on a 3T MRI.

Result: In FH+ subjects the thickness of the macular ganglion cell layer (GCL) and inner nuclear layer (INL) was specifically higher compared to FH- subjects (p=0.027 and p=0.018, respectively). There were no significant differences in peri-papillary retinal nerve fiber layer (ppRNFL) thickness between groups, but there were significant interactions between thickness of the mean global ppRNFL thickness with family history status, executive functions (p=0.024) and working memory (p=0.006), and a similar trend in episodic memory. The Bruch's membrane opening (BMO) area was similar in both groups (1.8 mm^2 ± 0.3). However, the BMO minimum rim width (BMO-MRW) was consistently shorter in the FH+ group across all sectors, reaching statistical significance in both eyes at the nasal inferior area (p=0.05).

Discussion: SD-OCT showed thicken macular ganglion cell layers and thinner optic nerve opening in high risk subject for AD. In addition, patterns of ppRNFL thickness correlated with cognition, suggesting that asymptomatic individuals at high AD risk due to parental family history present already in middle age with retinal alterations that may precede impending clinical symptoms.

Early characteristics of Thalassemia & Sickle cell in OCTA in the pediatric population

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Purpose Evaluation of early macular microvascular characteristics of patients with β-thalassemia, sickle cell disease (SCD) and healthy controls in the pediatric population using optical coherence tomography angiography (OCTA).

Methods Cross Sectional Retrospective Comparative study between patients with thalassemia, sickle cell treated at the Schneider children hospital and healthy controls. Records from 2004 until 2022 of patients with β-thalassemia & SCD who are followed in the hematologic clinic and the ophthalmologic clinic. Patients underwent full ophthalmological evaluation including visual acuity, refraction, slit-lamp examination, dilated fundus bio-microscopy, color fundus wide field imaging, OCT and OCTA.

Results A total of 51 eyes were included12 eyes in the sickle cell group, 16 eyes in the thalassemia group and 23 healthy controls. Mean age was 10.2±3.8 (3-18). In total 54.9% were female. Superficial vessel density (SVD) was the highest in the sickle cell group 47.42% (p=0.007) compared to the thalassemia group and the control group which were similar, 42.69% and 42.77% respectively. Flow density (FD) was statistically significant between the sickle cell group compared to the control group (p=0.03). In univariate analysis, central thickness (CT) was correlated significantly with sex (p=0.014), age (p=0.011) and FAZ (p<0.001); FD was correlated significantly with group type (p=0.036) and SVD (p<0.001); and SVD was correlated significantly with group type (p=0.01) and FD (P<0.001). In multivariate analysis linear regression FAZ was the only parameter which correlated significantly with CT in a negative pattern (p<0.001); furthermore in multivariate analysis linear regression, SVD was the only parameter which correlated significantly with the group type in a positive pattern (p<0.001).

Conclusions We demonstrated differences in the superficial vessel density in very young sickle cell compared to patients with thalassemia and healthy and normal controls using OCTA.

Intraocular injection of various hydrogels did not induce glaucoma in mice

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Purpose: To establish a new mouse glaucoma model using newly developed hydrogels based on short peptides and hyaluronic acid.

Methods: Two types of hydrogels of different compositions were injected intravitreally or intracamerally into the right eyes of 20 wild type (WT) mice. IOP was measured on days 0, 1, 2, 7, 8, 14 and 21 until euthanization on day 21. Histological analysis was performed for retinal thickness, RGCs count and axonal loss. Immunostaining for retinal inflammation was performed by Iba1.

Results: Following a single intracameral injection of either hydrogel solution, the IOP did not statistically significantly increase in study eyes (12.8±2.5 mmHg) as compared to control eyes (13.0±1.83 mmHg). The same was noted following a single intravitreal injection of either hydrogel solution, as the IOP did not statistically significantly increase in the study eyes (11.6±1.6 mmHg) as compared to control eyes (13.0±1.83 mmHg). Mean RGC counts were 22.9±3.5 cells/field in the intracameral group and 23.7±3.6 cells/field in the intravitreal group as compared to 26.3±2.8 cells/field in the control group. Inflammation staining revealed a severe inflammatory reaction in the retina.

Conclusions: The new hydrogel induced glaucoma model failed to increase IOP despite injections with solutions of different compositions intracamerally or intravitreally. Although the gel was demonstrated in the eye following injection by histological analysis, it did not block aqueous drainage. The inflammatory reaction was significant and may explain the RGC loss and gel degradation. Other gels should be designed for intraocular injection for future glaucoma models.

Rebound Effect in Gradual vs. Prompt Cessation of Atropine 0.01% treatment for Childhood Myopia

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Purpose: Our goal is to compare the rate of myopic progression following a rapid washout compared to a tapered cessation from 0.01% atropine drops.

Methods: This observational, retrospective study includes children treated with atropine 0.01% between 2017 and 2022. The gradual cessation group (gradual) treatment was applied by decreasing atropine drops one day from the weekly schedule every month, until a complete stop. The prompt cessation group (prompt) baseline treatment was conducted by immediately stopping all atropine use.

Results: Sixty-six patients were included in this study. The gradual group included 45 patients with a mean age of 13.06±2.41, 48% males. The prompt group included 21 patients with a mean age of 10.6±1.88, 52.3% males. Baseline average spherical equivalent (SE) was -6.38±3.14D (range -1.385D to -13.875D) in the gradual group and -4.64±2.71D (range -1.25D to -11.00D) in the prompt group ($p<0.01$). At last follow-up, the gradual group had lower mean SE myopia progression than the prompt group (-0.25±0.29D vs. -0.68±0.45D; $P=0.0152$) and less axial elongation (0.189±0.318 vs. 0.471±0.304; $P<0.01$). The mean follow-up time was 12.25±8.6 and 12.4±2.1 months in the gradual and prompt groups, respectively.

Conclusions: In the current study, a gradual cessation of atropine exhibited a positive effect in controlling the rebound effect following termination of treatment compared to prompt cessation of treatment.

Longitudinal Optical Coherence Tomography Indices in Idiopathic Intracranial **Hypertension**

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Purpose: Idiopathic intracranial hypertension (IIH) may result in optic nerve fibers loss and even atrophy. The exact timing of the optical coherence tomography (OCT) indices nadir and the factors that predict the patient's outcome are not known. We intended to determine the nadir timing and the factors that affect the nadir retinal nerve fiber layer (RNFL) thickness values.

Methods: The medical records of all IIH patients who were treated from December 2009 to January 2020 were retrospectively reviewed. The following data were recorded at presentation and nadir appointments: lumbar puncture opening pressure, body mass index (BMI), visual acuity, visual field (VF) mean deviation (MD), OCT RNFL, ganglion cell complex (GCC) values, and management.

Results: Of the 109 patients, 89 (81.7%) were women, with average age of 29.32±9.2 years and BMI of 32.22±5.9 kg. The average RNFL thickness at presentation was 261.9±110.7μ. The time to nadir was 7.9±6.3 months. The average RNFL and GCC thickness at the nadir appointment were 92.6 ±14.5 μ (41.3% showed thinning), and 77.9±27.8 μ (64.2% showed thinning) respectively. The Frisén disc edema stage and the presentation average RNFL thickness correlated with a longer time to nadir, r=0.28 (p=0.003) and (r= 0.239, p=0.012) respectively. The nadir average RNFL thickness and the nadir average GCC thickness (r= 0.315, p=0.001, r= 0.293, p=0.002 respectively) correlated with the MD at presentation. The median follow-up time was 40.4±2.4 months. During this time, 15 (13.7%) patients had one episode of recurrence.

Conclusions: Our results show that the final anatomical outcome of IIH episode resulted in RNFL and GCC thinning in a significant number of patients, and it is reached after a mean time of 8 months. The time to RNFL nadir and its values are in correlation with severity of presentation. These findings which indicate IIH patients warrant long term follow up.

An eye-tracking based dichoptic amblyopia home treatment is comparable to standard **occlusion for amblyopia: a multicenter randomized clinical trial (RCT)**

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Purpose: The effectiveness of dichoptic therapy for amblyopia has been debatable, with inferior performance when compared to standard patching in RCT's 1-3.

Methods: To compare the effectiveness and safety of a binocular-eye-tracking-based-home-treatment (CureSight) to patching, we conducted a multicenter RCT. 103 children aged 4≤9 years with anisometropic, small-angle strabismic, or mixed-mechanism amblyopia were enrolled at six sites.

Binocular treatment group used the CureSight for 90 min/day, 5 days/week for 16 weeks (120 hours). The treatment combined anaglyph glasses and an eye- tracker to induce dominant eye real-time blur around the around the central vision area on any available streamed video content. Patching group received 2-hour patching 7 days/week (224 hours).

The primary outcome was the improvement in the amblyopic eye distance visual acuity (AEDVA) from baseline at 16 weeks. Secondary outcomes included stereoacuity, binocular distance visual acuity (DVA), treatment adherence and safety.

Results: The binocular group DVA improvement was 0.28 logMAR (SD 0.13, $p<0.0001$) and 0.23 logMAR (SD 0.14, $p<0.0001$) in the patching group demonstrating non-inferiority (90% CI of difference [-0.008, 0.076]) of the binocular treatment group. Stereoacuity, improved by 0.40 log- arcseconds ($p<0.0001$). BVA improved by 0.13 logMAR ($p<0.0001$) in the binocular group, with similar improvements found in the patching group in both stereoacuity and BVA (0.46 log arcseconds, $p<0.0001$. 0.09 logMAR, $p<0.0001$), Adherence was significantly higher in the binocular vs. the patching group (91% vs. 83%, $p=0.011$). No serious adverse events were reported.

Conclusions:

Binocular treatment is noninferior to patching in amblyopic children aged 4 ≤9 years. High adherence may provide an alternative treatment option for amblyopia."

Color vision deficiency is associated with increased prevalence of amblyopia, strabismus and ametropia: A large population study

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Purpose: To examine the association of color vision deficiency (CVD) with other ophthalmic disorders including ametropia, amblyopia and strabismus in a large population study.

Methods: The retrospective, cross-sectional study included 916 388 Israeli army male recruits that had their pre-military medical assessment at the age of 16 to 18 years from 2000 to 2020. We examined the prevalence of ophthalmic disorders including amblyopia, strabismus and ametropia in army recruits with CVD compared to all other recruits with normal color vision. Demographic and socioeconomic data were also collected.

Results: The prevalence of amblyopia (1.12% vs. 0.71%, $p<0.001$), strabismus (1.10% vs. 0.82%, $p<0.001$), and ametropia (moderate – less than 6.00 diopters, 35.80% vs. 30.42%, $p<0.001$, and high, 3.01% vs. 2.29%, $p<0.001$) were all higher in the 37 029 (4.04%) army recruits with CVD compared with individuals with normal color vision. CVD was more common in individuals with a higher socioeconomic status (high 4.32% vs. low 3.86%, $p<0.001$) and varied according to recruits' origin. It was most frequent in individuals whose parents were born in former Soviet Union (4.81%) compared with other European countries (4.55%), North America (4.26%), Asia (3.27%) and Ethiopia (2.19%).

Conclusions: CVD is associated with increased risk of vision difficulties that are not related to color vision impairment alone. Screening in childhood for color vision deficiency could help in avoiding preventable vision loss."

The effect of reading direction on the Development Eye Movement (DEM) test results in Hebrew speaking children

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Purpose: The Developmental Eye Movement (DEM) test is commonly used for the clinical assessment of saccadic eye movements in children aged 6-13 years. The DEM was validated and developed for English-speaking children and was studied in nine languages, the primary language of participants involved reading from left (L) to right (R). The purpose of this study was to examine the effect of directional reading on the DEM results in Hebrew-speaking children who are accustomed to reading R to L.

Methods: Healthy Hebrew-speaking children, aged 6-13 years were divided into two age groups (6-9, 10-13 years). Children included had minimal near visual acuity of J1, no strabismus, stereoacuity of ≤60 seconds of arc and a near point of convergence of at ≤ 6 cm. The DEM test was performed twice from R to L and in the opposite direction, randomly. Comparisons between age groups on the horizontal and vertical reading speed and DEM ratio between the reading directions were analyzed by independent samples t-test, Mann-Whitney and Wilcoxon tests. Categorical parameters were analyzed by Chi-Square test and correlation between age and directionality was calculated by Pearson coefficient.

Results: A total of 92 children between the ages of 6.2 – 13.1 years were included. Fifty percent of the participants were females. The 6–9-year-old children's group consisted of 48 children and the 10-13 year old's group included 44 children. The mean vertical and horizontal time in both directions (R to L and L to R) of the younger group was significantly slower than that of the older group ($p<0.001$). Interestingly, the older children showed no significant difference in the horizontal time when they read from L-R and R-L ($p=0.2$, $p=0.7$; respectively). However, the younger children read quicker in their native direction (R-L) (71.5±25.9 sec) compared with L-R (76.0±31.4 sec, $p=0.01$). In both directions the ratio was significantly higher in the younger age group. A negative correlation between age and reading ratio was demonstrated ($p=0.001$).

Conclusions: A clear directional preference of R to L in children under the age of 10 years was seen. We suggest administering the test from R to L in young Hebrew-speaking children. These results may also apply to young Arab speaking children who also read from R to L.

Baseline Characteristics in the iREAD Study: Israel Refraction, Environment, and Devices Study

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Purpose: This study presents baseline data from a longitudinal study aiming to assess behavioral factors that may influence myopia in three groups of boys: ultra-Orthodox, religious, and secular who are known to have different prevalence of myopia and different behaviors and educational demands.

Methods: Ultra-Orthodox (N = 57), religious (N = 67), and secular (N = 44) Jewish boys (age 8.6±1.4 years) underwent cycloplegic autorefraction and axial length measurement. Time outdoors and physical activity were assessed objectively. Ocular history, educational factors, and near work were assessed with a questionnaire. Group effects were tested and mixed effects logistic and linear regression were used to evaluate behaviors and their relationship to myopia.

Results: The prevalence of myopia (≤-0.50D) varied by group (ultra-Orthodox: 46%, religious: 25%, secular: 20%, $P < .021$). Refraction was more myopic in the ultra-Orthodox group compared to the religious ($P = .003$) and secular ($P = .001$) groups. Ultra-Orthodox boys learned to read at a younger age ($P < .001$), spent more hours in school ($P < .001$), spent less time using electronic devices ($P < .001$), and on weekdays, spent less time outdoors ($P = .02$). Increased hours in school (OR 1.70 (1.08, 2.67)) and near work (OR 1.22 (1.01, 1.47)), but not time outdoors, increased the odds of myopia. Being ultra-Orthodox ($P<0.05$) and increased near work ($P = .007$) were associated with a more negative refraction.

Conclusions: Ultra-Orthodox boys had higher prevalence of myopia, learned to read younger, and spent more hours in school, with less time outdoors than religious and secular boys. Increased time in school and near work increased the odds of myopia. Belonging to the ultra-Orthodox group and having more hours of near work were associated with a more negative refraction.

Development and Validation of Self-Administrate Visual Acuity Near Chart

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Purpose: To describe the development and validation of a near Visual Acuity (VA) card test for self-administrate and home-based use in comparison to clinically used distance Snellen chart and near Rosenbaum Pocket Vision Screener (RPVS).

Methods: In a prospective study, a near VA card was developed, based on the RPVS chart, with additional lines, decimal (dec) units for each row and written instructions for self-use by the patients. Patients were recruited from ophthalmology clinics at Hadassah Medical Center and optometry clinics at Hadassah Academic College, having minimal best corrected VA (BCVA) of 0.1 Dec at least in one eye. Repeatability analysis was done on 38 patients that were tested twice in a weekly interval by the Snellen, RPVS and the new card. The BCVA of 240 additional patients was measured by clinicians on these tests. Of these, 73 patients also got an oral instructions and guiding video for self-test and their results were compared with the examination' results by a masked clinician. The primary outcome was the mean difference in VA between the self-administrate and those obtained by the clinician. Secondary outcomes included the correlation between distance Snellen chart and RPVS to the newly developed VA card.

Results: The mean age of all 278 participants was 42.5±19.4 years, 47% of them were women. Only the right eye entered the analysis. Repeatability analysis demonstrated a full positive correlation (Rs=0.99, P<0.001). Mean dec BCVA by the Snellen chart was 0.75±0.28, by the RPVS 0.82±0.29 and 0.84±0.28 in the new card (p=0.04). Comparison of the mean self-test by the new card of 73 patients to those obtained by the examiner revealed no significant difference (0.81±0.32 and 0.84±0.28, respectively; P=0.22). Bland and Altman analysis demonstrated a good agreement between the new card to the RPVS, and the ICC of the new card to the Snellen chart was 0.96.

Conclusions: The results of the newly developed VA card are well agreed with those of the standard near test and highly correlated with the Snellen results. The VA measured by the patients found to be very similar to those obtained by examiner. This test may serve as home-based for self-monitoring of patients.

Objective Quantification of Viewing Behaviours During Printed and Electronic Tasks in Emmetropic and Myopic Ultra-Orthodox Jewish Men

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Purpose: Ultra-Orthodox Jewish men are known to have a high prevalence of myopia, which may be due to intense near-work from an early age. This study objectively assessed near-viewing behaviours in ultra-Orthodox and non-ultra-Orthodox men in Israel for different tasks.

Methods: Ultra-Orthodox (n = 30) and non-ultra-Orthodox (n = 38) men aged 18-33 years participated. Autorefraction, visual acuity, height and Harmon distance were measured. An objective range-finding sensor was mounted on their spectacles while they performed four 10-minute tasks in a randomised order: 1) reading printed material, 2) writing printed material, 3) passive electronic and 4) active electronic tasks. Near-viewing distance and the number of viewing breaks were calculated for each task. Statistical analyses included student T-tests and Mann-Whitney between groups and repeated measures ANOVA or Friedman between tasks.

Results: For all tasks combined, a significantly shorter viewing distance was observed for the ultra-Orthodox (36.2 ± 7.0 cm) compared to the non-ultra-Orthodox group (39.6 ± 6.7, $P < 0.05$). Viewing distances for the passive reading and electronic tasks were shorter for the ultra-Orthodox group (36.9 ± 7.7 cm vs. 41.3 ± 8.1 cm, $P < 0.03$ and 39.0 ± 10.1 vs. 43.9 ± 9.3, $P<0.05$, respectively). Viewing distances were significantly different between all four tasks, with writing having the closest distance. No correlation was found between working distance and spherical equivalent or Harmon distance. However, a significant correlation was found in the ultra-Orthodox group between working distance and height for each task ($P < 0.04$, $R < 0.42$ for all). There was no difference in the number of viewing breaks between the groups.

Conclusion: When reading a book and viewing an iPad, ultra-Orthodox men demonstrated a closer objective working distance than non-ultra-Orthodox men. This shorter viewing distance may contribute to the high prevalence and degree of myopia in this population.

Pediatric refraction measurement with Inverse Shack-Hartmann device without cycloplegia

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Purpose: Refraction error is the most prevalent vision deficiency. This is becoming especially pervasive in children, as myopia reaches unprecedented proportions. Pediatric refraction measurements require the use of cycloplegia. Hence two visits are required to determine children refraction. An alternative method that will alleviate these limitations is desired.

Method: 35 children age 8-17 were enrolled. Refraction was determined using a new refraction measurement device by EyeQue Corp. and a standard autorefractor with and without cycloplegia. The new refraction device is based on the Inverse-Shack-Hartmann technology integrated in a binocular form factor presenting a stereoscopic background image simulating far vision. This was tested as the main mechanism for controlling the accommodation. All children underwent Ishihara color testing, cover test, phoropter testing, best corrected visual acuity, and slit lamp biomicrocopy. A Bland-Altman analysis was used to test the agreement between the autorefractor (Righton Retinomax K-plus 3) measurements and the EyeQue device measurements.

Results: A comparison between the EyeQue measurement without cycloplegia and the autorefractor measurement with cycloplegia shows a bias of -0.49D in spherical equivalent with limits of agreement of ±1.12D. This is comparable to the bias between the autorefractor measurements with and without cycloplegia of -0.75D and the EyeQue device with and without cycloplegia of -0.66D. Furthermore, the autorefractor with and without cycloplegia limit of agreement was ±1.04D, while the EyeQue device with and without cycloplegia limit of agreement was ±1.16D.

Conclusions: Rauscher et al. (2019) compared the Zeiss i.Profiler and found a bias of -0.55D with limits of agreement of ±1.1D. Harvey et al. (1997) compared the Nikon Retinomax and found a bias of -0.26D with limits of agreement of ±1.3D. Satou et al. (2019) compared the Welch-Allyn Spot and found a bias of -0.19D with limits of agreement of ±1.65D. Dahlmann-Noor et al. (2009) compared the PlusOptix Vision Screener and found a bias of over -1D with limit of agreement greater than ±2D. These results indicate that the EyeQue device performs similarly to a standard-of-practice autorefractor and better than other portable devices intended to be used with children. The device allows for effective accommodation mitigation without cycloplegia.

The Antibacterial Efficacy of High-Fluence PACK Cross-Linking can be Accelerated

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Purpose: To determine whether high-fluence photoactivated chromophore for keratitis cross-linking (PACK-CXL) can be accelerated.

Methods: Solutions of Staphylococcus aureus and Pseudomonas aeruginosa with 0.1% riboflavin were prepared and exposed to 365 nm ultraviolet (UV)-A irradiation of intensities and fluences from 9 to 30 mW/cm2 and from 5.4 to 15.0 J/cm2,respectively, representing nine different accelerated PACK-CXL protocols. Irradiated solutions and unirradiated controls were diluted, plated, and inoculated on agar plates so that bacterial killing ratios (BKR) could be calculated. Additionally, strains of Achromobacter xylosoxidans, Staphylococcus epidermidis, and Stenotrophomonas maltophilia were exposed to a single accelerated PACK-CXL protocol (intensity: 30 mW/cm2 , total fluence: 15 J/cm2).

Results: With total fluences of 5.4, 10.0, and 15.0 J/cm2, the mean BKR for S. aureus was 45.78%-50.91%, 84.13%-88.16%, and 97.50%-99.90%, respectively; the mean BKR for P. aeruginosa was 69.09%-70.86%, 75.37%-77.93%, and 82.27%-91.44%, respectively. Mean BKR was 41.97% for A. xylosoxidans, 65.38% for S. epidermidis, and 78.04% for S. maltophilia for the accelerated PACK-CXL protocol (30 mW/cm2, 15 J/cm2).

Conclusion: The BKR of high-fluence PACK-CXL protocols can be accelerated while maintaining a high, but strain-dependent BKR. The Bunsen-Roscoe law is respected in fluences up to 10 J/cm2 in S. aureus and P. aeruginosa, whereas fluences above 10 J/cm2 show strain dependence.

The effect of mydriatics on posterior synechia formation after combined pars plana vitrectomy, phacoemulsification, and intraocular lens implantation

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PURPOSE: To evaluate the influence of topical short-acting mydriatics on the formation of posterior synechia after combined surgery of pars plana vitrectomy (PPV) and phacoemulsification with intraocular lens (IOL) implantation.

DESIGN: Prospective randomized controlled trial.

PARTICIPANTS: Adult (>18 years old) patients who underwent combined surgery at a single tertiary hospital (Rabin Medical Center).

METHODS: Fifty-seven patients (57 eyes) who underwent combined surgery were randomly divided into two groups. The control group (29 eyes) received standard postoperative treatment (topical antibiotics and steroids). The study group (28 eyes) underwent combined surgery and received short-acting mydriatics together with standard therapy. Patients were followed up at weeks 1,4,8,12,16, and the final follow-up was at 24 weeks after combined surgery.

MAIN OUTCOME MEASURES: Primary outcome measure was the formation of posterior synechia during the 24-week follow-up period.

RESULTS: A total of 7 patients developed posterior synechia during the follow-up period (12%), 3 in the study group (11%) and 4 in the control group (14%). There was no statistical difference between the groups. Significant associations for the development of posterior synechia were surgery for retinal detachment, longer duration of surgery (>93 minutes), and the use of tamponade, in particular silicone oil.

CONCLUSIONS: In our study, the use of topical short-acting mydriatic drops after combined surgery, in addition to standard post-operative treatment, did not reduce the formation of posterior synechia. However, we identified several factors that may influence or act as predictors for the development of posterior synechia: surgery for retinal detachment, using silicone oil tamponade, and longer surgery duration. Our findings may aid in the standardization of post-combined surgery treatment and define potential at-risk patients which should be monitored more closely.

Short Term Evaluation Two Types of Specialty Soft Contact Lenses for Keratoconus

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Rigid gas permeable (RGP) contact lenses (CLs) for keratoconus (KC) may induce complications and discomfort, which may be alleviated by use of soft lenses for KC. This study compared objective outcome parameters obtained after two weeks of wear of SoftK2 (14.2 or 14.8mm diameter) and SoftK semiscleral (SoftKSS, 17.0mm diameter) lenses for KCs in a crossover design.

Methods

Patients with initial (Belin grades I or II) KC were fit with a CL for two-weeks and crossed over to the other CL for two-weeks. Low (10%) and high (100%) contrast visual acuity (VA), Peli Robson contrast sensitivity, mean mainly hours of wear, and the subjectively preferred lens were compared using repeated measures ANOVA or Friedman tests with post hoc testing.

Results

Eleven particiapnts (22 eyes, 5 male, mean age:38±9, range:25-55 years, mean refraction:-3.25±4.00/-4.00±4.00 D, mean K:7.10±0.42) were first fit with SoftKSS and crossed-over to SoftK2 lenses. High and low contrast VA was significantly improved with SoftKSS (0.81±0.15 and 0.41±0.16) and with SoftK2 (0.90±0.13 and 0.52±0.17) compared with the habitual condition (0.66±0.21 and 0.32±0.18) but were not significantly different from each other. Mean hours of wear (N=20 eyes, SoftKSS: 6.4 ±2.8, SoftK2: 6.4± 2.3) were not significantly different (p=0.97). Nine participants (80%) preferred the SoftK2 lens. Three male patients (6 eyes, mean age:39±11, range:27-47 years, mean refraction:-3.60±2.80/-3.50±2.00, mean K:7.00±0.44) were first fit with SoftK2 and crossed-over to SoftKSS, with recruitment of this arm still ongoing. High and low contrast visual acuity (VA) was not significantly improved with SoftKSS (0.81±0.17 and 0.46±0.22) and with SoftK2 (0.86±0.10 and 0.54±0.21) compared to their habitual presenting VA (0.64±0.35 and 0.41±0.27). Mean hours of wear (SoftKSS: 9.1± 2.2, SoftK2: 9.8±1.7) were not significantly different (p=0.81). All participants (100%) preferred the SoftK2 lens.

Conclusion:

Though there was no significant difference in outcome measurements of the two lens types, SoftK2 was subjectively preferred by the vast majority of participants.

Complications of Scleral Lens Wear Amongst Keratoconus Patients

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Purpose: To examine the prevalence of contact lens complications amongst scleral lens wearers suffering from keratoconus.

Methods: A retrospective study of 65 keratoconus patients who wore Irregular Corneal Design (ICD) toric 16.5 diameter scleral lens (Paragon vision sciences, Mesa, USA) made from Paragon HDS® (paflufocon B) raw material. 52 patients were fitted with scleral lenses in both eyes and 13 were fitted in one eye only. The average age of the wearers was 28.1 ± 8.01, the age ranging from 16 to 48 years. 57% of the patients were males.

The initial fitting examination included optical coherence tomography (OCT) device (Optopol, REVO 80, Zawiercie, Poland(and a thorough video slit lamp (CSO SL990 Digital LED Elite, Florence, Italy). Follow-up examinations were conducted after one week, one month and every six months thereafter. The patients were reminded to come for check-ups and each time filled-in a questionnaire related to adverse events related to lens wear. They were given a thorough slit lamp examination and had topography done. The patients were told to come to the clinic if they felt any change in their eye/eyes, especially redness, discomfort, drop in vision or pain.

Results: The patients wore the lenses for 10.77± 2.2 hours per day. maximum K (Kmax) and pachymetry measured, 62.31± 9.01 and 429.9±54.45 microns respectively. The average scleral vaulting and the visual acuity measured was 337.01±43.297 microns and 0.788±0.2 respectively. No staining of the cornea was observed at the follow-up visits. The most significant complications were limbitis and infiltrative keratitis (IK) having a prevalence of 1.54% and 3.08% respectively. The less significant complications found were mid-day fogging and bulbar hyperemia, giant pupillary conjunctivitis and limbal neovascularization. The prevalence being 15.38%, 18.46%, 9.23% and 7.69% respectively.

Conclusions: The most significant adverse events found were limbitis and infiltrative keratitis and less significant adverse events were mid-day fogging, bulbar hyperemia, giant pupillary conjunctivitis and limbal neovascularization. Large scale studies are required in order to answer the question whether these are the only complications found amongst keratoconus patients wearing scleral lenses.

Meibomian gland dysfunction in Fitted and Over the Counter Contact Lens Wearers compared with non-Contact Lens Wearing Controls

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Purpose: The relationship between contact lens (CL) wear and meibomian gland dysfunction (MGD) is equivocal. This study examined the relationship by comparing morphological, functional and subjective outcomes associated with MGD of over-the-counter (OTC) soft CL wearers, fitted soft CL wearers (Fitted), and non-CL wearing controls.

Methods: Habitual LogMAR visual acuity, non-invasive tear break-up time (NITBUT), TBUT, Schirmer test, Efron MGD grading, Meibum Quality Score (MQS), Meibum Expressibility Score (MES), Cobra HD meibography, and subjective dry eye (DE) and Ocular Surface Disease Index (OSDI) questionnaire scores were assessed. Measurements of the right eyes of the cohorts were compared using Kruskal-Wallis and Pearson Chi-Square tests for ordinal and categorical variables, respectively. Multivariate logistic regression examined if CL wear is an independent risk factor for MG abnormalities or ocular symptoms.

Results: Of the 128 participants (74% female); 43 were OTC (mean age: 23.0±4.6), 31 were Fitted (mean age: 22.2±3.1), and 54 were controls (mean age: 22.3±3.5). NITBUT, TBUT, Schirmer test, MGD grade, MQS, lower eyelid MG loss and OSDI score were not significantly different between the cohorts. OTC wearers had significantly lower VA (0.82±0.17) compared with controls (0.93±0.12, p=0.002). MES was significantly better for the controls (0.2±0.5) compared with the OTC (0.8±0.9, p<0.0008) and Fitted (0.6±0.7, p<0.01) cohorts. Upper eyelid MG loss was significantly lower in controls (11.2%±6.8%) compared with the OTC (18.6%±11.3%, p=0.001) and Fitted (16.9%±8.8%, p=0.02) cohorts. DE symptoms were more prevalent in OTC (3.7±2.4) compared with controls (2.3±2.1, p=0.002). OTC and Fitted CL wear was significantly associated with corneal staining (OR=3.42, 95% CI: 1.16–10.11, p=0.03 and OR=5.23, 95%CI: 1.89–14.48, p=0.001, respectively) and upper eyelid MG loss (OR=10.47, 95%CI: 1.14–96.29, p=0.04 and OR=16.63, 95%CI: 1.96–140.86, p=0.01, respectively). OTC CL wear was also significantly associated with abnormal meibum quality (odds ratio (OR)=12.87, 95% confidence interval (CI): 1.12–148.41, p=0.04), conjunctival staining (OR=12.18, 95%CI: 3.66–40.51, p=0.0005), and lid margin telangiectasia (OR=3.78, 95%CI: 1.55–9.21, p=0.003).

Conclusions: Soft CL wear was significantly associated with corneal staining and upper eyelid MG loss. OTC wear was also associated with DE symptoms, abnormal meibum quality, conjunctival staining, lid margin telangiectasia along with reduced VA. Findings stress the importance of CL fitting and follow-up.

Protective shield placed on the optical cylinder in patients after Osteo/odonto-keratoprosthesis (O/OKP): A case series

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Purpose: To describe four cases of placing a cellphone Silicon protective shield on the optical cylinder in patients post Osteo/odonto-keratoprosthesis (O/OKP) surgery - to treat and minimize prosthesis scratching and consequent visual loss.

Methods: Retrospective observational case series of four patients post O/OKP preformed between 2019 – 2022. In all cases, a protective silicone cellphone screen protector was cut using a 3mm dermal punch and placed on the optical cylinder. In one case (case 1), the protective shield smoothed a severely abrased optic cylinder and improved the patients' vision, and in the other three cases the protective shield was places to prevent future optical abrasions.

Results: In case 1 that presented with severe abrasion and deep scratches post OOKP, the Silicon shield improved the patients' BCVA from 6/20 to 6/8.5. In the other 3 cases (in which the optical cylinder was not abrased) – the Silicon shield was placed to prevent future abrasion and did not change the BCVA nor the refraction.

Conclusion: Placing a soft silicon protective shield on the optic cylinder in patients post O/OKP procedure helps to improve BCVA in patients with abrased optical cylinder and to prevent abrasions in an otherwise non-abrased optical cylinder. Placement of this shield is easy, cheap, safe and does not reduce BCVA nor changes refraction in these patients.

Scleral Contact Lens Designed to Reduce Ptosis

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(1)Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Faculty of Medicine, Hebrew University of Jerusalem ***Purpose:*** *To explore whether scleral contact lenses can be designed to reduce ptosis effectively.*

Methods: Eight patients, five males, with an average age of 39.3±14, were included in this study. All had monocular ptosis. Four had worn rigid gas permeable lenses, three post-trauma, one with an oculomotor palsy. To create a type of upper lid support, all these patients were fit with an asymmetrical scleral lens design with a superior limbal clearance of above 250 microns. The patients were also fitted with a soft lens. The upper lid marginal reflex distance (MRD) was measured without a lens, the soft lens, and the scleral lens using the Image Pro-Plus Software (Image Pro-Plus 6.0; Media Cybernetics, Silver Spring, MD, USA).

Results: The MRD did not change with the soft lens compared to without a contact lens. The MRD increased with the scleral lens compared with the soft lens with an average of +2.38±0.79 mm ($P<0.01$).

Conclusions: The superior excessive limbal clearance scleral lens design effectively decreased monocular ptosis in these patients.

Finite element modelling of geometrical factors affecting Descemet's membrane endothelial keratoplasty (DMEK) graft adherence

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Purpose: To perform and Finite element method (FEM) modelling of geometrical factors affecting Descemet's membrane endothelial keratoplasty (DMEK) graft adherence to the recipient cornea.

Methods: Solidworks CAD software and ANSYS analysis software were used to create a theoretical 3D model of the posterior surface of the recipient cornea, and of a DMEK graft. Simulation of stress distribution and deformations were modelled on grafts of different diameters, shapes (round, elliptical and hexagonal), and locations.

Results: In round and elliptical grafts, the largest deformations were observed on the edges of the horizontal meridian, and in hexagonal grafts, on the vertical meridian. For all graft shapes, graft deformations favoring detachment were increased with decreased graft diameter. Elliptical graft of 6*8mm diameters, aligned with the posterior corneal astigmatism, showed the lowest mechanical stress values. Both mean and maximal deformation values were higher in the decentered round grafts in comparison to centered ones.

Conclusion: Our FEM model demonstrated that larger graft diameter, graft centration, and elliptical graft shape oriented with the curvatures of the posterior cornea, all favored DMEK graft attachment to the recipient cornea.

Efficacy and Possible Advantage of Mini-scleral and Scleral Contact Lenses Over a Period of Twenty-four Months in Severe Dry Eye

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Purpose: To evaluate the possible advantage of scleral versus mini-scleral lenses and their respective efficacy in the rehabilitation of the cornea in severe dry eye over a period of twenty four months.

Methods: This study included 37 eyes of patients with severe dry eye. Their ages were 48±14 years, 58% women. The patients were divided into two groups, one group (10 patients) was fit with mini-scleral lenses and the second group (9 patients) was fit with full scleral lenses. Almost half (42%) of the patients had punctal plugs inserted prior to this study and they were divided equally between the two groups. The most common diseases of these patients were sjogren syndrome (7 patients), graft-vs-host disease (3 patients), ocular cicatricial pemphigoid (2 patients). The rest of the patients suffered from dry eye not a result of systemic disease or from medication intake. One patient was fit only unilaterally due to extreme dryness after treatment for primary acquired melanosis (PAM). Evaluations of visual acuity, corneal staining and conjunctival staining were conducted at baseline and at 24 months.

Results: There was a statistically significant decrease in corneal staining from 2.45 ± 1.54 to 1.03 ± 1.13 ($P<0.05$) based on the oxford scheme for grading ocular surface staining. The best-corrected visual acuity improved from 0.53 ± 0.29 to 0.74 ± 0.31 ($P<0.05$). There was no statistically significant reduction in conjunctival staining from baseline. This study did not show a clinically significant advantage to the full-size scleral lens above the mini scleral in either corneal staining or visual acuity. At the 24 months follow up 63.15% of the patients reported that they had discontinued lens wear primarily due to protein and mucin deposits.

Conclusions: Mini-scleral and scleral lenses are efficacious and well tolerated for use in severe dry eye syndrome up to 16 months. Though full scleral contact lenses afford a larger reservoir, they also seemed to attract more deposits. The full scleral contact lens was not superior to mini-scleral contact lens in reducing corneal staining or improving visual acuity.

Evaluation of IOL Power Calculation with the Kane Formula for Pediatric Cataract Surgery

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Purpose: To assess the accuracy of the Kane formula for intraocular lens (IOL) power calculation in the pediatric population.

Methods: The charts of pediatric patients who underwent cataract surgery with in-the-bag IOL implantation with one of two IOL models (SA60AT or MA60AC) between 2012-2018 in The Hospital for Sick Children, Toronto, Ontario, Canada, were retrospectively reviewed. The accuracy of IOL power calculation with the Kane formula was evaluated in comparison with the Barrett Universal II (BUII), Haigis, Hoffer Q, Holladay 1 and Sanders-Retzlaff-Kraff Theoretical (SRK/T) formulas.

Results: Sixty-two eyes of 62 patients aged 6.2 (IQR 3.2-9.2) years were included. The SD values of the prediction error obtained by Kane (1.38) were comparable with those by BUII (1.34), Hoffer Q (1.37), SRK/T (1.40), Holaday 1 (1.41) and Haigis (1.50), all $p>0.05$. A significant difference was observed between the Hoffer Q and Haigis formulas ($p=0.039$). No differences in the median and mean absolute errors were found between the Kane formula (0.54 D and 0.91±1.04 D) and BUII (0.50 D and 0.88 ± 1.00 D), Hoffer Q (0.48 D and 0.88 ± 1.05 D), SRK/T (0.72 D and 0.97 ± 1.00 D), Holladay 1 (0.63 D and 0.94 ± 1.05 D) and Haigis (0.57 D and 0.98±1.13 D), $p=0.099$.

Conclusions: This is the first study to investigate the Kane formula in pediatric cataract surgery. Our results place the Kane among the noteworthy IOL power calculation formulas in this age group, offering an additional means for improving IOL calculation in pediatric cataract surgery. The heteroscedastic statistical method was first implemented to evaluate formulas' predictability in children.

CEMENT OCCULAR INJURY LEADING TO ISOLATED CORNEAL ENDOTHELIAL DYSFUNCTION: A CASE SERIES OF A RARE ENTITY

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Purpose:
To present a rare significant complication, isolated endothelial injury, of a Roper-Hall 1/Dua 1-2 grade ocular chemical injury (a low injury grade). Thus, this rare complication represents a gap between the favorable prognosis of the chemical injury determined by the present available grading systems to the actual injury severity.

Methods:
A retrospective case series of 5 patients seen in our tertiary institute between January 2021 to March 2022.

Results:
A total of five patients presented to our tertiary institute following chemical injury of cement to their eye. In all, limbal area was only mildly affected (if at all), epithelium healed rapidly and there was no significant stromal involvement. At their initial visit, all were diagnosed with a Roper-Hall 1/Dua 1-2 chemical injury indicating a mild injury with favorable prognosis. Surprisingly, during their early follow up appointments, diffuse corneal edema with descemet folds was observed, indicating endothelial dysfunction. The treatment was modified accordingly by elevating topical steroid dosing and adding hypertonic saline drops, gradually leading to a full recovery with corneal clearing of the patient that weren't lost to follow up.

Conclusions:
Isolated endothelial dysfunction after ocular chemical injury, without significant involvement of other corneal tissues, is a rare but serious complication of the initial chemical injury. In this case series, this complication was unique to cement injury. We believe that the available grading systems do not fully address this issue - which obviously should not be graded as a mild injury as the available grading systems suggest. Thus, a modification to the present grading systems is warranted.

Relationship between Corneal Topographic Asymmetry and Epithelial Thickness Profile Map Patterns in Laser Vision Correction (LVC) Candidates

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Purpose: To explore a possible correlation between the topography patterns of the anterior axial cornea and the corneal epithelial layer as measured by optical coherence tomography (OCT) in corneas with suspicious anterior corneal topography and asymmetric epithelial thickness distribution.

Methods: This is a retrospective controlled study. A surgery center reviewed the records of 436 patients examined over one year for suitability for laser vision correction (LVC). The patients were categorized into two epithelial pattern groups: suspected keratoconus and corneal warpage. Among these patients, 48 (78 eyes) exhibited an asymmetric anterior corneal topography obtained by the Galilei-G4 (Ziemer, Biel, Switzerland). They were referred for epithelial mapping indices via OCT with anterior segment OCT (Optovue RTVue-100, Optovue Inc., Fremont, CA). No other irregularities, such as corneal thinning or posterior corneal abnormalities, were noted. In the corneal warpage pattern group, there were 38 patients (68 eyes), age 29.8±7.8 (range 19-35), 40% female and 45.16±1.33D, 1.32±0.49D and 512.1±37.2μ maximum keratometry (K max), inferior-superior index (I-S) and central corneal thickness (CCT) respectively. In the keratoconus group, there were ten patients (10 eyes) age 28.3±13.5 (range 19-55), 61.7% female and 45.09±1.13D, 1.47±0.88D and 505.5±49.3μ maximum keratometry (K max), inferior-superior index (I-S) and central corneal thickness (CCT) respectively.

Results: In the warpage pattern group, there was no correlation between the min or max epithelium thickness and the vertical coma or total coma aberrations. Asphericity asymmetry index (AAI) anterior, AAI posterior, Inferior-Superior index (I-S), Opposite Sector Index (OSI), Differential Sector Index (DSI), Surface Regularity Index (SRI) and Surface Asymmetry Index (SAI) also showed no correlation between the min/ max epithelium. There was no correlation between the standard deviation and the vertical coma or total coma, AAI anterior, AAI posterior, OSI, DSI, SRI and SAI. The only correlation observed was between the standard deviation of epithelium and the I-S (r=0.358, P= 0.0294). OCT epithelium measurements confirms 20% of the suspicious topography patterns and restored to LVC less than 82% of the patients.

Conclusions No association between corneal topography asymmetry metrics with asymmetric epithelial distribution was found. An inferior steep corneal topography does not correlate with a thicker epithelial layer.

Corneal injury: Expedited healing by alpha1-antitrypsin

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Purpose: To investigate the impact of AAT treatment on the healing process of corneal erosions.

Methods: Corneal abrasions of 2mm centrally located using Ocular burr ,were performed in wild-type (WT) mice which have normal serum AAT levels . Thirty mice WT groups have been classified into 2 equal groups by post operation care : Either normal Saline (a control group 1) , or a topical hAAT (group 2) .The abrasions area were quantified serially throughout 30 hours from wounding.

Serial photos were captured every 4 hours using a microscope connected to a camera base ,until full corneal abrasion closure occur.

Measurements of the corneal abrasions size were analyzed using IMAGE J software.

Results. Expectedly, all mice reached full wound closure 48 hours from wounding.

However, topically hAAT group displayed a statistically significant 2-fold faster healing at 12 hours compared to untreated saline control group (41.32 percent and 22.20 percent respectively)

Conclusion. These results suggest that treatment with topical hAAT accelerates corneal wound healing in mice model.

Such results can represent a promising therapeutic applications on humans corneal wound healing and other surface eye disease conditions.

Refractive Results Following Implantation of Multifocal, Monofocal and Monofocal with Increased Depth of Focus Intraocular Lenses After Cataract Surgery

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Purpose: To evaluate the effectiveness of the newly-designed Tecnis Eyhance (Johnson & Johnson (J&J)) monofocal Intra-ocular lens (IOL) in terms of visual parameters (visual acuity (VA) at different distances and glare conditions, contrast sensitivity and refraction) as well as the subjective comfort, compared to multifocal Tecnis Synergy (J&J) and monofocal Sensar (J&J) IOLs.

Methods: Uncorrected VA (UCVA) as well as the best corrected VA (BCVA) of post-cataract surgery participants were measured at distance (6 m), intermediate (70 cm) and near (40 cm) (Snellen chart, Log units). Contrast Sensitivity (CS) was measured at distance and near with correction (Pelli-Robson chart, Log units) and the subjective visual comfort was assessed by a questionnaire.

Results: Overall of 52 participants were included in this study (84 eyes); 40 eyes were implanted with Eyhance, 26 with Synergy and 18 with Sensar. The age of participants ranged between 48-82 years, the mean age was 70.2 ± 7.59 and 31 (59%) were women. No significant difference was found in the distance VA between all three lenses ($P>0.8$). However, the Synergy was significantly superior to the other lenses in the mean intermediate and near VA ($P<0.01$). The Eyhance had better mean CS compared to the Synergy at distance (1.38±1.5, 1.31±0.13; respectively, $P<0.05$) and at near (1.46±0.15, 1.36±0.17; respectively, $P<0.05$). Visual comfort assessed by the questionnaire demonstrated no difference between the three groups, yet analyzing the questions dealing with intermediate vision, the Synergy was preferable by the participants.

Conclusions: The newly-designed monofocal Eyhance IOL demonstrated better visual performance than the multifocal Synergy in the CS at distance and near, with the same VA for distance in these lenses as with the monofocal Sensar. All three lenses were reported to with the same visual comfort by the patients, yet the Synergy was preferable for VA at intermediate and near with better subjective quality of vision at intermediate.

MicroRNA-184 regulates corneal tissue turnover and active stem cell population

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Purpose: Very little is known about mechanisms that allow the heterogeneity of stem cell (SC) states in vivo. Recently, we identified an “outer” quiescent limbal SC (LSC) population that serves as reservoir SC pool and an “inner” active LSC population that maintains homeostasis. However, the molecular mechanism that controls these SC states is largely unclear. While various corneal disorders involve LSC dysfunction, the molecular mechanism is poorly understood. Here we aim to study microRNA-184 (miR-184), which its point mutation leads to congenital eye dystrophy, in the control of LSC state.

Methods: We performed in-situ hybridation the expression of miR-184 on stem and differentiated cells in wild type and miR-184 knockout (KO) mice. Nucleotide incorporation test and immunofluorescent staining were performed to uncover the impact of miR-184 on LSC populations, cell proliferation and differentiation state. Genetic “Confetti” lineage tracing and active K15-GFP transgene (green fluorescent protein downstream to the Krt15 promoter) allowed visualizing the dynamics of LSC populations and the presence of active LSCs in real time, respectively, in wild type and KO mice. Flow cytometry and quantitative real-time polymerase chain reaction and RNA sequencing were performed to reveal the molecular networks downstream to miR-184.

Results: In-situ hybridization suggests miR-184 is absent in quiescent LSCs, but expressed by active LSC population and by corneal progenitors that are committed to differentiation. miR-184-KO animals showed a virtually complete loss of the K15-GFP transgenic reporter expression, suggesting that miR-184 serves as a guardian of the active LSC state. Lineage tracing revealed an enhance LSC activity, hyper proliferation in both limbus and corneal compartments of miR-184-null. This Nucleotide incorporation test suggested that a higher cell loss is perfectly balances the increased cell division resulting in normal corneal epithelial thickness in mutants.

Conclusions: miR-184 regulates active LSC marker expression, the turnover rate of corneal renewal and LSC and corneal epithelial cell proliferation. Future studies will be needed to explore whether miR-184-disease-causing-mutatations lead to similar abnormalities and the molecular mechanism by which miR-184 controls these processes. A better understanding of these mechanism is essential for the broader understanding of SC fate decisions and for developing advanced therapeutics for corneal diseases.

Accuracy of Belin/Ambrósio Enhanced Ectasia display map prediction of corneal ectasias in patients with spherical corneas

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To assess the accuracy of topography maps in identifying abnormal posterior corneal surface in spherical corneas

Methods:

Data from Pentacam corneal topographies conducted in the Cornea unit in the Rabin Medical Center were retrospectively obtained, and 237 patients with corneal astigmatism £ 0.5 and back to front ratio less than 0.8 were defined as patients with spherical corneas. Correlation between total deviation value in the Belin/Ambrósio Enhanced Ectasia display map and parameters in the posterior and anterior elevation maps were assessed in order to determine the false positive rates of the abnormal D value in the study population.

Results:

TBD

Conclusion:

TBD"

Reprogramming to rescue total stem cell loss

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Purpose: Recently, we discovered that K15-GFP transgene (green fluorescent protein coding sequence under Krt 15 promoter) labels a population of active limbal epithelial stem cells (LSCs). Further, a complete surgical limbal epithelial removal (LER), was restored by the peripheral corneal committed cells that heal the denuded limbus and undergo reprogramming into LSC-like cells. Here we wish to investigate the molecular basis of the reprograming process and to what extent the dedifferentiated cells become similar to the LSCs-like cells at the molecular and functional level.

Methods: Surgical LER was performed in live K15-GFP mice and recovery was recorded at different time points by wholemount staining of quiescent and active LSC markers. Tissue samples were analyzed by RNA sequencing to expose the key process and mechanism of dedifferentiation. The ability of dedifferentiated LSCs to heal corneal debridement was assessed by Fluorescein dye staining.

Results: A full recovery of the two LSC-like compartments was implied by the reappearance of two segregated limbal zones hallmarked by the outer quiescent (IFITM3+/CD63+/GPHA2+) and inner active (K15-GFP+) LSCs that were detected around day 20 and 10, respectively. The dedifferentiated LSC-like cells efficiently healed corneal injuries and surprisingly, the wound closure rate was even faster than that of native LSCs. The RNA sequencing analysis illuminates key stages in reprograming of corneal committed cells into the functional LSC-like cells.

Conclusion: Altogether, this study suggests a remarkable plasticity of corneal epithelial cells and that dedifferentiated LSC-like cells behave as bona fide LSCs. Understanding the mechanistic aspect of dedifferentiation will further allow harnessing the innate regeneration mechanisms to optimize LSC-based therapy.

Coloboma-microphthalmia-anophthalmia in Iranian Jews: from human genetics to mouse studies

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Purpose: We sought to characterize clinically and decipher the molecular basis of apparently autosomal recessive isolated coloboma-microphthalmia-anophthalmia complex prevalent in Iranian Jews, mainly of the Mashad inbred community.

Methods: Clinical studies by ophthalmologists, followed by homozygosity mapping using SNP arrays and whole genome sequencing with segregation analysis using Sanger sequencing; Generation and studies of mutant transgenic mice.

Results: Affected individuals had various degrees of bilateral or unilateral coloboma, microphthalmia, or anophthalmia, with variability between individuals and between the eyes of the same individual. Homozygosity mapping identified a single 0.5Mb disease-associated locus (maximal LOD score 6.8). Whole genome sequencing identified several putative disease-causing variants within this locus. We identified and validated the disease-causing mutation through segregation analysis within the affected families, followed by generation and studies of mutant mice.

Conclusions: Autosomal recessive isolated coloboma/microphthalmia/anophthalmia with phenotypic variability between and within affected individuals is caused by a single nucleotide mutation affecting humans and mice.

The Use of Acoustic Manipulation of Intraocular Particles-In vitro and Ex vivo trial

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Purpose: feasibility and safety of acoustic manipulation technique for non-invasive control of intraocular particles.

Methods: We developed a novel non-invasive automated technique to generate standing acoustic waves in the anterior chamber (AC) that enables to control over the movement of intraocular particles. The safety and efficacy of the technique was tested on an Ex-vivo hyphema model. Twelve (7 study and 5 control) bovine eyes were injected with 0.1 cc of red blood cells (RBC). Eye movement was simulated to ensure equal distribution of the RBCs in the AC. Both control and study eyes were positioned in a vertical manner. The 7 study eyes were treated with the acoustic device using a standard treatment protocol.
The main outcome measures were clearance of visual axis at 5 and 60 minutes from baseline and ability to prevent accumulation of particles within the superior 180 Degrees of Schlemm's canal (SC). Biomicroscopy and histology were used to identify any adverse effects.

Results: At 5 minutes from baseline, the visual axis was clear in all study eyes. The visual axis was obscured in all of the control eyes at 1 hour from baseline. Accumulation of RBC within superior SC was also significantly lower in the study eyes (ratio between upper and lower SC- 1.4 in controls Vs 0.4 in study eyes, p-value=0.005). No signs of tissue damage were observed in either of the study eyes.

Conclusions: Using acoustic radiation forces we are able to direct particle movement within the anterior chamber. Applying acoustic manipulation techniques has the potential to reduce or even prevent secondary particle induced glaucoma development among patients at risk.

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Cobalt affiliation to the optic nerve

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Background and Aims: Visual dysfunction due to cobalt toxicity in hip implant patient is well reported but not well understood. The aim of the study was to explore the pathophysiology of cobalt toxicity related to visual impairment.

Methods: 114 wild type mice (WT, C57Bl6) were injected with cobalt-chloride in 3 different routes: single intravenous (IV) injection (high, medium, and low concentrations) n=44; single intravitreal (IVT) injection n=30, or daily repeated intraperitoneal (IP) injections (high dose/3 days, medium dose/14 days, and low dose/55 days) n=40. Immunodeficient transgenic NOD SCID Gamma mice (NSG, n=19), were also injected IVT, IP, and IV. Mice were euthanized after 7d, 3d, and one hour respectively. Another 10 NSG mice served as a control. WT IP injected mice underwent repeated ERG examinations and magnetic resonance imaging (MRI). Following euthenization, macroscopic, histological and immunohistochemistry evaluation was made for eyes and brain. Cobalt levels were measured in the blood, urine and tears by particle induced x-ray emission analysis (PIXE).

Results: following IV injection, cobalt administration was lethal to mice in high doses. Lower doses eliminated in urine within 2 hours. ERG records showed post-synaptic dysfunction. Apoptosis involved all retinal layers, but mainly the ONL. There was thinning of the retina, with preservation of RGCs. Activated microglia were detected in both WT and NSG mice. Intensive infiltration of lymphatic cells was also noted in the dura and optic nerves following IVT and IP injections MRI showed decreased signal of IVT injected optic nerves after 7 days as compared to the fellow nerve.

Conclusions: cobalt induces severe inflammation of the retina and optic nerves. It might be reversible following IV injection, but chronic exposure leads to thinning of the retina and optic neuropathy. The inflammatory reaction involves microglial cells, as demonstrated in NSG mice. the brain was also affected with meningitis and encephalitis.

3K3A-Activated Protein C prevents microglia activation, inflammasome formation and tightens the blood retinal barrier in ocular inflammation

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Introduction: The triad consisting of inflammation, blood-retinal-barrier (BRB) disruption, and neuronal degeneration characterizes most retinal pathologies such as age-related macular degeneration, diabetic retinopathy and posterior uveitis. Currently, treatments are not able to address all these targets using a single therapy. 3K3A-Activated Protein C (APC) is a recombinant variant of the physiological anticoagulant APC molecule with diverse cytoprotective properties. We previously demonstrated 3K3A-APC's anti-inflammatory properties in a murine model of posterior inflammation. However, the mechanisms behind its action and its effect on BRB are yet to be determined.

Purpose: To expand on the molecular mechanisms by which 3K3A-APC reduces inflammation in the eye and to prove its clinical efficacy when given after the establishment of ocular inflammation.

Methods: The study was performed using the endotoxin-induced uveitis (EUI) mouse model. Intravitreal (ITV) injection of lipopolysaccharide (LPS) was used to induce retinal inflammation. Four hours after EIU, 3K3A-APC or saline were administered ITV to the same eyes. Inflammatory cell recruitment and extravasation were determined in retinal flatmounts stained with the myeloid anti-CD11b marker. Microglial activation was assessed using immunofluorescence staining of the retinal cryosections using the microglial marker Ib1a. Retinal flatmount staining with the immune markers anti-NLRP3 and anti-Il1-β was used to assess NLRP3 inflammasome activation. Retinal blood barrier integrity was studied by tracing the tight junction protein Zonula Occludens 1 (ZO1).

Results: 3K3A-APC treatment significantly decreased leukocyte numbers and inhibited leukocyte extravasation from blood vessels into the retinal parenchyma when administered 4 hours after ITV LPS injection. Resident microglia, which underwent an inflammatory transition following LPS injection, remained quiescent in eyes treated with 3K3A-APC. Inflammation-associated increase in retinal thickness, observed in LPS-injected eyes, was diminished by 3K3A-APC treatment. 3K3A-APC treatment inhibited inflammasome activation, determined by lower levels of NLRP3 and its downstream effector IL-1β. ZO1 clustering in the retinal pigment epithelium border, noted in 3K3A-APC treated eyes, suggests a barrier protective effect of 3K3A-APC on outer BRB.

Conclusions: Our results highlight the pleiotropic protective properties of 3K3A-APC in ocular inflammation and suggest its potential use as a novel treatment for retinal diseases associated with inflammation.

Characterization of neurite extension in rat photoreceptors precursors (rPRP) – in vitro model

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Purpose: In outer retinal degenerative diseases photoreceptor cells are lost, whereas the remaining retinal layers are relatively intact. A potential treatment approach for these diseases is transplantation of pluripotent-derived photoreceptors. to replace the degenerated ones. One of the main limitations of this approach is the successful integration of the transplanted cells and the formation of de novo synapses through neurites extensions of the transplanted cells.

The aim of this work is the investigation of the effect of different molecules on neurite extension enhancement in rat photoreceptor precursors (rPRP) which serve as a cell source for cell replacement therapy in our project.

More specifically we study the contribution of GTPase RhoA and its kinase, ROCK, which are known to be part of the cytoskeleton organizers. Recent works have shown that inhibition of ROCK, affects neuronal sprouting, specifically in PRPs.

Methods: To investigate its effect on our cell model, we dissociated retinas of P1 Rats and seeded dissociated cells on glass coverslips. Cells were cultured for 3 days and treated with araC, to eliminate glial cells and ROCK inhibitor, Y-27, in different concentrations.

Cells were stained with anti-CRX antibody and actin marker, phalloidin and lengths were measured by Leica application suite X ruler.

RNA was extracted and RNA-seq was performed for control and Y-27 treatments.

Organotypic retinal culture of RCS rats for 3 and 7 days with multi micro-well and micro-tubes device was generated to examine the efficiency of different treatments for cell integration and synapse establishment.

Results: We quantified the average axonal length per cell for each treatment and observed a significant increase at 50μM and 100μM of Y-27 and observed a saturation at 200μM.

We examined more factors that regulate the expression of the transcription factor CREB, e.g., forskolin and CGS hydrochloride, which regulate neurite sprouting, but to no avail.

RNA-seq analysis mainly revealed the upregulation of phototransduction and CREB pathways. Specifically of lhx8, rho and pde6b genes, apparently due to the large number of cells survived after T-27 treatment.

The organotypic retinal culture performed preservation for 7 days and neurite extension of rPRP through micro-wells.

Conclusions: The results presented here form the basis for the enhancement of neurite extension and the formation of synapses between the host retina and the transplanted cells thus tackling one of the main challenges facing cell replacement-based vision restoration.

A new rat model for retinal degeneration: The GCaMP6f+\- RCS-\- Rat

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Purpose: Outer retinal degeneration is one of the most common causes of blindness in the western world; the two prevalent diseases Age Related Macular Degeneration and Retinitis Pigmentosa are still considered incurable. Our research aims at developing an animal model which can significantly enhance the functional evaluation of treatment modalities aimed at vision restoration in these patients.

Methods: The development of the novel rat model is based on a new breed in which Royal College of Surgeons (RCS) rats, a well-known animal model with outer retinal degeneration, is crossbred with the transgenic rat line LE-Tg(Thy1-GCaMP6f)7, in which the genetic calcium indicator GCaMP6f is expressed under the Thy1 promotor.
Using OCT imaging, Confocal Scanning laser Ophthalmoscopy (cSLO) and histology, the fluorescence of the RGC in the LE-Tg(Thy1-GCaMP6f)7 rat was validated. In addition, retinae of this breed were isolated and mounted on a Multi-Electrode Array, with photoreceptors facedown, and both optical (brief LED flashes) and electrical stimulations were performed. The feasibility of visualizing the RGC and their functionality was inferred from the robust calcium signals observed upon RGC activation either by light or electrical activation.
We then cross bred the animals to obtain the desired breed, which requires two generations, while genotyping the offspring using PCR.

Results: Our results reveal that in the LE-Tg (Thy1-GCaMP6f)7 rat the RGC are healthy and are readily distinguishable in our cSLO imaging. Moreover, we were able to obtain light driven responses in the isolated retinae, albeit using high luminance contrast levels. In addition, the subretinal electrical stimulation revealed the feasibility of the investigation of activation thresholds and the building of strength duration curves.
The next step of this research is the characterization of the newly obtained animal breed and the investigation of the electrically induced RGC cells in the novel blind animal model.

Conclusion: This developed breed will prove to be a vital tool in the investigation of the efficacy of vision restoration strategies.

The retinal pathways triggered by Amyloid-β42: RNA-sequencing and pathway analysis in rats

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Purpose:

Amyloid-beta (Aβ), a family of polypeptides prone to self-assemble into aggregates is a significant component of drusen, thus implicated in age-related macular degeneration (AMD). We have previously showed that Aβ42 is retinotoxic and that the oligomeric Aβ42 is more toxic than fibrillar Aβ42. The mechanism of retinotoxicity exerted by these two Aβ42 species is still unknown. Here we aimed to map the effects of Aβ42 on retinal gene expression in rats. We hypothesized that the retinal response to oligomeric or fibrillar Aβ42 will have shared pathways, but the effects of oligomeric Aβ42 will include additional pathways mediating the more acute and profound toxicity compared to fibrillar Aβ42.

Methods:

Adult female Sprague-Dawley rats were employed. In each rat the right eye was intravitreally injected with 10µl fibrillar Aβ42 or vehicle (n=3), or oligomeric Aβ42 or vehicle (n=4). The rats were sacrificed, and the neurosensory retina was explanted 4 days or 30 days after treatment. High-quality RNA samples were extracted, and transcriptome analysis using RNA-sequencing (RNA-seq) was performed. A Gene Ontology analysis was conducted in IPA and in R software using DOSE and enrichplot. (IPA, Qiagen Inc., R Core Team, Vienna, Austria)

Results:

In retinas extracted 4 days after fibrillar Aβ42 injection, a total of 13 genes were differentially expressed, of which 10 were upregulated and 3 were downregulated. At 4 days after oligomeric Aβ42, we found a total of 52 differentially expressed genes of which 31 were up-regulated and 21 were down-regulated in the treated retinas versus controls. Pathway analysis showed that both fibrillar Aβ42 and oligomeric Aβ42 are involved in regulation of cholesterol metabolism. However, in addition, regulation of the adaptive immune system and phagocytosis emerged as activated cascades in response to Aβ42 oligomers. Interestingly, a single injection of oligomeric Aβ caused upregulation of complement factor H (CFH). At 30 days after oligomeric Aβ42 injection the apoptotic pathway was highly enriched.

Conclusions:

The differential retinotoxicity of oligomeric vs fibrillar Aβ42 may be related to activation of an inflammatory response and dysregulation of phagocytosis. The expression of CFH, strongly associated with AMD risk in human subjects, suggests relevance of Aβ in the disease. Characterizing the downstream effects of Aβ structures can promote our understanding of the fundamental pathophysiology of Aβ-related retinal degeneration and may provide insight into potential AMD treatment strategies.

Glucose intolerance and subsequent ocular pathology - Effects of photoperiod and food: evidence from a study in a diurnal rodent

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Purpose: Type 2 diabetes mellitus (T2DM) and its ocular complications, such as cataract and diabetic retinopathy (DR) have been linked to circadian rhythm-disturbances. Using a unique diurnal animal model, the sand rat (Psammomys obesus) we examined the effect of circadian disruption by short photoperiod acclimation on the development of T2DM and related ocular pathologies.

Methods: We experimented with 48 male sand rats. Variables were day length (short photoperiod, SP, vs. neutral photoperiod NP) and diet (standard rodent diet vs. low-energy diet). Blood glucose, the presence of cataract and retinal pathology were monitored. Histological slides were examined for lens opacity, retinal cell count and thickness.

Results: Animals under SP and fed standard rodent diet (SPSR) for 20 weeks had higher baseline blood glucose levels and lower glucose tolerance compared with animals kept under NP regardless of diet, and under SP with low energy diet (SPLE). Animals under SPSR had less cells in the outer nuclear layer, a lower total number of cells in the retina, and a thickened retina. Higher blood glucose levels correlated with lower number of cells in all cellular layers of the retina and thicker retina. Animals under SPSR had higher occurrence of cataract, and a higher degree of cataract, which correlated with higher blood glucose levels.

Conclusion: Sand rats kept under SPSR develop cataract and retinal abnormalities indicative of DR, whereas sand rats kept under NP regardless of diet, or under SPLE, do not. These ocular abnormalities significantly correlate with hyperglycemia.

Retina resuscitation following death

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Purpose:

To date, it is widely believed that human neural tissues in general and in particular retinal neurons, lose their functionality rapidly following death or prolonged ischemia. Recent publications have rekindled the hope that indeed light signalling in the retina can be revived following prolonged ischemia periods. Here we extensively dissect the several aspects of retinal cells function following prolonged ischemia and resuscitation not previously reported on.

Methods:

The isolated retina of Long Evans Rats (Wild type) served as a model for the investigation of the effect of enucleation (beginning of ischemia) to re-oxygenation time on the responses of the various retinal cells. Towards this end, the eyeball was enucleated and placed in unoxygenated Ringer's for various time durations (T=0, T=15, T=30min). The retina was then isolated in oxygenated Ringer's solution and mounted on a Multi-Electrode-Array with the RGCs facing the electrodes. The effect of ischemia on several features of responses induced by 1sec flashes were investigated, namely: the number of active RGCs, the firing rate of the RGCs, the various properties of the their receptive field, and the amplitude of the various components of the electroretinogram.

Results:

Retinal response to light was completely abolished following an ischemic time of 20 min. The main exciting observation is that retinal function can be rescued by re-oxygenation even following a long ischemic time of up to 30 min. Notwithstanding the successful resuscitation, the recovered ON-response ERG amplitude gradually decreased with increasing ischemia time (up to 2-fold) whereas the OFF-response decreased to a lesser extent. Moreover, the viability of the RGCs following resuscitation decreased with increasing ischemia time as inferred by the decrease in firing rate (up to 3-fold).

Conclusions:

We introduce here a robust in-vitro model for the investigation of various interventions aimed at preservation of neural tissue during ischemia. These results offer hope for the resuscitation of retinal or other neural tissue even after prolonged ischemia times.

Using Random Forest Classifier for predicting the clinical outcome of chemical induced ocular injury

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Purpose: Sulfur mustard induced ocular injury may recover following an acute phase or deteriorate into an irreversible chronic pathology. Early detection of eyes at risk to develop the chronic pathology may assist in providing unique monitoring and treatments only to relevant cases. In this study, we evaluated a machine-learning model for predicting the development of chronic pathology based on clinical data of the acute phase.

Methods: Clinical data from 166 rabbit eyes that were exposed to SM vapor was used retrospectively. The data included a comprehensive clinical evaluation of the cornea, eyelids and conjunctiva at different time points post exposure using a semi-quantitative clinical score. A machine-learning model, based on random forest classifier, was trained to predict the development of corneal neovascularization, the main clinical manifestation of the chronic pathology, at 4w post exposure, using clinical data collected three weeks earlier.

Results: The overall accuracy in predicting the clinical outcome of SM-induced ocular injury was 73%. The accuracy in identifying eyes at risk to develop corneal neovascularization and future healed eyes was 75% and 59%, respectively. The most important parameters for accurate prediction were conjunctival secretion and corneal opacity at 1w and corneal erosions at 72h post exposure.

Conclusions: Predicting clinical outcome of SM-induced ocular injury based on the clinical parameters of the acute phase, using a machine-learning model, is demonstrated for the first time. Although the prediction accuracy was limited, probably due to the small dataset, the results pointed out towards several parameters during the acute injury that are important for the prediction of SM-induced chronic pathology.

Point mutation in P63 leads to limbal stem cell deficiency that is rescued by a small molecular weight compound

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Purpose: The pathogenesis of genetic limbal stem cells deficiency (LSCD) is not well understood and therapeutic options are limited due to gap of knowledge and the lack of reliable animal models. We therefore aimed to develop an in-vivo mouse model of genetically induced limbal stem cells deficiency (LSCD), use it to study the disease etiology and explore new therapeutic strategies.

Methods: Clinical diagnosis and genetic analysis was performed for LSCD patients to identify disease-causing mutation. A conditional mouse model with the mutation specifically expressed in patients was established. The expected abnormalities in the limbus, cornea and Meibomian glands were analyzed by microscopy, histology and immunofluorescent staining of wholemount and tissue sections and abnormal pathway were exposed by RNA-sequencing. Limbal stem cell clonal dynamics were exposed by quantitative lineage tracing and the therapeutic potential of a small molecular weight compound was examined.

Results: P63L514F was discovered as a new LSCD-disease causing mutation. We established a new conditional P63+/L514F strain that exhibits mild neovascularization that aggravates with age and eventually leads to loss of corneal transparency. Histological and immunofluorescent staining analyses revealed thickening of the corneal epithelium, abnormal presence of goblet, conjunctival and immune cells in the corneal center. Genetic lineage tracing showed abnormal size, orientation and survival of limbal stem cell-derived clones in mutant, in line with impaired wound repair. RNA sequencing analysis confirmed an enrichment of mucus secretion pathways, vascularization, and immune response. Finally, systemic treatment with PRIMA-1MET significantly inhibited the development of the LSCD phenotype and improved wound healing response.

Conclusions: P63 plays a crucial role in corneal morphogenesis and adult LSC maintenance. The new P63+/L514F strain is a useful model studying LSCD pathogenesis. PRIMA-1MET has promising therapeutic potential for the treatment of P63-related LSCD. This study paves the way for further investigation of PRIMA-1MET in clinical trials.

Imaging optic nerves following crush damage in mice Stephen Richard
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Purpose: In animal studies, the mechanical crush of the optic nerve posterior to the globe often serves as a good preclinical model to study neuronal survival and regeneration in optic neuropathies. In this study, our goal was to image the optic nerve using axonal flow.

Methods: Optic Nerve Crush was induced in the right eye of C57/Bl6 wild-type (WT) mice under anesthesia. The fidelity of retrograde RGC axonal transport and regenerating RGC axons were quantified using Cholera-toxin B (CTB) – Alexa fluor tracer intravitreal injections. The mice underwent magnetic resonance imaging using manganese intravitreal injection, to demonstrate intracellular contrast enhancement along the optic nerve. The retinae and optic nerves were harvested at days 3, 7, and 21 post-ONC induction. Histological analysis was performed to confirm the retinal ganglion loss.

Results: The CTB-tracer injections to the eyes revealed axonal flow impairment in the ONC-eyes but not in the control contralateral eyes. The axonal flow impairment was also demonstrated by mouse brain MRI scans. The RGC Count and retinal thickness were reduced, especially at days 21 post-ONC induction. The TUNEL assay showed significant apoptosis-mediated retinal cell death on day 3.

Conclusions: Our data demonstrate axonal flow impairment in two different modes, namely CTB labeling and mouse brain Magnetic Resonance Imaging. our findings are in line with previous studies characterizing the ONC model.

Limbal stem cell regulation by biomechanical cues

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Purpose: Stem cells' (SCs) decision to self-renew or differentiate largely depends on the external control of their niche. However, the complex mechanisms that underlie this crosstalk are poorly understood. To address this question, we focused on the corneal epithelial SC model in which the SC niche, known as the limbus, is spatially segregated from the differentiation compartment.

Method: The stiffness of the limbus and cornea were measured by atomic force microscopy and in Lysyl Oxidase (LOX) transgenic animals. The expression of the Yes-associated protein (YAP), a putative mediator of the mechanotransduction pathway and of various stem/differentiation markers were explored under different matrix rigidity conditions in vitro and in vivo. The contribution of YAP and mechanotransduction pathways on LSC function was explored under homeostasis, wound healing and in dedifferentiation model.

Results: The unique biomechanical property of the limbus is linked with the nuclear localization of YAP and stemness. YAP inhibition or substrate stiffening induced differentiation under homeostasis and perturbed recovery of the LSC population following injury. In vitro experiments revealed that substrates with the rigidity of the corneal differentiation compartment inhibit YAP localization and induce differentiation, a mechanism that is mediated by the TGFb-SMAD2/3 pathway.

Conclusions: LSC can sense biomechanical niche signals and manipulation of mechano-sensory machinery or its downstream biochemical output may bear fruits in LSC expansion for regenerative therapy.

3K3A-Activated Protein C treatment exerts anti-inflammatory effects and inhibits choroidal neovascularization in a murine model

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Introduction: Choroidal neovascularization (CNV), a major pathology in many ocular diseases, especially in age-related macular degeneration (AMD), is mainly driven by over-expression of vascular endothelial growth factor (VEGF). Data also support inflammation, recently highlighted as a major player in the pathogenesis and progression of AMD. 3K3A-APC is a genetically engineered variant of human-activated protein C (APC) optimized for human therapeutic use. Our group confirmed that, similarly to its actions in the CNS, 3K3A-APC acts as a broad-spectrum cytoprotective molecule in the retina, indicating that 3K3A-APC can inhibit CNV growth in a murine model, which is accompanied by reduced VEGF levels at sites of CNV formation.

Aim: To elaborate our previous findings of 3K3A-APC's ability to inhibit CNV development, not only via anti-VEGF properties, but also through a broader, anti-inflammatory effect.

Methods: CNV was induced by laser photocoagulation on C57BL/6J mice. CNV development was confirmed in-vivo by fluorescein angiography (FA) 4 days post-laser. 3K3A-APC were injected intravitreally immediately following CNV detection on FA. Myeloid and microglia cell detection (using CD11 and anti-ionized calcium-binding adapter molecule 1 (IBA-1) markers) as well as inflammatory products (Nod-like receptor family pyrin domain containing 3 (NLRP3) and Interleukin 1β (IL-1β)) were confirmed and compared between treatment and control. CNV area, volume and vascular penetration were evaluated using 3D confocal imaging of FITC-dextran.

Results: 3K3A-APC treatment significantly decreased microglia and inflammatory cells recruitment to RPE-choroid area. 3K3A-APC treatment inhibited inflammasome activation as indicated by the reduction in NLRP3 and IL-1β levels at CNV lesion sites along with inhibition of leakage and growth of CNV.

Conclusions: Our results indicate that 3K3A-APC exert a protective anti-inflammatory effects in the retina from CNV development through the reduced presence of inflammatory cells and inflammasome inhibition. Our results warrant further investigation in order to evaluate the potential use of 3K3A-APC as a novel treatment for CNV, paving a new direction, treating CNV by using the promising, wide-spectrum, cytoprotective 3K3A-APC molecule.

Study on the BAF (SWI/SNF complex) subunits BAF155 and BAF170 activities in the development and maintenance of pigmented eye lineages in mammals.

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Introduction: Organogenesis of the vertebrate eye depends on different progenitor domains that undergo complex morphogenesis and gradual differentiation in coordinated manner in process which entails activity of multiple signaling pathways and transcription factors (TFs). The roles of chromatin remodelers in the gradual development of neuroectodermal eye lineages is currently mostly unknown.
The BAF (SWI/SNF) chromatin remodeling complexes were shown to play key roles in neural differentiation, directing cell differentiation through lineage specific activity of different alternative assemblies that directly interact with tissue specific TFs. The Baf155 (Smarcc1) and Baf170 (Smarcc2) are the two obligatory scaffold subunits of the BAF complexes. Baf155 is considered to function in progenitor cells in contrast to the Baf170 containing complexes, which primarily function during tissue differentiation.

Purpose: To study the roles of Baf155 and Baf170 and their functional redundancy in cells of the pigmented lineage in the eye.

Methods: we have analyzed the phenotype of Baf155 and Baf170 conditional knockout in cells of pigmented lineage: Baf155-cKO; Baf155flox/flox;DctCre and Baf170-cKO; Baf155flox/flox;DctCre compared to control litter mates. The phenotype analysis included ERG, OCT, histology and immunolabeling for detecting of cell specific markers on tissue sections.

Results: This analysis revealed partial functional redundancy between Baf155 and Baf170 and importantly exposed a unique role for Baf155 in retinal function in old mice and for the development of the optic nerve.

Conclusions: Baf155 in pigmented cells of the optic cup is revealed to play key role in formation of the optic nerve and for retinal functions. Current efforts are to further uncover the role of the Baf155 in eye development and possible relation to degenerative eye diseases such as age-related macular degeneration (AMD) and glaucoma.

Unusual Agressive Orbital Infection: 4 cases. 0 0

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Background:
Orbital Infections are a challenge and need rapid investigation and treatment as they can have devastating consequences for the patient.

Methods:
4 cases of aggressive unusual aggressive life or sight threatening orbital infection are reported.

Results:
There were 2 adults and 2 children. 3 cases had serious life threatening disease, and one had serious local eyesight threatening disease.
Causes of infection were Trichinosis, Apophysomyces elegans mucormycosis, Erysipelas, and Molluscum Contagiousum.

Conclusion:
Unusual causes of Orbital Infection are easily overlooked if not searched for and can present a real risk to the patient.

Orbital Dermoids with spillage. 3 cases 0 0

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Background:

Deep Orbital Dermoids can be a challenge to treat following spontaneous spillage and its resulting intense inflammation in surrounding tissues.

Methods:

3 cases of Deep Orbital Dermoid with spontaneous spillage are reported. Neuroimaging was performed in all cases showing Deep orbital Dermoid in the Superior lateral quadrant of the Orbit. All cases involved deep cavitation into the bone one with, and two without, a boney fistula .

Results:

All cases underwent surgery to excise the lesion. One had late complications in spite of careful primary excision to remove the entire mass.

Conclusion:

Deep Orbital Dermoids should always be completely removed. They are not simple cases and incomplete excision can occur despite an experienced surgeon’s best efforts resulting in long term or late complications.

Calcium levels in tears and association with nasolacrimal duct obstruction

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Purpose:
Nasolacrimal duct obstruction occurs when the nasal passageways cannot properly drain tear liquid from the eyes. It is mostly considered idiopathic, but the recurrent use of epinephrine or Actinomyces Israeli infections may lead to dacryolith formation and subsequent obstruction. Previous studies have shown an association between nasolacrimal duct obstruction and elevated blood calcium levels. This study aimed to investigate the elemental composition of tears for a possible correlation with nasolacrimal duct obstruction using Particle Induced X-ray Emission (PIXE) analysis.

Methods:
15 patients with nasolacrimal duct obstruction and 15 healthy participants adjusted for age and gender participated in the study. Two tear samples (one of each eye) and blood samples were collected from each participant. Tears and blood samples were collected on a Schirmer paper filter and elemental composition was analyzed by PIXE.

Results:
PIXE analysis showed statistically significant higher levels of sodium, chlorine, phosphorus, and sulfur in tears samples of the study group as compared to samples of the control group. We found low calcium levels in both groups with no significant difference. In the study group, tear samples from eyes with obstruction compared to fellow eyes with no obstruction did not demonstrate any significant difference in elemental composition.

Conclusions:
Patients with nasolacrimal duct obstruction have a different elemental composition than healthy people. This data may help to determine the etiology of nasolacrimal duct obstruction in different patients. High calcium levels in tears is not a risk factor for nasolacrimal duct obstruction. We suggest that tears may be used as a biomarker to predict subjects at risk for nasolacrimal duct obstruction.

Quality of Life After Eyelid Ptosis Repair Surgeries

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Purpose: To evaluate the long-term effect of different eyelid ptosis repair surgeries on patient's quality of life.

Methods: This retrospective study included patients that underwent eyelid ptosis repair surgery at our institution between the years 2016-2021. All patients completed the 18-questions post-interventional Glasgow Benefit Inventory (GBI) questionnaire via telephone interview.

Results: Of 56 patients included in the study, 50 patients underwent muller's muscle-conjunctival resection (MMCR), 4 had levator aponeurosis advancement (LAA) surgery and two patients undergone the Fasanella procedure. The mean total GBI score (SD) score was 57.5 (±4.72) after an average follow up period of 2 years. No statistically significant correlation was found between the GBI score and the type of surgical repair.

Conclusions: The MMCR procedure, as well as other surgical techniques of eyelid ptosis repair, has a positive, long-term effect on patient's quality of life. Quality of life was not affected by the type of surgical repair, given good patient selection.

Orbital Fat Density as a Diagnostic Tool in Pre-septal and Orbital Cellulitis

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Purpose: To evaluate the measurement of orbital fat density as a tool for diagnosing post-septal involvement in cases of uncertain preliminary differential diagnosis of orbital and periorbital cellulitis (OC and POC).

Methods: Retrospective cohort study including all patients with a clinical diagnosis OC or POC who underwent contrast-enhanced computerized tomographic scans during 10 years at a single medical center. Intraconal fat density was measured by Hounsfield units (HU) in 6 delineated surfaces at the axial plane. Main outcome measures were HU values at the initial and final diagnoses.

Results: Fifty-seven patients were included, 43 males (75%), mean±SD age was 17±19 years. The mean HU measurement was -52±18 HU for the involved side vs. -63±13 for the uninvolved side ($P<0.001$). HU values of both orbits were strongly correlated ($R=0.42$, $P=0.001$). The values were higher in cases of a final diagnosis of OC in the involved side ($P<0.001$), and in the nasal vs. temporal intraconal fat bilaterally ($P<0.001$). The initial POC diagnosis of 20 patients (35%) was revised to OC based on imaging and clinical course. Stratification of the patients into 4 groups based on initial and final diagnoses yielded a similar pattern for both the involved and the uninvolved sides.

Conclusions: Intraconal fat density measurements can assist in the primary assessment of orbital involvement in patients with an uncertain initial diagnosis. An HU value higher than
-50 is suggestive of orbital involvement. The contralateral orbit may show radiographic involvement. The nasal intraconal fat density may better reflect orbital involvement.

Cryptophthalmos: Associated Syndromes and Genetic Disorders

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Purpose: Cryptophthalmos is a rare congenital condition caused by anomalous eyelid development where the eyelid folds do not develop or fail to separate. Cryptophthalmos can be unilateral or bilateral and can occur in isolation or as part of an underlying syndrome. We aim to identify genetic syndromes associated with cryptophthalmos to facilitate genetic diagnosis.

Methods: We performed a retrospective medical records review of all patients diagnosed with cryptophthalmos followed at a single center. The analysis included medical history, clinical examination findings, and genetic testing results.

Results: Thirteen patients were included, 10 (77%) males, mean age of 2.4 years. Eight (61%) had bilateral cryptophthalmos, 4 (31%) had complete cryptophthalmos. Associated ocular abnormalities included corneal opacities (13/13, 100%), upper eyelid colobomas (12/13, 92%), and microphthalmia/clinical anophthalmia (3/13, 23%). All cases of complete cryptophthalmos had bilateral disease. An underlying diagnosis was identified in 10/13 (77%) cases, including Fraser syndrome (5/10), amniotic band syndrome (1/9), FREM1-related disease (1/9), Goldenhar syndrome (1/9), MOTA syndrome (n=1), and CELSR2-related disease (n=1).

Conclusion: Cryptophthalmos is a rare disorder with challenging management. This is the first report of an association between cryptophthalmos and biallelic CELSR2 variants. All cases, including unilateral ones, should be prioritized for genetic evaluation, especially with extra-ocular involvement, given the equal diagnostic success rate between groups.

Magnetic Resonance Diffusion-Weighted Imaging in Differentiating Lacrimal Gland Lymphoma

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Purpose: To determine the role of diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) in differentiating inflammatory process and malignant lymphoma of the lacrimal gland.

Methods: A retrospective analysis of all subjects who underwent lacrimal gland biopsy and MR imaging with DWI sequences during a 10-year period at the Sheba Medical Center, Israel. The lacrimal glands' ADC values were documented bilaterally by blinded observers and correlated with the final histology verified diagnoses.

Results: Twenty-eight patients were included, 19 females (68%) with mean±SD age of 48.1±25.7 years. The right orbit was involved in 14 cases (50%), left in 13 (46%); one patient (4%) had bilateral involvement. Seventeen cases (61%) had a final diagnosis of idiopathic inflammation or dacryoadenitis, and six cases (21%) were diagnosed with lymphoma. Additional diagnoses included pleomorphic adenoma in 3 (11%), adenoid cystic carcinoma, and hemangiopericytoma. Lower mean ADC values were observed in the lymphoma vs. inflammatory group (1.03X10-3 Vs. 1.45X10-3, P=0.02).

Conclusion: Restricted diffusion on MR imaging can serve as a diagnostic tool in the differentiation between inflammatory processes of the lacrimal gland and lymphoma.

Magnetic resonance dacryocystography may provide enhanced spatial and temporal resolution in the assessment of functional epiphora

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Purpose: To assess the role of magnetic resonance dacryocystography (MRDCG) in eyes with functional epiphora.

Methods: Prospective eyes with epiphora were included if no alternative cause of epiphora was found on clinical examination, were patent on syringing (≤20% reflux), had no obstruction or stenosis on DCG, and had an abnormal DSG. Eyes underwent MRDCG with a qualitative assessment of block, stenosis or patency and quantitative measurement of tear transit time. Measurements were compared to asymptomatic fellow eyes and to historical reference values from asymptomatic eyes.

Results: We included 26 symptomatic eyes of 19 patients (median age 63 years). There was a block on MRDCG in 18 (69%) eyes, stenosis in 4 (15%), and patency in 4 (15%) eyes. The block occurred at the sac-nasolacrimal duct (NLD) junction in 9 (50%), proximal NLD in 5 (28%) eyes, mid-NLD in 1 (5.6%) eye and distal NLD in 1 (5.6%) eye. No contrast was observed in the lacrimal system in 2 eyes. The median transit times to the sac, NLD, inferior meatus, first 25%, and first 50% of the fundus-to-nose distance were 22, 63, 118, 34 and 84 seconds, respectively. Transit times to the sac, NLD and times to fill the first 25% and 50% of the fundus-to-nose distance were significantly longer than historical values from asymptomatic lacrimal systems ($p = <0.001, 0.002, 0.035$ and 0.017, respectively).

Conclusion: MRDCG showed a high proportion of block and stenosis and longer tear transit times in the lacrimal drainage system in eyes with functional epiphora.

Basosquamous carcinoma an increasingly important entity: Immuno-stains contributing to its pathological diagnosis 0 0 Purpose: This study seeks to use immunohistochemistry in order to differentiate between BSC, BCC, and squamous cell carcinoma (SCC).

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Introduction: Basosquamous carcinoma (BSC) of the head and neck represents an aggressive tumor in a sensitive surgical area. Its distinction from more indolent tumors such as basal cell carcinoma (BCC) may be difficult yet is critical prior to treatment with Hedgehog pathway inhibitors such as Vismodegib.

Methods: We conducted a retrospective study in which patient files and formalin-fixed paraffin-embedded blocks were obtained from the Emek Medical Center Institute for Pathology and Cancer Research archives. Thirty-eight cases of basosquamous cell carcinoma, 39 control cases of basal cell carcinoma, and 39 control cases of squamous cell carcinoma from the face, scalp, and neck areas were analyzed between 2012 and 2017.

Results: Using tissue microarrary, each case had the following immunostains applied to it: p16, BCL2, BCL6, CK903, CD10, EMA, and CK19. A predictive model for basosquamous carcinoma was then developed using multivariate logistic regression analysis with backwards selection. BCL2 (OR 0.045, $p<0.05$), CK19 (OR 0.068, $p<0.0001$), and p16 (OR 28.902, $p<0.0001$) together comprised a highly predictive model with an AUC of 0.8871.

Conclusion: We believe that this model can be an important adjunct tool in diagnosing this difficult entity

Outcome of Silicone Sling Frontalis Suspension in Isolated Uncomplicated Congenital Ptosis vs. Complicated Ptosis

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Purpose: To compare the outcome of silicone sling frontalis suspension (FS) surgery in children with isolated uncomplicated congenital ptosis (IUCP) vs. children with complicated ptosis.

Methods: A retrospective medical chart review of all pediatric patients who underwent silicone sling FS surgery between 2009-2020 at a single center were included. Patients were divided according to ptosis type: IUCP vs. complicated ptosis. Pre-and post-operative margin-to-reflex distance (MRD1) measurements were determined from clinical photographs. Main outcome measures were differences in improvement in eyelid height, reoperation rate, and timing between the groups.

Results: Two-hundred and eight children were included: 139 IUCP and 69 complicated cases, 83 females (40%), mean (±SD) age at intervention was 1.9±2.9 years. Complicated cases included: blepharophimosis epicanthus inversus syndrome (n=35), Marcus Gunn jaw winking (n=12), oculomotor palsy (n=8), congenital fibrosis of extraocular muscles (n=3), chronic progressive external ophthalmoplegia (n=3), and others. Mean MRD1 improved by an average of 1.6 mm in both groups. Repeat ptosis repair was performed in 50/171 (29%) patients without a history of failed ptosis procedures, and this rate was similar between IUCP and complicated cases. Children under 3 years of age had higher rates of repeat ptosis repair than older children (n=59/175, 34% vs n=5/33, 15%, p=0.03 chi2).

Conclusions: Silicone sling frontalis suspension has a favorable outcome in 70% of pediatric patients. Preoperative and final MRD1 and reoperation rates were similar between both groups, suggesting that despite the higher complexity in atypical cases, the outcome is similar.

Re-surgery for Congenital Ptosis: Characteristics, Success Rates and Predicting Factors

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Purpose: Re-operation for congenital ptosis has added morbidity. The purpose of the current study is to examine the risk and to find predictive factors for first surgery failure in patients with congenital ptosis.

Methods: This is a retrospective9, cohort study. Analysis of all patients with congenital ptosis who underwent their first ptosis correction surgery between 2010 to 2020 at Sheba Medical Center was performed.

Results: Sixty patients (36 male and 24 female) underwent ptosis surgery for congenital ptosis Twenty nine patients (48.33%) underwent Frontalis Sling (FS), 13 patients (21.67%) underwent Levator muscle (LM) surgeries- 9 Levator Resection (LR) and 8 External Levator advancement (LAA) and 18 patients (30%) underwent Müller's muscle-conjunctival resection (MMCR).
Eighteen patients (30%) underwent a second ptosis surgery. The unadjusted risk of second ptosis surgery was almost fourfold amongst males with ptosis relative to females with ptosis (HR, 3.90; 95% CI, 3.67-547; p=0.033) and higher amongst younger individuals (HR, 4.23; 95% CI, 3.33-5.62; p=0.042).
Older age was protective against the risk of second ptosis surgery (adjusted OR, 0.50; 95% CI, 0.21-0.60; p<0.001), whereas male sex was associated with an increased likelihood of second ptosis surgery (adjusted OR, 3.33; 95% CI, 1.64-3.98; p<0.001)

Conclusions: An increased risk of failure of the first surgery was found among male patients, younger patients, and patients with more severe ptosis before the first surgery. Awareness of those factors is beneficial for clinicians and parents.

The surgical management and outcomes of kissing nevi of the eyelids

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Purpose: A kissing nevus is a rare congenital melanocytic lesion, located in adjacent areas on the upper and lower lids. Literature regarding surgical management is limited. Our aim was to describe the surgical management and outcomes in patients with kissing nevi.

Methods: Medical chart review was conducted for all patients who underwent kissing nevi surgical repair in Moorfields Eye Hospital, London and The Children's Hospital of Philadelphia between 2006 and 2021. Demographics, ocular and medical history, lesion characteristics, surgical intervention, and outcomes were collected and analyzed. Main outcome measures were surgical interventions as well as functional and cosmetic outcomes.

Results: Thirteen patients were included, median age at presentation was 16.93 years (±20.07, 4-61). The most common indication for surgery was cosmetic. None of the patients had a family history of kissing nevi. The mean number of surgeries per patients during the follow up period was 1.9 (±1.3, 1-5). Initial procedure included incisional biopsy in 3 cases (23%) and complete excision and reconstruction in 10 cases (77%). Surgery involved the upper and lower anterior lamella in all cases, the upper posterior lamella in 4 patients (31%), and the lower posterior lamella in 2 patients (15%). Local flaps were utilized in 3 cases and grafts in 5 cases. Complications included: trichiasis (n=2, 15%), lower eyelid ectropion (n=2, 15%), mild ptosis (n=1, 8%), and upper/lower punctal ectropion (n=1, 8%). Twelve patients (92%) were satisfied with the final functional and cosmetic outcome. No recurrences or malignant transformations were observed.

Conclusion: Surgical management of kissing nevi can be challenging, and commonly includes the use of local flaps or grafts, often requiring multiple interventions. The surgical approach should be personalized based on lesion size and location, proximity to and involvement of eyelids' anatomical landmarks, and individual facial characteristics. Surgical management has a favorable functional and cosmetic outcome in the majority of patients.

Eyelid-Light Reflex in Patients with Unilateral Horner's Syndrome

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Purpose: The physiologic function of the Müller's muscle has not been clearly defined. A previous study demonstrated eyelid retraction synchronized with pupil dilation after transition from photopic to scotopic conditions. This "eyelid-light reflex" was hypothesized to adjust the position of the eyelids as the pupil dilates under scotopic conditions and to involve the Müller's muscle. The purpose of the current study was to evaluate the role of the sympathetic nervous system and the Müller's muscle in this suggested reflex arc in patients with Horner's syndrome.

Methods: A video scan of the anterior segment of 10 patients (20 eyes) with unilateral Horner's syndrome was performed using OCT infra-red mode in photopic and scotopic conditions, and the transition between the two conditions was recorded. The affected side with sympathetic denervation was the study group, while the contralateral unaffected side of the same patients served as a control group. The main outcome measures were change in superior lid margin to reflex distance (MRD1), and vertical palpebral fissure height (PFH) between photopic and scotopic conditions. A sub-analysis was performed between the study group and healthy control group from the previous study.

Results: On average, MRD1 and PFH differed significantly between the study and control group in both photopic and scotopic conditions ($p < 0.05$). Transitioning from photopic to scotopic conditions, MRD1 increased by 315±276 μm ($p<0.05$) and 723±432 μm ($p<0.05$) in the study and control groups, respectively, while the PFH increased by 219±374 μm ($p<0.05$) and 642±719 μm ($p<0.05$), respectively. The mean changes in MRD1 and PFH during transition between these two conditions were significantly greater in the control group compared to the study group ($p < 0.05$). The mean change in MRD1 and PFH in the study group was also significantly different from those observed in the healthy control group from our previous study ($p<0.05$).

Conclusions: Eyelid retraction after transition from photopic to scotopic conditions was significantly diminished in eyelids with sympathetic denervation compared with the unaffected contralateral side of the same patients. This observation supports the hypothesis that the sympathetic nervous system and the Müller's muscle serve as the efferent arm of the "eyelid-light reflex.

Pre and post operative excyclotorsion in fundus photos

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Purpose:
To investigate preoperative clinical features and postoperative results in patients undergoing strabismus operation.

Methods:
Seven patients, four males and three females, mean age is 11 years (age 3.5-29) who underwent strabismus surgery, and had pre and post operation fundus photos for excyclotorsion, were included. The files were reviewed for clinical data, and complete orthoptic exam. Fundus photos (DSplus) were analyzed for torsion.

Results:
Seven of the patients were asymptomatic for torsion. Four patients had suppression due to strabismus, as measured by Worth forth dot. Mean angle of exotropia before the operation was 24 prism diopter (PD) at near (SD+13), and post operation 3 PD (SD+5 PD). Distance measurements before the surgery were 29 PD (SD + 6), and after the operation 5 PD (SD+8 PD). Visual acuity was good in all patients, (good >6/12); eye movement was full in all gaze directions, with bilateral inferior oblique overaction and V pattern in all seven patients. One had abnormal head position (chin up). None had Trauma in the past or previous cranial surgery. Excyclotorsion (degree) was documented in 7 patients on clinical exam, and was measurable on fundus photos in 4 patients.

Conclusions:
Excylotorsion was documented in clinical exam and could be measured on fundus photos. None of the patients complained on tortional diplopia, However, torsion might cause suppression and amblyopia in few cases with minor deviation."

The effect of body mass index reduction on intraocular pressure in a large prospective cohort of apparently healthy individuals in Israel

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Purpose: To investigate the effect of change in body mass index (BMI) on intraocular pressure (IOP) in a large cohort of apparently healthy volunteers who underwent an annual comprehensive screening examinations.

Methods: This study included individuals who were enrolled in the Tel Aviv Medical Center Inflammation Survey (TAMCIS) and had IOP and BMI measurements at their baseline and follow up visits. Relationships between BMI and IOP and the effect of change in BMI on IOP were investigated.

Results: A total of 7,782 individuals had at least one IOP measurement at their baseline visit, and 2,985 individuals had ³2 visits recorded. The mean (SD) IOP (right eye) was 14.6 (2.5) mm Hg and mean (SD) BMI was 26.4 (4.1) kg/m2. IOP positively correlated with BMI levels (r=0.16, p<0.0001). For individuals with morbid obesity (BMI≥35 kg/m2) and ³2 visits, a change in BMI between the baseline and first follow-up visits correlated positively with a change in the IOP (r=0.23, p=0.029). Subgroup analysis of subjects who had a reduction of at least 2 BMI units showed a stronger positive correlation between change in BMI and change in IOP (r=0.29, p<0.0001). For this subgroup, a reduction of 2.86 kg/m2 of BMI was associated with a reduction of 1 mmHg in IOP.

Conclusions: BMI loss correlated with reduction in IOP, and this correlation was more pronounced among morbidly obese individuals. Reducing BMI to normal levels may have a positive effect on IOP, especially in morbid obesity.

Direct selective laser trabeculoplasty in open angle glaucoma study design: a multicentre, randomised, controlled, investigator-masked trial (GLAUrious)

Modi Goldenfled (1) Michael Belkin (2) & the GLAUrious study group
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Methods and analysis : Multicentre, randomized, controlled, investigator-masked study. Inclusions: Participants were aged >= 40 years with OAG, including exfoliative or pigmentary glaucoma, or ocular hypertension with untreated or washed out IOP 22–35mmHg. Treatments: DSLT: 120 shots, 3 ns, 400 µm spot size, energy 1.4–1.8 mJ delivered at the limbus over 2 s. SLT: approximately 100 shots, 3 ns, 400 µm spot size administered 360 degrees at the limbus using any gonioscopy lens, energy 0.3–2.6 mJ. A sample size of 164 is sufficient to detect a non-inferiority margin of 1.95 mmHg for change from baseline IOP. The primary efficacy outcome is the difference between the two treatment groups between the mean (washed out for medicated patients) baseline IOP and the mean (washed out for medicated patients) IOP measured at 6months. Secondary efficacy outcomes include between-group differences in mean percentage reduction in IOP at 3, 6 and 12 months; the proportion of participants with at least 20% reduction in IOP from baseline at 6 months; and the change in mean number of topical hypotensive medications at 12 months compared with baseline. All treatments will be administered by an unmasked ophthalmologist. All post-randomisation IOP measures will either be collected using a masked technique or by a masked ophthalmologist. Safety measures include all ocular adverse events (AEs). Quality of life and patient satisfaction will be evaluated with the Glaucoma Quality of Life (GQL-9)9 10 and a standardised questionnaire.

Results: Final levels of IOP will be presented .

Conclusions: DSLT is performed without physically touching the cornea, and preliminary studies have shown that it is a more rapid and simpler technique when compared with SLT. Further, it has been suggested that it could be more easily administered in patients in whom contact techniques prove problematic or where anatomical obstacles exist, such as narrow iridocorneal angles or prominent facial bones. The same study demonstrated similar IOP-lowering effect in both DSLT and SLT, and suggested that DSLT resulted in less corneal injury, inflammation and postoperative discomfort when compared with standard SLT. Benefits of DSLT may include a faster and simpler treatment, less postoperative inflammation and less subjective discomfort. In addition, the procedure does not require use of a Goniolens and therefore has the potential to increase the accessibility of glaucoma care throughout the world. This study will determine the efficacy and safety of the new Eagle system.

Addition of MiSight 1 day Contact Lensess with Combination of Low-concentration Atropine in for Myopia Control Treatment

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Purposes: To assess the decrease in myopia progression and rebound effect using topical low-dose atropine compared to with and without contact lenses for myopic control.

Methods: This retrospective review study included 32 children aged 9.7±1.8 (range 6 to 13.5) followed over thee years. All had a minimum myopia increase of 1.00D the year prior to treatment. Children were divided into two groups and a control group. One treatment group included 15 children aged 10.2±2.0 (range 6 to 13.5) with an average prescription of 4.3±1.3D (sphere equivalent (SE) range of -2.75 to -6.00D), treated with 0.01% atropine for two years (A0.01%) and afterword treated with MiSight-1-day double focus contact lenses (DFCL) combined with 0.01% atropine (A0.01%+DFCL) for followed one year after that. The second group included 17 children aged 9.3±1.6 (range 6 to 13.0) that function as control group with an average prescription of 3.8±0.9D (SE range of -2.50 to -5.75D) wearing single vision spectacles)SV).

Results: There was an increase in SE myopia progression in the SV group of 1.22±0.44D, 1.25±0.52D and 1.13±0.36D in the first, second, and third years, respectively. Myopia progression in A0.01 was 0.438±0.21D($P<0.01$) and 0.51±0.39D ($P<0.01$) in the first and second years, respectively. In A0.01%+DFCL, myopia progression was 0.395±0.32D in the third year($P<0.01$). Half a year after cessation of atropine treatment, rebound effect was measured at -0.19±0.25D in A0.01%+DFCL group.

Conclusions: Monotherapy low-dose atropine combined with peripheral blur contact lenses was clinically effective in decreasing myopia progression. A low rebound effect was found after therapy cessation. Combination therapy did not present an advantage over monotherapy.

Fundus photos of Optic disc pallor in line with optical coherence tomography and support clinician diagnosis.

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Introduction and aims Pallor of the optic nerve head is a clinical sign of optic neuropathy, now can be documented with non dilated pupil fundus camera. Optical coherence tomography (OCT) add quantification of nerve fiber layers thickness, and allows follow-up of progressive loss. The aim of this study is to compare between fundus photos and OCT measurement of injured optic nerves.

Methods

This is a retrospective research data based on the Heidelberg OCT imaging test (SL-OCT Heidelberg Engineering GmbH, Heidelberg, Germany) and non-dilated pupil fundus camera (Drsplus, Icare, Padova, Italy) used in patients with optic neuropathy. Patients who have been examined in the ophthalmology clinics of Bnai Zion medical center in 2020 till 2022, with optic neuropathy, and had documented data of both OCT and fundus photo were included. The patients' files were reviewed for data including demographic, systemic medical, eye exam, etiologies of optic nerve disease, time duration and imaging if available (brain MRI or CT). OCT results of average thickness of both optic nerves , also per each quadrant, were collected. Fundus images have been graded based on the degree of the optic pallor to mild, moderate, or severe pallor subjectively.

Results

Included 50 patients, 100 eyes, mean age 48 yo, 26 male 24 females with mean follow up of 1 year. In adults (84%), etiologies were mainly inflammation (X) and Ischemic (Y). in children, main cause of optic nerve pallor was gliomas (70%). Mean OCT thickness of RNFL was 57 in the diseased optic nerve and 99 microns in the healthy eyes. The sensitivity of fundus photos was 85.48%, Specificity 46.66%, PPV 76.8%, NPV 60.9%, +LR 1.6, -LR 0.3111. OCT sensitivity was 82.25%, Specificity 76.66%, PPV 87.9%, NPV 67.6%, +LR 3.524, -LR 0.2315

Conclusions

Non-mydriatic ocular fundus photography were found in line with clinical diagnosis and OCT measurements. The optic nerve pallor was graded according to its appearance, and compared to the fellow eye. OCT added measurements by microns. Developing a computerized technology, like artificial intelligence, may help interpret fundus images quantitively in the future. In this study we found that easily available fundus photo contribute to OCT exams in documentation, follow up and treatment of patients with optic neuropathy. Advanced technologies, as eye-tracking enable the fundus camera capturing photos of eyes with poor vision, low cooperation and even nystagmus. Fundus photos have been proved as more user friendly and don't require significant patient cooperation.

Incidental Unilateral Macular findings in Children

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Background: Unilateral incidental macular findings are rare. This study aims to examine the unilateral macular lesions in the paediatric population.

Methods: A retrospective cohort design. Review of a clinical paediatric ophthalmology database of a tertiary medical center to identify all children with incidental unilateral macular findings, examined by trained paediatric ophthalmologists during 2016-2021.The distinct diagnoses and features of findings are elaborated.

Results: Of 20 children identified with unilateral, incidental, macular findings, mean age was 7.8 ± 3.4 years, 50% (n=10) were females, and 55% (n=11) had right eye involvement. The most common finding was torpedo maculopathy (50%, n=10), followed by macular scar (20%, n=4), discoid maculopathy (15%, n=3), pigmentary changes (10%, n=2), hamartoma of the retina and retinal pigment epithelium (RPE) (5%, n=1). None of the lesions changed after a mean follow-up duration of 2.3 ± 1.5 (SD) years. Visual acuity in the involved eye was equal to that in the contralateral eye in 90% (n=18) of patients and did not change from initial to final visit.

Conclusions: This is the first study we know of that describes consecutive incidental macular findings in the paediatric population. We found the majority (90%) of patients had benign, stable, non-vision threatening findings within a mean follow up period of 2.3 years. Stable, long-term follow-up after macular findings should be considered, as choroidal neovascular membrane or another vision threatening alteration may form.

Key words: Unilateral macular lesion, Incidental Torpedo maculopathy, Macular scar, Discoid maculopathy.

Combination Low-Concentration Atropine and Contact Lenses for Myopia Control

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Purpose: To ascertain the effectivity of 0.01% atropine (A0.01%) treatment to inhibit myopia progression and the possible additive potency with peripheral defocus contact lenses over three years and the rebound effect one year after cessation of treatment.

Methods: This retrospective study included 127 children aged 8–15 years, divided into three treatment groups: A0.01% and single vision (SV) spectacles (At, n=36), A0.01% and peripheral defocus contact lens (At+PDCL, n=30), 0.01%At and dual focus (At+DF, n=25) and a control group prescribed SV spectacles (n=36). Cycloplegic spherical equivalence refraction (SER) was measured every six months during three years of treatment and one year after cessation.

Results: Myopia progression decreased over three years of treatment, more during the second and third years than the first, to a statistically significant degree in the A0.01% monotherapy group(PXXX): In the first, second, and third years respectively in the At group -0.42±0.34D, -0.19±0.18, -0.22±0.19D, in the At+PDCL group -0.26±0.21D, -0.14±0.37D and -0.15±0.31D, in the At+DF group -0.22±0.15D, -0.15±0.22D, and -0.11±0.14D. Myopia progressed one year after cessation of treatment: -0.29±0.28D in the At group, -0.13±0.28D in the At+PDCL group, and -0.09±0.18D in the At+DF group. There was no statistically significant difference in myopia progression between groups At and At+PDCL or At+DF after three years ($P<0.05$).

Conclusions: Low-dose atropine has been substantiated in this cohort as an effective treatment to decelerate myopia progression over three years, more effective in the second and third years of treatment. The combination treatment did not exhibit a statistically significant advantage over monotherapy in this cohort. The dual focus lens group exhibited a statistically lower rebound effect compared to the monotherapy group.

Alga-derived 9-Cis-β-Carotene rescues cones and reduces retinal microglial cell activation

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Purpose: In previous preclinical and clinical studies we demonstrated that oral treatment with the 9-cis β-carotene (9CBC)-rich Dunaliella alga significantly improved retinal function in RP patients and patients with mutations in RDH5, a visual cycle enzyme. In vivo oral treatment with the alga extract rescued retinal function and promoted photoreceptor survival in RPE65/rd12 mice, suggesting that 9CBC, a 9-cis-retinal precursor, may present a promising safe treatment strategy for RP associated with visual cycle defects. However, remained. The aim of this study was to determine the 9CBC the mode of action (MOA).

Methods: Eye caps of RPE65/rd12 mice were incubated in media supplemented with 9CBC, all-trans-beta carotene (ATBC) or vehicle for 18 hours. Retinas were fixed and sections were stained with antibodies directed against S-cone opsin and M-cone opsin. The number of positively stained cells per retinal section was determined. The potency of 9CBC to reduced microglia cell activation was determined in primary RCS rat retinal microglia cell cultures.

Results: 1mM 9CBC extracted from Dunaliella alga enhanced M- and S-cone survival in RPE65/rd12 eyecups in-vitro by 2 and 4 folds, respectively, compared to placebo. By contrast, supplementing the media with 1mM all-trans beta Carotene resulted in nearly 2-fold lower cone survival compared with placebo treatment. 9CBC treatment reduced the size of LPS-activated microglial cells by 1.77 fold ($p<0.0001$ compared with placebo treatment), to a level similar to that of non-activated cells.

Conclusion: 9CBC MOA includes two mechanisms: increasing cone survival and reducing retinal microglia activation. This study supports the feasibility of using 9CBC for treatment of retinal degeneration.

Prediction of Progression to Scar in Age Related Macular Degeneration
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Cannabinoids receptors and inflammatory markers characterization in experimental autoimmune uveitis (EAU)

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Purpose: To furter characterize the cannabinoid system in the posterior segment of the eye in response to intraocular inflammation (IOI), and correlate the expression with inflammatory cytokines.

Methods: EAU was induced in C57BL/6J mice using the uveitogenic 161-180 amino acid fraction of human intra-retinal-binding-protein. We have previously demonstrated that IOI usually appeared at day 10, peaked at 17 to 21 days, and gradually declined at 28 days post EAU induction. We also demonstrated the increased expression of cannabinoid 2 receptor (CB2R) prior to the appearance of CD4 cells. In the current study, CB1R and CB2R markers were stained in ocular sections and flat mounts. Gene expression using RT-PCR of CBDR1 and CBDR2 and cytokine panel, IL-1, IL-6, IL-10, IL-12, IL-17, TNFα, TGFβ, INFγ, NFkB, were evaluated by primer-probe TaqMan assay (Thermofisher).

Results: CB2R expression appeared on day 4 and peaked at day 17; Retina sections showed CB2R immunostaining mainly in retinal ganglion cell (RGC), inner nuclear and outer plexiform layers.
CB1R immunostaining was found mainly in retinal nerve fiber and RGC layers in both control and EAU mice retinas. RNA expression of CB1R using RT-PCR remained similar at all time points. Inflammatory cytokines showed increased expression that correlated with clinical inflammatory grading of each individual mouse and with overall mice mean grading.
Acute phase cytokines, IL-1 and IL-6, peaked at day 17 and decreased substantially at day 21. Inhibitory and regulatory cytokines, IL-10 and TGFβ increased at a late phase on days 10-17 and peaked in day 21.

Conclusions: Both Cannabinoid receptors were found in retinal layers as described. While CB2R and the expression of inflammatory cytokines correlated with IOI, CB1R was found to be present in the retina with no fluctuation noted in our model. These preliminary results may pave our way to study possible effects of cannabinoids on IOI.

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A Simple Automated Process for Bulk Download of Optical Coherence Tomography Scans

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Purpose: The goal of this study was to develop an automated method for efficiently downloading a large number of OCT scans from the Heidelberg Spectralis platform to create a large dataset for big data and deep learning research, as a practical solution to real-world problems.

Methods: The study group consisted of all age-related macular degeneration (AMD) patients treated at the Hadassah University Hospital retina clinic between 2010 and 2021. Electronic medical records and OCT scans were extracted. A macro was created using Visual Basic Application (VBA) and Excel (Microsoft) to automate the export process and anonymize the patients' OCT scans in compliance with hospital policy. OCT scans were extracted as Heidelberg proprietary E2E files.

Results: The VBA macro was used to export a total of 94,789 E2E files from 2807 patient records, with an average processing time of 4:19 minutes per volume scan (SD 3:34 min). The entire process took approximately 202 hours to complete over a period of 24 days. In a smaller sample, the macro method for downloading volume scans was found to be significantly faster per file than the manual method ($t= 8.59$, $p < .001$). The macro method took an average of 3:53 minutes per patient, while the manual method took an average of 11:05 minutes per patient. Exporting the files during off-clinic and working hours resulted in significantly faster processing times compared to during working hours ($t = 5.77$, $p < .001$).

Conclusion: This study demonstrated the feasibility of using VBA and Excel to automate the bulk image download process for a specific medical imaging platform. The specific steps and techniques may vary depending on the software and hospital constraints.

A fully automatic AI doctor assistant tool for explainable detection and staging of age-related macular degeneration in 3D macular SD-OCT scans

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Purpose: With a currently estimated 170 million individuals affected by age-related macular degeneration (AMD) worldwide and an aging population, the need for Optical coherence tomography (OCT) imaging and classification by experts already outgrowing clinical capacity.
We aimed to develop a deep learning automatic doctor assistant tool which can be implemented in clinical practice and classify these as healthy, non-neovascular or neovascular (nAMD), as well as provide explainability heatmaps.

Methods: Database setup and extraction: We included 100 eyes with normal macular OCT and 175 eyes which converted from non-neovascular to neovascular AMD at Tel-Aviv Medical Center. Over 6000 OCT images were systematically exported (Heyex2, Heidelberg Spectralis) to DICOM format, de-identified and only pixel information preserved.
Dataset labelling was performed by junior and senior graders: Each B-scan image out of 3D scans was labeled as (1) normal, (2) non-neovascular AMD, (3) nAMD.
Dataset was split to train and validation set (80/20). The test set consisted of 750 OCT images from an external database.
Training model: We trained an ImageNet pre-trained deep learning classifier using Pytorch framework, and implemented explainability methods, highlighting parts on the image that led to the classification. We then used a data-driven approach to decide how to classify each volumetric scan based on the image classifier using both label and confidence.

Results: The model achieved 98% accuracy on the balanced validation set of the 2D images, 98% accuracy on the balanced external test set of the 2D images and 94% accuracy on the 3D scans validation set. We combined the models to create an external SD-OCT viewer with doctor assistance tools: The output classification is done on the 3D scan level and for every single 2D B-Scan image. Explainability for the physician is provided as the tool presents heatmaps within the images for the different pathologies classified (e.g fluid, drusen, irregular RPE etc.).

Conclusions: The proposed deep learning tool can effectively classify OCT images as well as volume scans as normal, non-neovascular and neovascular AMD in a real-life population. Furthermore, it allows the physician to see which biomarkers were pivotal in the decision-making process. By combining these abilities, we believe AI doctor assistant tools can be implemented soon in physician's workflow to speed up AMD diagnosis and accurate classification.

Machine learning for classification Proliferative Diabetic Retinopathy in Latino and African American Cohorts

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Purpose: Use machine learning to identify the factors that can predict proliferative diabetic retinopathy (PDR) in African American (AA) and Latin American (LA) patients.

Methods: We analyzed electronic medical records of 1024 patients with type 2 diabetes who were treated at the Bronxcare Hospital eye clinic between January and December 2019. Demographic and clinical parameters, including age, gender, fasting glucose, HDL, LDL, creatinine, eGFR, and ACR, and retinopathy status were collected. We compared the performance of the balanced random forest model to other machine learning techniques, including logistic regression, support vector machine, k-nearest-neighbors, and decision-tree algorithms. To further explain the results of the model, we used the SHAP (SHapley Additive exPlanations) method to identify the contribution of each feature to the model's predictions.

Results: The balanced random forest model outperformed the other models in predicting PDR in both AA and LA populations, achieving an AUC of 83%. The model had a particularly strong performance in AA populations with an AUC of 83.7%, and a slightly lower performance in LA populations with an AUC of 81.8%. When considering gender, the model performed exceptionally well in the female LA population with an AUC of 87.1%, but also had good results in the male LA cohort with an AUC of 79.9%. The SHAP analysis showed that the factors related to PDR had different impacts on AA and LA patients, with even greater variations between genders. The optimal cutoff values for identifying patients at risk for PDR also varied according to gender and ethnicity.

Conclusions: Our study demonstrates the potential of machine learning in identifying individuals at risk for PDR and helping clinicians in prioritizing them for timely testing. The findings also emphasize the need to take both ethnicity and gender into account when analyzing the risk factors for PDR in diabetic patients.

Pachyvitelliform Maculopathy: Optical Coherence Tomography Analysis of a Novel Entity

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Purpose To describe the optical coherence tomography features of pachyvitelliform maculopathy (PVM), an acquired vitelliform lesion (AVL) associated with pachychoroid disease.

Methods This study was a retrospective, multicenter, observational analysis.
Medical records and multimodal imaging were reviewed in all patients with pachychoroid disease. Visual acuity, central choroidal thickness (CCT), AVL dimensions, total choroidal area (TCA), luminal choroidal area (LCA), stromal choroidal area (SCA) and choroidal vascular index (CVI) were measured in all eyes with PVM and compared with normal age-matched control eyes.

Results Mean age of the PVM group (17 eyes of 17 patients) was 71.4 years. Average follow-up was 33.2 months. Baseline VA was 20/40 in the PVM group and declined to 20/100 ($p=0.006$). AVL's were all detected overlying pachyvessels with OCT and were all hyperautofluorescent with fundus autofluorescent imaging. Mean CCT in the PVM group was significantly greater (358.4 μm) than the CCT in the control group (226.9 μm, $p<0.001$). Retinal pigment epithelium (RPE) disruption was present in 64.7% of eyes with PVM at baseline and 41.2% developed macular atrophy at the end of follow-up.

Conclusions Pachyvitelliform maculopathy, defined by the presence of AVL associated with pachychoroid features, is a distinct novel entity of the pachychoroid disease spectrum. This study suggests a possible pathogenesis of RPE dysfunction secondary to a thick choroid, leading to accumulation of undigested photoreceptor outer segments and AVL. Clinicians should be aware of this common cause of vitelliform lesions and the poor visual prognosis due to the high risk of atrophy development.

Endophthalmitis in patients receiving Anti-VEGF injections for retinal pathologies: clinical outcome and disease quiescence.

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Purpose: To characterize the clinical profiles, causative agents, clinical outcome of patients post endophthalmitis.

Methods: clinical records, causative agent and management of each case of endophthalmitis post intravitreal anti-vascular endothelial growth factor (VEGF) injections for retina pathologies recorded between 1st of January 2006 and the 30th of May 2022 were retrieved from the electronic medical records. The visual and anatomic changes immediately prior to the episode of endophthalmitis were compared to the visual and anatomic outcomes at 2 years.

Results: Eleven post injection endophthalmitis eyes in 10 patients (n = 3 females; 30%) were identified and their mean age was 64.5±20.4 years. The mean last recorded best corrected visual acuity (BCVA), immediately prior to the episode of endophthalmitis was 60.5±23.4 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The BCVA dropped to 29.1±29.4 and 36.0±26.8 ETDRS letters at presentation with endophthalmitis and 6 months follow-up; p=0.24 and 0.041, respectively. However, by 1 year and 2 years follow-up, the mean BCVA returned to values similar to baseline values prior to the episode of endophthalmitis (41.0±23.7 and 41.0±30.7 ETDRS letters; p=0.078, and p=0.095, respectively). In all culture positive cases (7/11), the organism identified was staphylococcus epidermidis. Four of the 11 eyes (2 with neovascular age related macular degeneration (NVAMD), 1 with Myopic choroidal neovascularization (CNV) and 1 with retina vein occlusion (RVO)) experienced disease quiescence and didn't require additional anti-VEGF injections up to 2 years follow-up.

Conclusion: These results indicate that vision lost due to endophthalmitis post anti-VEGF injections could be regained by 2 years. It also indicates that disease quiescence post endophthalmitis may not only occur in eyes treated for NVAMD, but also in eyes with myopic CNV and RVO.

Long-term outcomes of anti-vascular endothelial growth factor treatment in peripapillary subretinal neovascular membrane due to age-related macular degeneration

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Purpose: To report the long-term outcomes of anti-vascular endothelial growth factor (VEGF) treatment in eyes with peripapillary subretinal neovascular membrane (PSRNM) associated with age-related macular degeneration (AMD).

Methods: A retrospective cohort study included patients with AMD related PSRNM. Eyes were treated with anti-VEGF according to pro re nata regimen. Inactivation index was calculated as the proportion of disease inactivity from the total follow up time.

Results: Sixty-seven eyes of 66 consecutive patients were included in the study; mean follow-up time was 53.2 months. Best corrected visual acuity (BCVA) remained stable for the first four years of follow up with a significant deterioration in BCVA thereafter. Baseline BCVA was a significant predictor of final BCVA ($p<0.001$). The mean inactivation index was 0.38±0.23. Subretinal fluid (SRF) at presentation was significantly associated with decreased inactivation index ($p <0.05$). Worse baseline BCVA, SRF and pigment epithelium detachment (PED), male sex and younger patient age were associated with increased risk for recurrence after first inactivation ($p < 0.05$).

Conclusion: The use of anti-VEGF agents in the treatment of AMD related PSRNM managed to preserve BCVA in the first four years of follow-up. Male sex, SRF and PED at presentation and baseline BCVA are associated with increased risk for PSRNM recurrence after the first inactivation and should prompt careful follow up in these patients.

Prospective evaluation of vitreous traction on retinal lattice degeneration and atrophic holes by swept-source optical coherence tomography.

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Purpose: To evaluate the use of swept source optical coherence tomography (SS-OCT) versus fundus examinations by slit-lamp biomicroscopy for detecting vitreous traction and sub-retinal fluid (SRF) on areas of atrophic holes and lattice degeneration in the periphery of the retina.

Methods: Treatment-naïve patients with atrophic holes or lattice degeneration in the retina periphery, and without visual symptoms were recruited between March and November 2022. Patients were examined by a retina specialist, and for each lattice and/or atrophic hole an annotation was made to indicate whether there was local traction or SRF. Then the patients underwent ultrawide field imaging, and peripheral SS-OCT (Silverstone, Optos), biometry and auto-refractometry. An observer that was masked to the clinical annotations of the retina specialist evaluated the imaging studies. We then calculated the correlation between the findings identified on SS-OCT vs. those of the retina specialists.

Results: Twenty-one eyes in 15 patients (n = 6 females; 40%) were included, and the mean age was 29.2±13.9 years. Twenty eyes were myopic, while one was emmetropic. The median spherical equivalence was -2.8 (interquartile range -11.2 to -2.3) and the mean axial length was 26.2±2.4. Overall, 7 atrophic holes and 29 lattice degeneration foci were identified both clinically and on SS-OCT. Traction and SRF was identified in 12 and 6 foci on exam, vs. 6 and 4 foci on SS-OCT, respectively. The interclass correlation coefficient for the identification of traction and SRF by fundus exam vs SS-OCT was 0.511 (95% Confidence interval (CI) 0.073-0.748, p=0.012) and 0.474 (95% CI -0.043-0.735, p=0.033), respectively.

Conclusion: These results suggest that SS-OCT may provide an additional alternative for visualizing and monitoring vitreous traction and SRF on lattice degeneration and atrophic holes in the peripheral retina. This could potentially help in guiding treatment decision in particular patients at risk of retinal detachment.

Topographic correlation between anatomical and functional macular measures in patients treated with hydroxychloroquine

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Purpose: Prolonged use of hydroxychloroquine (HCQ) has the potential to cause irreversible retinopathy, characterized by parafoveal outer retinal thinning. Multifocal electroretinogram (mfERG) can detect early subtle functional changes which may be also antecedent to a visible photoreceptor loss detectable on optical coherence tomography (OCT). We aimed to evaluate correlations between outer nuclear layer thickness and electroretinographic macular measures in corresponding topographic locations in patients treated with HCQ.

Methods: Consecutive patients at Tel Aviv Medical Center referred for suspected HCQ maculopathy who underwent MFERG and SD-OCT between 2015 and 2021 were included. Demographic and clinical details regarding HQC treatment were recorded. OCT images and mfERG exams were divided into nine regions defined by three rings: central foveal (1mm diameter), inner macular (pericentral, 3mm), outer macular (peripheral 6mm), and each ring into four quadrants, nasal, temporal, superior, and inferior (ETDRS grids). For each region, average mfERG responses (nV/deg2) and outer nuclear layer (ONL) thickness (μm) were measured. We tested for statistical correlations between OCT and mfERG response in corresponding regions.

Results: 50 eyes of 25 patients were included (mean age 52±14), 92% were female. Mean treatment time with HCQ was 12±9 years, mean cumulative dose 1345±1126 gr. Six patients had signs of HCQ toxicity. Mean ONL thickness was 88±13 μm, 66±12 μm, and 54±9 μm in the fovea, pericentral, and peripheral rings, respectively. MfERG response measured 33±15 , 16±7, and 10±4 nV/deg2 μm in the corresponding rings, respectively. Comparison between right and left eye within each patient revealed high statistically significant correlation for all OCT and mfERG measures. ONL thickness in the inner and outer nasal rings was statistically significantly correlated with duration of HCQ treatment ($p=0.004$ and 0.044, respectively) and cumulative HQC dose of HCQ ($p= 0.008$ and 0.038, respectively). In the pericentral areas, ONL thickness was statistically significantly correlated with mfERG responses ($p<0.034$).

Conclusions: Within patients treated with HCQ, we showed a strong symmetry in OCT and mfERG measures in corresponding macular areas between right and left eyes. Anatomical OCT and functional mfERG significantly correlated in corresponding topographic areas. Nasal parafoveal retinal thickness is significantly correlated with duration and cumulative dose of HCQ.

Genetic analysis of 250 index cases with inherited retinal diseases using a panel of 351 retinal genes

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Purpose: Inherited retinal diseases (IRDs) are extremely heterogeneous with at least 350 causative genes, making genetic diagnosis a complicated task. The Hadassah-IRD cohort includes more than 2200 families, in about 35% the causative gene is unknown. Our aim was to evaluate the efficiency of a gene panel as a quick and reliable tool for IRD genetic analysis.

Methods: Saliva or DNA samples extracted from blood were sent to Blueprint Genetics for “Retinal Dystrophy” panel analysis including 351 genes, of them 37 are mitochondrial genes. Blueprint pipeline constituting next generation sequencing (NGS) of single nucleotide variations (SNVs) and structural variants (SVs) was applied followed by using various interpretation tools.

Results: The analysis includes 250 samples, 177 were analyzed thus far. The cause of disease could be identified in 56% of cases. A clear difference was obtained between newly recruited cases that were not analyzed by other tools (66% solved) and cases that were previously analyzed by NGS panels or whole exome sequencing (WES) with 22% solved.
As for the mode of inheritance, 74% of the solved cases were autosomal recessive (AR), 11.5% were X-linked (XL), 7.3% were autosomal dominant (AD) and 3.1% were mitochondrial. Interestingly, in 15% of solved cases SV were identified as the cause of disease. The most common identified genes were EYS and ABCA4 (9% of cases each) and the most common mutations were c.1297_1298insAlu and c.1355_1356del (5% of cases each). We also identified an EYS variant that is located in the 5’UTR and suspected to be pathogenic, probably be disrupting a control region. In-line with our previous IRD carrier analysis, we identified heterozygous AR mutations that are not related to the disease in 36% of cases.

Conclusions: The studied NGS-based IRD panel was found to be efficient in gene identification and yielded results that were similar to previous WES studies in the same population. Some variants were mis-interpreted by the pipeline and therefore multiple analysis tools are recommended to obtain more accurate annotation of potential disease-causing variant. Furthermore, the analysis revealed both SVs and non-coding variants should be screened and analyzed to obtain more accurate results. In addition, reporting of causing as well as carrier mutations will provide genetic counselors with stronger preventive measures in disease prevention, especially with consanguineous and intracommunity marriages.

A novel HPS5 acceptor splice-site mutation causing Hermansky Pudlak Syndrome type 5

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Purpose: Three affected siblings of two branches of a Bedouin consanguineous kindred presented with nystagmus, mild cutaneous and ocular hypopigmentation, and a history of easy bruising, recurrent epistaxis, and severe bleeding after uneventful surgery, commensurate with a diagnosis of Hermansky Pudlak Syndrome (HPS). We aimed to identify the molecular basis of HPS in the studied kindred.

Methods: Affected individuals were studied following informed consent and approval of Soroka Medical Center IRB. Senior ophthalmologist and geneticist determined phenotype. Linkage analysis, testing 13 family members, was done using SNP arrays and Sanger sequencing was done for HPS5 coding exons. Segregation analysis of the putative pathogenic variant was done using Sanger sequencing

Results: Linkage analysis delineated a 17 Mbp disease-associated homozygosity locus on chromosome 11 (LOD score of 2.4), containing HPS5. HPS5 sequencing identified a novel homozygous splice-site mutation, c.285-2, A>G, near the end of intron 4. The mutation is in a highly evolutionary conserved residue (phyloP p-value under 10^-7) and is likely pathogenic (CADD score 34).

Conclusions: The novel HPS5 mutation causing HPS in the Bedouin kindred is in a highly conserved splice acceptor site, likely resulting in an aberrant transcript. The HPS5 protein is part of the Biogenesis of Lysosome-related Organelle Complexes 2 (BLOC-2) together with proteins HPS3 and HPS6. BLOC-2 is involved in the formation and migration of lysosomal-related endosomal compartments and is crucial in melanosome formation and maturation.

Variants in the WDR45 gene within the OPA-2 locus associate with isolated X-linked optic atrophy

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Objective: To identify the molecular basis of X-linked optic atrophy.

Methods: Case series and molecular analysis of two families of Jewish Ashkenazi decent with early onset bilateral optic atrophy. Whole exome sequencing (WES) and bioinformatic analysis were performed, followed by Sanger sequencing and segregation analysis.

Results: In both families, male siblings (3 in family #1, 2 in family #2) presented with early onset isolated bilateral optic atrophy. The sibling's healthy mother (and in the second family also one healthy sister) had a mild presentation, suggesting a carrier state and an X-linked inheritance pattern. All subjects were otherwise healthy, apart from mild learning disability and autism spectrum disorder in two siblings of the second family. Mutations in known optic atrophy genes were excluded. Analysis revealed a point mutation in the WDR45 gene - a missense mutation in the first family: WDR45 (NM_007075.3) c.107C>A; p.Pro36His (ClinVar SCV002569138); a splice site mutation in the second family: WDR45 (NM_001029896.2) c.236-1G>T (ClinVar SCV002569139); located on Xp11.23 (OPA2 locus). Both mutations are novel and predicted as pathogenic. In both families the mutation was seen with full segregation with the disease, occurring in all affected male subjects and in one allele of the carrier females, and none of the healthy subjects.

Conclusions: Among two families with isolated X-linked optic atrophy, molecular analysis revealed novel mutations in the WDR45 gene in full segregation with the disease. This gene has not previously been described to be associated with isolated optic atrophy, and resides within the OPA2 locus, previously described to associate with X-linked optic atrophy. Taken together, these findings suggest that mutations in the WDR45 gene are responsible for isolated X-linked optic atrophy.

An intronic REEP6 variant causes autosomal recessive retinitis pigmentosa in Arab-Muslim patients

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Purpose: Splicing is an important process that is required for an accurate protein translation. It is a highly precise post-transcriptional step that depends on conserved and cis-acting elements. A nucleotide change in these regions might lead to aberrant splicing. Inherited retinal diseases (IRDs) are a large group of heterogenous phenotypes caused by variants in over 350 genes. Multiple studies showed that even when using whole exome sequencing (WES) or whole genome sequencing (WGS), the cause of disease is found in 50-75% of cases. It's therefore reasonable to assume that non-canonical intronic disease-causing variants might account for some of the remaining cases. In the current study we aim to identify the cause of disease in multiple Arab-Muslim families with autosomal recessive (AR) retinitis pigmentosa (RP).

Methods: DNA samples were screened for variants using the smMIPs targeted panel of 85 genes underlying RP and Leber congenital amaurosis (LCA).Variants were analyzed and annotated using Franklin server. Various in silico tools were used for predicting the effect of the identified variant on splicing. Sanger sequencing was performed for variant confirmation and segregation.

Results: We identified 6 patients who belong to 3 Arab-Muslim families from Jerusalem. The patients are homozygous for c.518-9G>A in intron 4 of the receptor expression enhancing protein 6 (REEP6) gene. This variant obtained a very high delta score of 0.99 using the SpliceAI tool, predicting it to be splice-altering and highly deleterious. Clinical analysis revealed patients ages to range between 14-65 years and their visual acuity varies from 0.1-0.8. ERG testing was performed and at the age of 55 it was undetectable. All 6 patients were diagnosed with typical RP. An in vitro splicing analysis is currently being performed.

Conclusions: Hundreds of variants in >200 IRD genes have been reported in the Israeli and Palestinian populations, none of which were reported in the REEP6 gene. The variant we identified is the 1st report of the association of REEP6 and ARRP in our populations.

An In-Depth Single-Gene Worldwide Carrier Frequency and Genetic Prevalence **Analysis of CYP4V2 as the cause of Bietti Crystalline Dystrophy**

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Purpose: Bietti crystalline dystrophy (BCD) is a rare monogenic autosomal recessive (AR) chorioretinal degenerative disease caused by biallelic mutations in CYP4V2. The aim of the current study was to perform an in-depth calculation of worldwide carrier frequency and genetic prevalence of BCD using gnomAD data and comprehensive literature CYP4V2 analysis.

Methods: CYP4V2 gnomAD data and reported mutations were used to calculate carrier frequency of each variant. An evolutionary-based sliding window analysis was used to detect conserved protein regions. Potential exonic splicing enhancers (ESE) were identified using ESEfinder.

Results: We identified 1171 CYP4V2 variants, 156 of which were considered pathogenic, including 108 reported in BCD patients. Carrier frequency and genetic prevalence calculations confirmed that BCD is more common in the East-Asian population with ~19M healthy carriers and 52K individuals who carry biallelic CYP4V2 mutations and are expected to be affected. Additionally, we generated BCD prevalence estimates of other populations, including African, European, Finnish, Latino and South Asian. Worldwide, the estimated overall carrier frequency of CYP4V2 mutation is 1:210 and therefore ~37M individuals are expected to be healthy carriers of a CYP4V2 mutation. The estimated genetic prevalence of BCD is about 1:116,000 and we predict that ~67K individuals are affected with BCD worldwide.

Conclusions: Our analysis estimates BCD prevalence and revealed large differences among various populations. Moreover, it highlights advantages and limitations of the gnomAD database. This analysis is likely to have important implication for genetic counseling in each studied population, for better genetic and clinical diagnosis of this under-diagnosed phenotype, and for developing clinical trials for potential BCD treatments.

Genotype-phenotype associations in Israeli PRPF31 retinitis pigmentosa patients

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Purpose: Mutations in the PRPF31 gene, encoding a pre-mRNA splicing factor, are the second most common cause of autosomal dominant retinitis pigmentosa (RP). Disease severity may vary even between carriers of the same mutation. Yet, the association between the type of PRPF31 mutation and the natural history of the disease remains inconclusive. Here, we analyzed inter-familial and intra-familial variations in the natural history of the disease in Israeli PRPF31-RP patients carrying heterozygous nonsense point mutations, frameshifts, a splice site mutation, large deletions, and an exon insertion.

Methods: 20 patients (age 11-85 years) from 10 Israeli PRPF31-RP families underwent a complete ophthalmic assessment including best-corrected visual acuity (BCVA), SD-OCT imaging, and ERG.

Results: Six families had nonsense point mutations [c.1108G>T,p.E370*; c.1165C>T,p.Q389*), one family had a frameshift mutation (c.689delA, p.K230Rfs*9), one family had a large deletion in exon 1, one family had a splice site mutation (c.697+1G>A) and one family had a large exon insertion with no frameshift (c.A820insTCGTGACATCTACCACATCGTACG). The c.1165C>T patient had additional probably harmful heterozygous mutations in the MERTK (c.773C>A,p.A258E) and RIMS1 (c.1088G>T,p.R363L) genes. Three subjects with the c.1108G>T mutation and one subject with the deletion in exon 1 showed incomplete penetrance. Smaller ellipsoid zone area, ERG a-, and b-waves were recorded in patients with complete penetrance, in association with the patient's age. BCVA was maintained between 0.0-0.1 logMAR until the age of 60 years, excluding the patient with the exon insertion who presented with BCVA of 0.23 logMAR at the age of 33 years. The ellipsoid zone area became smaller with patients' age, and was highly correlated with patients' binocular maximal dark-adapted b-wave (Pearson's correlation r=0.944, p=0.000041) and isolated rod-mediated (Pearson's correlation r=0.969, p= 0.000004) ERG responses. Cone-mediated flicker ERG response negatively correlated with age (Spearman's correlation r=-0.726, p=0.011). The patient with the additional mutations in the MERTK and RIMS1 genes had a relatively mild phenotype.

Conclusions: In this Israeli PRPF31 RP cohort, disease severity varied between patients, even among individuals with the same mutation. Although disease severity is associated with the patients' age, patients at early age can present with a severe disease. The nonsense mutations did not appear to cause less severe disease compared to insertions/deletions/frameshifts.

RNA Editing of relatively common worldwide Mutations causing inherited retinal diseases using the endogenous Adenosine Deaminase Acting on RNA enzyme

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Purpose: Adenosine to inosine (A-to-I) RNA editing is a process by which adenosines are selectively converted to inosines in double-stranded RNA (dsRNA) substrates by the adenosine deaminase acting on RNA (ADAR) enzyme. The two major ADAR genes are ubiquitously expressed and can be used as a possible new genetic therapeutic approach. Our strategy is to induce editing of disease-causing mutations by recruiting ADAR to the mutation specific site aiming to edit the appropriate codon. dsRNA is not naturally formed around disease-causing mutations, so we are using guide RNA (gRNA) complementary to our target sequence, to induce the formation of dsRNA. For our study, we performed RNA editing of 3 common worldwide mutations that cause inherited retinal disease (IRDs).

Methods: For the USH2A nonsense mutation, we used a yeast model to select an efficient gRNA, by measuring yeast survival and percentage of editing by NGS. This gRNA was then produced and chemical modifications were added. For the missense mutations we used the same modifications. Our reporter system is a fluorescence-expressing plasmid, containing mCherry, a gene cassette with the mutation and EGFP. This plasmid is transfected into HeLa cells over expressing ADAR, to test the gRNAs. RNA Editing level and off targets were measured through Sanger sequencing and NGS. To analyze all samples simultaneously we create an Rstudio code with BAM files used as input and return as outputs an excel file including a table with percentage editing and a Heat Map.

Results: Based on the GRID dataset, we choose 3 common worldwide IRD-causing mutations: USH2A-c.11864G>A, GUCY2D-c.2513G>A and NR2E3-c.932G>A that are amenable to RNA editing by ADAR. Our yeast model identified a 30-mer +R/G motif gRNA and a 60-mer gRNA for USH2A. In HeLa cells overexpressing ADAR the 60-mer gRNA showed higher levels of editing (29% compared to 9%). Therefore we used 60-mer gRNAs for the two missenses mutations. GUCY2D showed editing levels of 12%, and no editing was evident with the NR2E3 gRNA. Off target analysis, revealed 3 off target sites, out of 17 potential sites, that are edited with a maximum level of 50% of the target base editing level.

Conclusions: RNA editing utilizing the endogenous ADAR enzyme could be the next genetic therapeutic approach in order to treat IRD. Our future plans include a new system to find better gRNAs and get higher levels of editing by testing pool of gRNA. The Rstudio code allows simultaneous analysis of multiple different experiments and is an important tool in evaluating the success of RNA editing.