

Issue 315

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

Eye (Lond). 2017 Feb 10. [Epub ahead of print]

One-year real-world outcomes in patients receiving fixed-dosing aflibercept for neovascular age-related macular degeneration.

Almuhtaseb H, Kanavati S, Rufai SR, Lotery AJ.

Purpose: To investigate 1-year visual and anatomic outcomes of intravitreal aflibercept for neovascular age-related macular degeneration (nAMD) given at a fixed 8-weekly interval.

Methods: Retrospective, single-practice data analysis from an electronic medical record system of 255 eyes (223 patients) with treatment-naïve nAMD receiving 8-weekly aflibercept.

Results: Mean logarithm of the minimum angle of resolution best-corrected visual acuity (BCVA) improved from 0.66 at baseline to 0.50 at month 11 ($P<0.0001$). Mean central retinal thickness (CRT) decreased from 311 μm at baseline to 211 μm at month 11 ($P<0.0001$). Our mean VA gain of eight ETDRS letters was comparable to the VIEW 1 and VIEW 2 Trials' results at the end of year 1. After loading at month 5, mean BCVA was 0.48 ($P<0.0001$), and mean CRT was 235 μm . At month 5, 143 eyes (56%) were inactive defined by the absence of macular haemorrhage and intraretinal fluid (IRF) and subretinal fluid (SRF) on optical coherence tomography, and 112 eyes (44%) remained active. At month 11, 136 eyes (53%) were inactive, and 119 eyes (47%) remained active. At month 11, 77% of inactive eyes after loading remained inactive, and 77% of the active eyes after loading remained active. At month 11, mean BCVA of the inactive group was 0.51, and mean BCVA of the active group was 0.48 ($P=0.54$).

Conclusions: Aflibercept administered by fixed dosing over 1 year improved VA and macular morphology in treatment-naïve eyes. Active lesions at month 11 do not have worse VA outcomes compared with inactive lesions. The macular status after loading is a reliable indicator of disease activity at the end of year 1.

PMID: 28186507

Adv Ther. 2017 Feb 10. [Epub ahead of print]

The Clinical Effectiveness of Ranibizumab Treat and Extend Regimen in nAMD: Systematic Review and Network Meta-Analysis.

Danyliv A, Glanville J, McCool R, Ferreira A, Skelly A, Jacob RP.

INTRODUCTION: Neovascular age-related macular degeneration (nAMD) is a chronic eye condition that causes severe deterioration of vision and ultimately blindness. Two vascular endothelial growth factor inhibitors are approved for nAMD treatment in Europe: ranibizumab and aflibercept. The European license for ranibizumab was updated with an individualized "treat and extend" (T&E) regimen, which involves more proactive treatment based on changes in best corrected visual acuity (BCVA) and/or anatomical outcomes. The aim of this publication is to compare the efficacy of the ranibizumab T&E regimen with other approved

dosing regimens for nAMD on the basis of outcomes identified from a systematic review and subsequent NMA.

METHODS: Following a systematic search of publications, to identify relevant studies, a repeated-measures network meta-analysis (NMA) was performed to estimate the relative effectiveness of ranibizumab T&E versus approved dosing regimens of ranibizumab and aflibercept. The analysis focused on licensed treatment regimens for nAMD. We examined mean change from baseline in BCVA on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

RESULTS: The systematic literature review identified 22,949 records, of which 23 studies were included in the NMA. At 12 months, the ranibizumab T&E dosing regimen vs ranibizumab pro re nata (PRN) was associated with small differences in change in BCVA, between 1.86 letter gain at 12 months and 2.35 letter gain at 24 months. A similar difference was observed in the aflibercept dosing regimen versus ranibizumab T&E ; 1.94 letter gain at 12 months and 3.31 letter gain at 24 months. All doses of ranibizumab and aflibercept showed similar effectiveness, and the differences between treatment options were not significant.

CONCLUSION: This study used novel repeated-measures NMA to synthesize efficacy results when treatment effects were reported at multiple follow-up times. This repeated-measures NMA suggests that treating patients with the ranibizumab T&E regimen yields similar effectiveness compared to other approved ranibizumab and aflibercept dosing regimens for nAMD treatment.

PMID: 28188433

Int Ophthalmol. 2017 Feb 7. [Epub ahead of print]

Comparison of efficacy of intravitreal ranibizumab between non-vitrectomized and vitrectomized eyes with diabetic macular edema.

Chen YY, Chen PY, Chen FT, Chen YJ, Wang JK.

PURPOSE: To compare the efficacy of intravitreal ranibizumab between non-vitrectomized and vitrectomized eyes with diabetic macular edema (DME).

STUDY DESIGN: A retrospective, nonrandomized, and comparative study.

METHODS: From May 2013 to March 2016, 148 eyes of 148 patients with treatment-naïve center-involving DME were reviewed in one institution. Forty-six eyes underwent prior vitrectomy at least 3 months ago, and 102 eyes did not receive any vitrectomy. Three monthly then PRN intravitreal ranibizumab treatments were performed in all the patients with monthly follow-up for 6 months. Primary outcome measures included change in central foveal thickness (CFT) and best-corrected visual acuity (BCVA) at month 6.

RESULTS: The CFT significantly reduced, and the BCVA significantly improved 6 months after ranibizumab injections in either vitrectomized or non-vitrectomized groups ($p < 0.05$). There was no difference between vitrectomized and non-vitrectomized eyes in baseline characteristics. Significantly better final BCVA and visual gain were found in non-vitrectomized eyes than in vitrectomized eyes ($p = 0.01$ and 0.03 , respectively). Final CFT and CFT decrease were significantly greater in non-vitrectomized group than in vitrectomized group ($p = 0.02$ and 0.006 , respectively). Injection number of ranibizumab was 4.12 ± 0.58 in non-vitrectomized eyes, significantly less than that in vitrectomized eyes (5.05 ± 0.71) during 6-month period ($p < 0.001$). There were no severe systemic/ocular adverse effects in both groups.

CONCLUSIONS: Intravitreal ranibizumab was helpful for either vitrectomized or non-vitrectomized eyes with DME in short-term follow-up. Anatomical and functional improvements were greater in non-vitrectomized patients than in vitrectomized cases.

PMID: 28176171

Clin Ophthalmol. 2017 Jan 24;11:223-231. eCollection 2017.

Combination verteporfin photodynamic therapy ranibizumab-dexamethasone in choroidal neovascularization due to age-related macular degeneration: results of a phase II randomized trial.

Gallemore RP, Wallsh J, Hudson HL, Ho AC, Chace R, Pearlman J.

PURPOSE: To assess whether combination therapy (CT) reduces retreatments when compared to ranibizumab monotherapy (RM), while safely maintaining similar vision outcomes.

METHODS: In this 24-month trial, patients with age-related macular degeneration (AMD) were randomized to 1) quarter-fluence or 2) half-fluence triple therapy (verteporfin photodynamic therapy [vPDT] + ranibizumab + dexamethasone), 3) half-fluence double therapy (vPDT + ranibizumab), or 4) RM. The primary outcomes were number of retreatment visits and change from baseline in visual acuity (VA) at 12 months.

RESULTS: One hundred sixty-two subjects enrolled. There were 4.0 (P=0.02), 3.2 (P<0.001), 4.1 (P=0.03), and 5.7 retreatment visits through month 12, and 5.9 (P=0.03), 4.3 (P<0.001), 5.9 (P=0.02) and 8.7 through month 24, in groups 1, 2, 3, and 4, respectively (P-value comparing with RM). Month 12 VA score change from baseline (95% confidence interval) was +3.6 (-0.9 to +8.1), +6.8 (+2.4 to +11.1), +5.0 (+0.6 to +9.3), and +6.5 (+1.7 to +11.4), respectively.

CONCLUSION: CT resulted in significantly fewer retreatment visits than a RM regimen at months 12 and 24. VA results appeared similar although wide confidence intervals preclude conclusions regarding vision outcomes.

PMID: 28182161 PMCID: PMC5279866

Cutan Ocul Toxicol. 2017 Feb 6:1-12. [Epub ahead of print]

Ocular surface effects of repeated application of povidone iodine in patients receiving frequent intravitreal injections.

Saedon H, Nosek J, Phillips J, Narendran N, Yang YC.

BACKGROUND: The aim of this study was to investigate the patient reported symptoms and objective signs of tear film and ocular surface abnormalities experienced by patients undergoing repeated exposure to povidone iodine as a consequence of requiring frequent intravitreal injections for wet macular degeneration.

METHODS: This was a prospective study of consecutive patients who had received recent povidone 5% solution for sterile preparation of intravitreal injection less than 3 months prior to inclusion with a total of at least 3 intravitreal injections for macular degeneration. Each patient had one study eye which was undergoing regular intravitreal injection and a fellow eye which was not undergoing any injections. Each patient underwent evaluations of various tear film parameters on a single occasion for both eyes. The primary outcome was severity of dry eye symptoms as measured by the Schein dry eye questionnaire. The secondary outcomes were tear film osmolality and corneal punctate staining using the Oxford Grading Scale.

RESULTS: A total of 90 patients were included in the study. 43.3% n = 39, were using ocular lubricating medication on a regular basis. A significantly greater proportion of study eyes had a Schein dry eye questionnaire score of 7 or higher; 12.2%, n = 11 amongst study eyes vs 4.4%, n = 4 amongst control, fellow eyes (p < 0.05). In terms of secondary outcomes, the study eyes had a slightly higher mean tear film osmolality compared to control, fellow eyes: 305.5 ± 1.7 in study eyes vs 302 ± 1.6 in control eyes although this difference was not statistically significant (p = 0.087). The study eyes had statistically significantly worse corneal staining as determined by the Oxford grading scale; 0.69 in study eyes vs 0.58 in control, fellow eyes (p = 0.02).

CONCLUSION: Our results confirm the detrimental impact of repeated application of povidone iodine for intravitreal injection procedures on symptoms of dry eyes as experienced and reported by patients.

PMID: 28166657

J Ocul Pharmacol Ther. 2017 Feb 6. [Epub ahead of print]

Intravitreal Antiangiogenic Therapy of Uveitic Macular Edema: A Review.

Kozak I, Shoughy SS, Stone DU.

Abstract: Uveitic (or inflammatory) macular edema (UME) is one of the most common cause of visual impairment in patients with uveitis and the most frequent structural complication of uveitis. The use of antiangiogenic agents in the management of macular edema due to inflammation is a fairly new approach. It is not entirely clear if these agents should be used as an adjunct to anti-inflammatory therapy or if they can be used as stand-alone agents in edema due to infections where immunosuppressive therapy could be detrimental to the resolution of infection. This treatment paradigm is largely borrowed from large randomized trials in other retinovascular diseases. Similar prospective studies are needed to clarify the role of antiangiogenic therapy in UME.

PMID: 28165851

Ophthalmology. 2017 Feb 1. [Epub ahead of print]

Factors Associated with Worsening Proliferative Diabetic Retinopathy in Eyes Treated with Panretinal Photocoagulation or Ranibizumab.

Bressler SB, Beaulieu WT, Glassman AR, Gross JG, Jampol LM, Melia M, Peters MA, Rauser ME; Diabetic Retinopathy Clinical Research Network.

PURPOSE: To compare rates and identify predictive factors for events that represent worsening of proliferative diabetic retinopathy (PDR) in eyes treated with panretinal photocoagulation (PRP) or ranibizumab.

DESIGN: Randomized clinical trial (55 United States sites).

PARTICIPANTS: Three hundred ninety-four study eyes from 305 adults with PDR, visual acuity (VA) 20/320 or better, and no history of PRP.

INTERVENTION: Panretinal photocoagulation or intravitreal ranibizumab injections (0.5 mg/0.05 ml).

MAIN OUTCOME MEASURES: Time from randomization to a composite PDR-worsening outcome defined as the first occurrence of vitreous hemorrhage, retinal detachment, anterior segment neovascularization, or neovascular glaucoma.

RESULTS: Through 2 years, the cumulative probability of worsening PDR was 42% (PRP) versus 34% (ranibizumab; hazard ratio [HR], 1.33; 99% confidence interval [CI], 0.90 to 1.98; $P = 0.063$). Worse baseline levels of diabetic retinopathy severity (Early Treatment Diabetic Retinopathy Study scale) were associated with increased risk of worsening PDR, regardless of treatment group (64% [high-risk PDR or worse] vs. 23% [moderate PDR or better]; HR, 3.97; 99% CI, 2.48 to 6.36; $P < 0.001$). In the PRP group, eyes receiving pattern scan versus conventional single-spot PRP also were at higher risk for worsening PDR (60% vs. 39%; HR, 2.04; 99% CI, 1.02 to 4.08; $P = 0.008$), regardless of the number of spots placed or the number of sittings to complete the initial PRP. Eyes in both groups with vision-impairing (VA 20/32 or worse) center-involved diabetic macular edema (DME) at baseline were required to receive ranibizumab for center-involved DME. Therefore the composite outcome was compared by treatment in the subgroup of eyes that did not have vision-impairing center-involved DME at baseline. For these eyes, the rate of PDR-

worsening was greater with PRP than ranibizumab (45% vs. 31%; HR, 1.62; 99% CI, 91.01 to 2.60; P = 0.008).

CONCLUSIONS: In eyes with PDR, ranibizumab resulted in less PDR worsening compared with PRP, especially in eyes not required to receive ranibizumab for center-involved DME. Although anti-vascular endothelial growth factor therapy requires a more frequent visit schedule than PRP, these findings provide additional evidence supporting the use of ranibizumab as an alternative therapy to PRP for PDR, at least through 2 years.

PMID: 28161147

Graefes Arch Clin Exp Ophthalmol. 2017 Feb 4. [Epub ahead of print]

Combined VEGF and PDGF inhibition for neovascular AMD: anti-angiogenic properties of axitinib on human endothelial cells and pericytes in vitro.

Siedlecki J, Wertheimer C, Wolf A, Liegl R, Priglinger C, Priglinger S, Eibl-Lindner K.

PURPOSE: Drugs currently approved for neovascular age-related macular degeneration (nAMD) offer anti-VEGF monotherapy only. Platelet-derived growth factor (PDGF) signaling is pivotal to pericyte-induced stabilization of choroidal neovascularizations (CNV), and causes partial anti-VEGF resistance. No combination therapy for VEGF and PDGF has been approved yet. Axitinib is a tyrosine kinase inhibitor interfering with VEGF and PDGF signaling, and has been approved for the treatment of renal cell carcinoma. This study evaluates anti-angiogenic properties of axitinib in an in-vitro model of choroidal neovascularizations in nAMD.

METHODS: Human endothelial cells (HUVEC) and human pericytes (hPC-PL) were treated with axitinib doses ranging from 1.0 ng/ml to 10 µg/ml. Cellular viability and proliferation were assessed with a modified MTT assay. VEGF- and PDGF-stimulated migration was observed in modified Boyden chambers. Formation of capillary structures was evaluated on Cultrex basement membrane.

RESULTS: Proliferation was significantly inhibited in both cell lines in a dose-dependent manner. VEGF and PDGF significantly induced, whereas simultaneous axitinib normalized cellular migration in HUVEC and pericytes. On growth-factor-reduced Cultrex, VEGF induced the formation of capillary structures, while axitinib significantly reverted this effect. Axitinib reduced the amount of vessel associated tissue on full growth factor Cultrex. All effects on both cell lines were observed in non-toxic concentrations of axitinib.

CONCLUSIONS: Axitinib inhibits angiogenesis in endothelial cells and pericytes via VEGFR and PDGFR modulation in vitro. Further studies are needed to elucidate whether axitinib may also improve therapy of CNV in AMD in vivo by interference with pericyte stabilization of pathological vessels.

PMID: 28161830

Biol Pharm Bull. 2017;40(2):145-150.

Development of a Sustainable Release System for a Ranibizumab Biosimilar Using Poly(lactic-co-glycolic acid) Biodegradable Polymer-Based Microparticles as a Platform.

Tanetsugu Y, Tagami T, Terukina T, Ogawa T, Ohta M, Ozeki T.

Abstract: Ranibizumab is a humanized monoclonal antibody fragment against vascular endothelial growth factor (VEGF)-A and is widely used to treat age-related macular degeneration (AMD) caused by angiogenesis. Ranibizumab has a short half-life in the eye due to its low molecular weight and susceptibility to proteolysis. Monthly intravitreal injection of a large amount of ranibizumab formulation is a burden for both patients and medical staff. We therefore sought to develop a sustainable release system for treating the eye with ranibizumab using a drug carrier. A ranibizumab biosimilar (RB) was incorporated into

microparticles of poly(lactic-co-glycolic acid) (PLGA) biodegradable polymer. Ranibizumab was sustainably released from PLGA microparticles (80+% after 3 weeks). Assay of tube formation by endothelial cells indicated that RB released from PLGA microparticles inhibited VEGF-induced tube formation and this tendency was confirmed by a cell proliferation assay. These results indicate that RB-loaded PLGA microparticles are useful for sustainable RB release and suggest the utility of intraocular sustainable release systems for delivering RB site-specifically to AMD patients.

PMID: 28154252

Other treatment & diagnosis

Dan Med J. 2017 Feb;64(2).

Elderly people need an eye examination before entering nursing homes.

Jensen H, Tubæk G.

INTRODUCTION: It is well documented that eye diseases develop with ageing and thus more elderly people have a visual handicap. It is important that the elderly are examined well, that they have the correct prescription and optimal aids. This is especially applicable to those residing in nursing homes.

METHOD: In this study, an eye examination was offered to all residents in 11 nursing homes. The examination was conducted by an optometrist who brought her own equipment. A medical history was recorded, an eye examination conducted, and the ophthalmologist assessed the records and evaluated the optical coherence tomography images. Personnel were given a questionnaire concerning their assessment of the residents' visual abilities.

RESULTS: Among 502 potential residents, 371 were examined, whereas 131 could not participate. A total of 22% were visually impaired, 13% socially blind and 13% were unable to cooperate. A total of 32% were well-described having correct optics, 15% were recommended glasses and 36% were referred to an ophthalmologist for further diagnostics or check-up. The most frequent cause of impaired vision was cataract and age-related macular degeneration. For many of the residents, no diagnosis was registered, and the staff had no knowledge of the cause of their resident's vision impairment. Furthermore, in one of every four cases, staff were unaware that the resident's vision was impaired.

CONCLUSION: It is recommended that everyone who is referred to a retirement home receives an eye examination and that nursing home staff are given relevant knowledge that will allow them to assist the residents in a proper way due to vision-related issues.

PMID: 28157061

IEEE Trans Med Imaging. 2017 Feb 8. [Epub ahead of print]

Joint segmentation of retinal layers and focal lesions in 3D OCT data of topologically disrupted retinas.

Novosel J, Vermeer K, de Jong JH, Wang Z, Van Vliet L.

Abstract: Accurate quantification of retinal structures in 3D optical coherence tomography data of eyes with pathologies provides clinically relevant information. We present an approach to jointly segment retinal layers and lesions in eyes with topology-disrupting retinal diseases by a loosely coupled level sets framework. In the new approach, lesions are modelled as an additional space-variant layer delineated by auxiliary interfaces. Furthermore, the segmentation of interfaces is steered by local differences in the signal between adjacent retinal layers thereby allowing the approach to handle local intensity variations. The accuracy of the proposed method of both layer and lesion segmentation has been evaluated on eyes affected by central serous retinopathy and age-related macular degeneration. Additionally, layer

segmentation of the proposed approach was evaluated on eyes without topology-disrupting retinal diseases. A good agreement between the segmentation performed manually by a medical doctor and results obtained from the automatic segmentation was found for all datatypes. The mean unsigned error for all interfaces varied between 2.3 and 11.9 μm (0.6 - 3.1 pixels). Furthermore, lesion segmentation showed a Dice coefficient of 0.68 for drusen and 0.89 for fluid pockets. Overall, the method provides a flexible and accurate solution to jointly segment lesions and retinal layers.

PMID: 28186886

OMICS. 2017 Feb;21(2):114-122.

Toward Postgenomics Ophthalmology: A Proteomic Map of the Human Choroid-Retinal Pigment Epithelium Tissue.

Dammalli M, Murthy KR, Pinto SM, Murthy KB, Nirujogi RS, Madugundu AK, Dey G, Nair B, Gowda H, Keshava Prasad TS.

Abstract: Ophthalmology and visual health research have received relatively limited attention from the personalized medicine community, but this trend is rapidly changing. Postgenomics technologies such as proteomics are being utilized to establish a baseline biological variation map of the human eye and related tissues. In this context, the choroid is the vascular layer situated between the outer sclera and the inner retina. The choroidal circulation serves the photoreceptors and retinal pigment epithelium (RPE). The RPE is a layer of cuboidal epithelial cells adjacent to the neurosensory retina and maintains the outer limit of the blood-retina barrier. Abnormal changes in choroid-RPE layers have been associated with age-related macular degeneration. We report here the proteome of the healthy human choroid-RPE complex, using reverse phase liquid chromatography and mass spectrometry-based proteomics. A total of 5309 nonredundant proteins were identified. Functional analysis of the identified proteins further pointed to molecular targets related to protein metabolism, regulation of nucleic acid metabolism, transport, cell growth, and/or maintenance and immune response. The top canonical pathways in which the choroid proteins participated were integrin signaling, mitochondrial dysfunction, regulation of eIF4 and p70S6K signaling, and clathrin-mediated endocytosis signaling. This study illustrates the largest number of proteins identified in human choroid-RPE complex to date and might serve as a valuable resource for future investigations and biomarker discovery in support of postgenomics ophthalmology and precision medicine.

PMID: 28186866

Retina. 2017 Feb 6. [Epub ahead of print]

ASSOCIATION OF DRUSEN VOLUME WITH CHOROIDAL PARAMETERS IN NONNEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Balasubramanian S, Lei J, Nittala MG, Velaga SB, Haines J, Pericak-Vance MA, Stambolian D, Sadda SR.

PURPOSE: The choroid is thought to be relevant to the pathogenesis of nonneovascular age-related macular degeneration, but its role has not yet been fully defined. In this study, we evaluate the relationship between the extent of macular drusen and specific choroidal parameters, including thickness and intensity.

METHODS: Spectral domain optical coherence tomography images were collected from two distinct, independent cohorts with nonneovascular age-related macular degeneration: Amish (53 eyes of 34 subjects) and non-Amish (40 eyes from 26 subjects). All spectral domain optical coherence tomography scans were obtained using the Cirrus HD-OCT with a 512 $\times$ 128 macular cube (6 $\times$ 6 mm) protocol. The Cirrus advanced retinal pigment epithelium analysis tool was used to automatically compute drusen volume within 3 mm (DV3) and 5 mm (DV5) circles centered on the fovea. The inner and outer borders of the choroid were manually segmented, and the mean choroidal thickness and choroidal intensity (i.e., brightness) were calculated. The choroidal intensity was normalized against the vitreous and nerve fiber

layer reflectivity. The correlation between DV and these choroidal parameters was assessed using Pearson and linear regression analysis.

RESULTS: A significant positive correlation was observed between normalized choroidal intensity and DV5 in the Amish ($r = 0.42$, $P = 0.002$) and non-Amish ($r = 0.33$, $P = 0.03$) cohorts. Also, DV3 showed a significant positive correlation with normalized choroidal intensity in both the groups (Amish: $r = 0.30$, $P = 0.02$; non-Amish: $r = 0.32$, $P = 0.04$). Choroidal thickness was negatively correlated with normalized choroidal intensity in both Amish ($r = -0.71$, $P = 0.001$) and non-Amish ($r = -0.43$, $P = 0.01$) groups. Normalized choroidal intensity was the most significant constant predictor of DV in both the Amish and non-Amish groups.

CONCLUSION: Choroidal intensity, but not choroidal thickness, seems to be associated with drusen volume in Amish and non-Amish populations. These observations suggest that choroidal parameters beyond thickness warrant further study in the setting of age-related macular degeneration.

PMID: 28169876

Neurophotonics. 2017 Jan;4(1):011012. Epub 2017 Feb 6.

Semiautomated segmentation and analysis of retinal layers in three-dimensional spectral-domain optical coherence tomography images of patients with atrophic age-related macular degeneration.

Hu Z, Shi Y, Nandan K, Sadda SR; APGS Study Group.

Abstract: Historically, regular drusen and geographic atrophy (GA) have been recognized as the hallmarks of nonneovascular age-related macular degeneration (AMD). Recent imaging developments have revealed another distinct nonneovascular AMD phenotype, reticular pseudodrusen (RPD). We develop an approach to semiautomatically quantify retinal surfaces associated with various AMD lesions (i.e., regular drusen, RPD, and GA) in spectral domain (SD) optical coherence tomography (OCT) images. More specifically, a graph-based algorithm was used to segment multiple retinal layers in SD-OCT volumes. Varying surface feasibility constraints based on the presegmentation were applied on the double-surface graph search to refine the surface segmentation. The thicknesses of these layers and their correlation with retinal functional measurements, including microperimetry (MP) sensitivity and visual acuity (VA), were investigated. The photoreceptor outer segment layer demonstrated significant thinning with a reduction in MP sensitivity and VA score when atrophic AMD lesions were present. Regular drusen and RPD were separately segmented on SD-OCT images to allow their characteristics and distribution to be studied separately. The mean thickness of regular drusen was found to significantly correlate with the VA score. RPD appeared to be distributed evenly throughout the macula and regular drusen appeared to be more concentrated centrally.

PMID: 28180131 PMCID: PMC5294229 [Available on 2018-02-06]

Arch Soc Esp Oftalmol. 2017 Feb 3. [Epub ahead of print]

Difficulties in the management of retinal capillary haemangiomas associated with von Hippel Lindau disease. [Article in English, Spanish]

Pastor-Montoro M, Hurtado-Montalbán N, Martínez-Morales JA, Villegas-Pérez MP.

CLINICAL CASE: A 29-year-old female with bilateral retinal capillary haemangiomas (RCH). A genetic analysis was carried out due to the suspicion of von Hippel-Lindau (VHL) disease, with negative results on 2 occasions. There was progression of the RCH in the left eye, leading to a macular epiretinal membrane. The patient was treated with laser, intravitreal ranibizumab, and vitrectomy. Finally, a third genetic test detected a de novo mutation in the VHL gene, and led to the genetic diagnosis.

DISCUSSION: VHL syndrome causes a complex ocular disease with a difficult diagnosis that requires early treatment of the RCH in order to modify its visual prognosis.

PMID: 28169069

Neuroophthalmology. 2013 Sep 24;37(5):192-197. eCollection 2013.

Functional Magnetic Resonance Imaging in Patients with the Wet Form of Age-Related Macular Degeneration.

Lešták J, Tintěra J, Karel I, Svatá Z, Rozsival P.

Abstract: The study is designed to determine the relationship between the progress of the wet form of age-related macular degeneration and the activity of the visual cortex examined using functional magnetic resonance imaging. Ten patients with the wet form of age-related macular degeneration (9 female and 1 male) with a mean age of 74.7 years (58-85 years) at various stages of bilateral involvement of the disease were included. Patients did not suffer from any other ocular nor neurological disease. All the patients underwent functional magnetic resonance imaging examinations with stimulation of both eyes using a black-and-white checkerboard of size 25.8 × 16.2 degrees. The group was compared with a group of healthy subjects with an average age of 54.1 years (45-65 years). For statistical evaluation, the Mann-Whitney U test was used. Comparing the extent of visual cortex activations we found a statistically significant difference between both the groups ($p = 0.0247$). However, the dependence of functional magnetic resonance imaging activity on visual acuity was not statistically significant ($p = 0.223$). We conclude that in patients with the wet form of age-related macular degeneration, lower functional magnetic resonance imaging activity of the visual cortex was found compared with the control group of healthy subjects. Dependence of functional magnetic resonance imaging activity on visual acuity was not statistically significant.

PMID: 28167987 PMCID: PMC5291073

Comput Biol Med. 2017 Jan 27;82:80-86. [Epub ahead of print]

Comparing humans and deep learning performance for grading AMD: A study in using universal deep features and transfer learning for automated AMD analysis.

Burlina P, Pacheco KD, Joshi N, Freund DE, Bressler NM.

BACKGROUND: When left untreated, age-related macular degeneration (AMD) is the leading cause of vision loss in people over fifty in the US. Currently it is estimated that about eight million US individuals have the intermediate stage of AMD that is often asymptomatic with regard to visual deficit. These individuals are at high risk for progressing to the advanced stage where the often treatable choroidal neovascular form of AMD can occur. Careful monitoring to detect the onset and prompt treatment of the neovascular form as well as dietary supplementation can reduce the risk of vision loss from AMD, therefore, preferred practice patterns recommend identifying individuals with the intermediate stage in a timely manner.

METHODS: Past automated retinal image analysis (ARIA) methods applied on fundus imagery have relied on engineered and hand-designed visual features. We instead detail the novel application of a machine learning approach using deep learning for the problem of ARIA and AMD analysis. We use transfer learning and universal features derived from deep convolutional neural networks (DCNN). We address clinically relevant 4-class, 3-class, and 2-class AMD severity classification problems.

RESULTS: Using 5664 color fundus images from the NIH AREDS dataset and DCNN universal features, we obtain values for accuracy for the (4-, 3-, 2-) class classification problem of (79.4%, 81.5%, 93.4%) for machine vs. (75.8%, 85.0%, 95.2%) for physician grading.

DISCUSSION: This study demonstrates the efficacy of machine grading based on deep universal features/transfer learning when applied to ARIA and is a promising step in providing a pre-screener to identify individuals with intermediate AMD and also as a tool that can facilitate identifying such individuals for clinical studies aimed at developing improved therapies. It also demonstrates comparable performance between computer and physician grading.

PMID: 28167406

Invest Ophthalmol Vis Sci. 2017 Feb 1;58(2):907-913.

Is Choroidal or Scleral Thickness Related to Myopic Macular Degeneration?

Wong CW, Phua V, Lee SY, Wong TY, Cheung CM.

PURPOSE: The relative contribution of mechanical and vascular factors to the pathogenesis of myopic macular degeneration (MMD) is unclear. To address this gap, we examined the association of choroidal thickness (CT) and scleral thickness (ST) with MMD.

METHODS: Prospective, clinic-based case series of 62 eyes of 41 patients with high myopia (≤ -6 diopters or axial length ≥ 26.5 mm). Swept-source optical coherence tomography (SSOCT) was performed to measure subfoveal CT and ST. Myopic macular degeneration was graded from fundus photographs according to the International Meta-Analysis for Pathologic Myopia (META-PM) classification. Presence of MMD was defined as META-PM category ≥ 2 and severe MMD was defined as category ≥ 3 .

RESULTS: The distribution of MMD severity was 15 (24.2%) in category 1, 28 (45.2%) in category 2, 10 (16.1%) in category 3, and 9 (14.5%) in category 4. Correlation of MMD severity was strong for subfoveal CT ($r = -0.70$, $P < 0.001$) but weak for subfoveal ST ($r = -0.31$, $P = 0.01$). Subfoveal CT, but not ST, was independently associated with presence of MMD (age and gender adjusted odds ratio [OR] per 10 μm decrease in CT 1.41, $P = 0.002$), and subfoveal CT, but not subfoveal ST, was significantly thinner in eyes with severe MMD ($\geq$ category 3) than in eyes with mild MMD (CT: $31.5 \pm 40.5 \mu\text{m}$ versus $82.0 \pm 57.1 \mu\text{m}$, $P < 0.001$; ST: $261.6 \pm 78.5 \mu\text{m}$ versus $297.0 \pm 73.8 \mu\text{m}$, $P = 0.09$).

CONCLUSIONS: We demonstrated significant thinning of the choroid with increasing MMD severity. In contrast, ST was weakly correlated with MMD. These data suggest progressive loss of choroid may be important in the pathogenesis of MMD.

PMID: 28166316

Retina. 2017 Feb 3. [Epub ahead of print]

PREDICTIVE FACTORS FOR DEVELOPMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: A Spectral-Domain Optical Coherence Tomography Study.

Fragiotta S, Rossi T, Cutini A, Genga PL, Vingolo EM.

PURPOSE: To investigate the risk factors predictive for the development of neovascular age-related macular degeneration (NVAMD) by means of spectral-domain optical coherence tomography.

METHODS: Retrospective study of 73 eyes graded Stage 2 and Stage 3 according to the AMD International Grading System with minimum follow-up of 24 months. Drusenoid pigment epithelial detachment, hyperreflective foci, external limiting membrane, inner ellipsoid band, and retinal pigment epithelium integrity were analyzed at baseline and last follow-up. Binary logistic regression model analyzed significant predictors of neovascular conversion.

RESULTS: The discontinuity of external limiting membrane, inner ellipsoid band, and retinal pigment epithelium bands were significantly more prevalent in the NVAMD group at baseline and last follow-up ($P < 0.001$). Hyperreflective foci represented the single most important predictor of neovascular conversion (Exp [B], 15.15; $P = 0.005$) as confirmed by Kaplan-Meier curve ($P = 0.002$). Drusenoid pigment epithelial detachment width was significantly greater in NVAMD group than control subjects at baseline and last follow-up ($P < 0.001$), and its delta value also resulted a significant neovascular predictor (Exp [B], 0.99; $P = 0.04$).

CONCLUSION: Hyperreflective foci significantly increase the risk of NVAMD progression. The delta width of drusenoid pigment epithelial detachment also predicts disease progression, integrating the stratification of NVAMD progression risk.

PMID: 28166160

Asia Pac J Ophthalmol (Phila). 2017 Jan-Feb;6(1):70-79.

The Use of Microperimetry to Detect Functional Progression in Non-Neovascular Age-Related Macular Degeneration: A Systematic Review.

Wong EN, Chew AL, Morgan WH, Patel PJ, Chen FK.

Abstract: We reviewed the current literature on the ability of microperimetry to detect non-neovascular age-related macular degeneration (AMD) disease progression. The index test was retinal sensitivity measurement assessed by microperimetry and comparators were other functional measures (best-corrected and low-luminance visual acuities, and fixation stability) and structural parameters [retinal thickness, choroidal thickness, and area of geographic atrophy (GA) determined by color fundus photographs, short-wave or near-infrared fundus autofluorescence]. The reference standard was area of GA. The literature search was conducted in January 2016 and included MEDLINE, EMBASE, the Cochrane Library, Biosis, Science Citation Index, ProQuest Health and Medicine, CINAHL, and Highwire Press. We included 6 studies that enrolled 41 eyes with intermediate AMD (from a single study) and 80 eyes with GA secondary to AMD. Retinal sensitivity measured by microperimetry was the only functional measure that consistently detected progression in each cohort. Insufficient reported data precluded meta-analysis. Various microperimetry parameters were used to assess cohort-level change in retinal sensitivity, but the methods of analysis have yet to mature in complexity in comparison with established glaucoma field progression analysis. Microperimetry-assessed retinal sensitivity measurement may be more sensitive in detecting progression than other functional measures in non-neovascular AMD. However, the lack of standardized testing protocol and methods of progression analysis hindered comparison. Harmonization of testing protocol and development of more robust methods of analyzing raw microperimetric data will facilitate clinical implementation of this valuable retinal assessment tool.

PMID: 28161925

Ophthalmology. 2017 Jan 30. [Epub ahead of print]

Histologic and Optical Coherence Tomographic Correlates in Drusenoid Pigment Epithelium Detachment in Age-Related Macular Degeneration.

Balaratnasingam C, Messinger JD, Sloan KR, Yannuzzi LA, Freund KB, Curcio CA.

PURPOSE: Drusenoid pigment epithelium detachment (DPED) is a known precursor to geographic atrophy in age-related macular degeneration (AMD). We sought histologic correlates for spectral-domain (SD) optical coherence tomography (OCT) signatures in DPED and determined the frequency and origin of these OCT signatures in a clinical cohort of DPED eyes.

DESIGN: Laboratory imaging and histologic comparison, and retrospective, observational cohort study.

PARTICIPANTS: Four donor eyes with histopathologic diagnosis of AMD (2 with nonneovascular DPED and 2 with neovascular pigment epithelium detachment [PED]) and 49 eyes of 33 clinic patients with nonneovascular DPED more than 2 mm in diameter.

METHODS: Donor eyes underwent multimodal ex vivo imaging, including SD OCT, then processing for high-resolution histologic analysis. All clinic patients underwent SD OCT, near-infrared reflectance, and color photography.

MAIN OUTCOME MEASURES: Histologic correlates for SD OCT signatures in DPED, estimate of coverage by different retinal pigment epithelium (RPE) phenotypes in the DPED surface; frequency and origin of histologically verified SD OCT signatures in a clinical cohort of DPED eyes, and comparisons of histologic features between neovascular PED and DPED resulting from AMD.

RESULTS: Intraretinal and subretinal hyperreflective foci as seen on SD OCT correlated to RPE cells on histologic examination. Hypertransmission of light below the RPE-basal lamina band correlated with dissociated RPE. Subretinal hyperreflective material resulting from acquired vitelliform lesions

corresponded to regions of apically expelled RPE organelles. In the clinical cohort, all histologically verified reflectivity signatures were visible and quantifiable. The appearance of intraretinal hyperreflective foci was preceded by thickening of the RPE-basal lamina band. Compared with PEDs associated with neovascular AMD, DPEDs had different crystallization patterns, no lipid-filled cells, and thinner basal laminar deposits.

CONCLUSIONS: Multiple RPE fates in AMD, including intraretinal cells that are highly prognostic for progression, can be followed and quantified reliably using eye-tracked serial SD OCT. This information may be particularly useful for obtaining an accurate timeline of incipient geographic atrophy in clinic populations and for quantifying anatomic end points and response to therapy in AMD clinical trials.

PMID: 28153442

Pathogenesis

Oncotarget. 2017 Feb 1. [Epub ahead of print]

Nitration of tyrosines in complement factor H domains alters its immunological activity and mediates a pathogenic role in age related macular degeneration.

Krilis M, Qi M, Madigan MC, Wong JW, Abdelatti M, Guymer RH, Whitelock J, McCluskey P, Zhang P7, Qi J, Hunyor AP, Krilis SA, Giannakopoulos B.

Abstract: Nitrosative stress has been implicated in the pathogenesis of age related macular degeneration (AMD). Tyrosine nitration is a unique type of post translational modification that occurs in the setting of inflammation and nitrosative stress. To date, the significance and functional implications of tyrosine nitration of complement factor H (CFH), a key complement regulator in the eye has not been explored, and is examined in this study in the context of AMD pathogenesis. Sections of eyes from deceased individuals with AMD (n = 5) demonstrated the presence of immunoreactive nitrotyrosine CFH. We purified nitrated CFH from retinæ from 2 AMD patients. Mass spectrometry of CFH isolated from AMD eyes revealed nitrated residues in domains critical for binding to heparan sulphate glycosaminoglycans (GAGs), lipid peroxidation by-products and complement (C) 3b. Functional studies revealed that nitrated CFH did not bind to lipid peroxidation products, nor to the GAG of perlecan nor to C3b. There was loss of cofactor activity for Factor I mediated cleavage of C3b with nitrated CFH compared to non-nitrated CFH. CFH inhibits, but nitrated CFH significantly potentiates, the secretion of the pro-inflammatory and angiogenic cytokine IL-8 from monocytes that have been stimulated with lipid peroxidation by-products. AMD patients (n = 30) and controls (n = 30) were used to measure plasma nitrated CFH using a novel ELISA. AMD patients had significantly elevated nitrated CFH levels compared to controls (p = 0.0117). These findings strongly suggest that nitrated CFH contributes to AMD progression, and is a target for therapeutic intervention.

PMID: 28159936

Sci Rep. 2017 Feb 10;7:42546.

Gene Transfer of Prolyl Hydroxylase Domain 2 Inhibits Hypoxia-inducible Angiogenesis in a Model of Choroidal Neovascularization.

Takei A, Ekström M, Mammadzada P, Aronsson M, Yu M, Kvant A, André H.

Abstract: Cellular responses to hypoxia are mediated by the hypoxia-inducible factors (HIF). In normoxia, HIF- α proteins are regulated by a family of dioxygenases, through prolyl and asparagyl hydroxylation, culminating in proteasomal degradation and transcriptional inactivation. In hypoxia, the dioxygenases become inactive and allow formation of HIF transcription factor, responsible for upregulation of hypoxia genes. In ocular neoangiogenic diseases, such as neovascular age-related macular degeneration (nAMD), hypoxia seems pivotal. Here, we investigate the effects of HIF regulatory proteins on the hypoxia pathway in retinal pigment epithelium (RPE) cells, critically involved in nAMD pathogenesis. Our data indicates that,

in ARPE-19 cells, prolyl hydroxylase domain (PHD)2 is the most potent negative-regulator of the HIF pathway. The negative effects of PHD2 on the hypoxia pathway were associated with decreased HIF-1 α protein levels, and concomitant decrease in angiogenic factors. ARPE-19 cells stably expressing PHD2 impaired angiogenesis in vitro by wound healing, tubulogenesis, and sprouting assays, as well as in vivo by iris-induced angiogenesis. Gene transfer of PHD2 in vivo resulted in mitigation of HIF-mediated angiogenesis in a mouse model of nAMD. These results may have implications for the clinical treatment of nAMD patients, particularly regarding the use of gene therapy to negatively regulate neoangiogenesis.

PMID: 28186209 PMCID: PMC5301234

Mater Sci Eng C Mater Biol Appl. 2017 Apr 1;73:300-309. Epub 2016 Nov 24.

Controlled surface morphology and hydrophilicity of polycaprolactone toward human retinal pigment epithelium cells.

Shahmoradi S, Yazdian F, Tabandeh F, Soheili ZS, Hatamian Zarami AS, Navaei-Nigjeh M.

Abstract: Applying scaffolds as a bed to enhance cell proliferation and even differentiation is one of the treatment of retina diseases such as age-related macular degeneration (AMD) which deteriorating photoreceptors and finally happening blindness. In this study, aligned polycaprolactone (PCL) nanofibers were electrospun and at different conditions and their characteristics were measured by scanning electron microscope (SEM) and contact angle. Response surface methodology (RSM) was used to optimize the diameter of fabricated nanofibers. Two factors as solution concentration and voltage value were considered as independent variables and their effects on nanofibers' diameters were evaluated by central composite design and the optimum conditions were obtained as 0.12g/mL and 20kV, respectively. In order to decrease the hydrophobicity of PCL, the surface of the fabricated scaffolds was modified by alkaline hydrolysis method. Contact time of the scaffolds and alkaline solution and concentration of alkaline solution were optimized using Box Behnken design and (120min and 5M were the optimal, respectively). Contact angle measurement showed the high hydrophilicity of treated scaffolds (with contact angle 7.48°). Plasma surface treatment was applied to compare the effect of using two kinds of surface modification methods simultaneously on hydrolyzed scaffolds. The RPE cells grown on scaffolds were examined by immunocytochemistry (ICC), MTT and continuous inspection of cellular morphology. Interestingly, Human RPE cells revealed their characteristic morphology on hydrolyzed scaffold well. As a result, we introduced a culture substrate with low diameter (185.8nm), high porosity (82%) and suitable hydrophilicity (with contact angle 7.48 degree) which can be promising for hRPE cell transplantation.

PMID: 28183612

Clin Ophthalmol. 2017 Jan 17;11:179-184. eCollection 2017.

Circulating monocytes and B-lymphocytes in neovascular age-related macular degeneration.

Hector SM, Sørensen TL.

BACKGROUND: Individuals with neovascular age-related macular degeneration (AMD) have altered number and distribution of retinal macrophages and show changes in circulating antibodies. We wanted to investigate the corresponding precursors, with subpopulations. We therefore measured monocyte and B-lymphocyte populations in individuals with neovascular AMD.

DESIGN: This was an observational case-control study.

PARTICIPANTS OR SAMPLES: A total of 31 individuals with neovascular AMD and 30 healthy age-matched controls were included.

METHODS: Patients and controls were interviewed, and ophthalmological examination included visual acuity assessment using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, spectral domain

optical coherence tomography (SD-OCT), slit-lamp examination and fundus photography. Moreover, venous blood was drawn and prepared for flow cytometry. Cells were gated and measured for surface markers.

MAIN OUTCOME MEASURES: Relative amounts of monocytes and B-lymphocytes with subsets, as well as selected surface markers, were measured.

RESULTS: The two groups did not significantly differ in age, smoking history, body mass index, physical activity or C-reactive protein (CRP). Total monocytes (percentage of all leukocytes) were lower in the neovascular AMD group (median 5.5%) compared with the level in the control group (6.5%; P-value: 0.028). The percentage of intermediate monocytes positive for cluster of differentiation 11b (CD11b) was lower for AMD patients (99.4%) compared with 100% for the control group (P-value: 0.032).

CONCLUSION: We observed lower numbers of monocytes, which show a potentially impaired ability to migrate across the endothelial wall in patients with neovascular AMD. These subtle changes could potentially lead to an imbalance in the recruitment of macrophages into the retina during disease development.

PMID: 28176950 PMCID: PMC5261845

Mol Ther. 2012 Apr;20(4):788-797. Epub 2016 Dec 6.

Stanniocalcin-1 Rescued Photoreceptor Degeneration in Two Rat Models of Inherited Retinal Degeneration.

Roddy GW, Rosa RH Jr, Youn Oh J, Ylostalo JH, Bartosh TJ Jr, Choi H, Lee RH, Yasumura D, Ahern K, Nielsen G, Matthes MT, LaVail MM, Prockop DJ.

Abstract: Oxidative stress and photoreceptor apoptosis are prominent features of many forms of retinal degeneration (RD) for which there are currently no effective therapies. We previously observed that mesenchymal stem/stromal cells reduce apoptosis by being activated to secrete stanniocalcin-1 (STC-1), a multifunctional protein that reduces oxidative stress by upregulating mitochondrial uncoupling protein-2 (UCP-2). Therefore, we tested the hypothesis that intravitreal injection of STC-1 can rescue photoreceptors. We first tested STC-1 in the rhodopsin transgenic rat characterized by rapid photoreceptor loss. Intravitreal STC-1 decreased the loss of photoreceptor nuclei and transcripts and resulted in measurable retinal function when none is otherwise present in this rapid degeneration. We then tested STC-1 in the Royal College of Surgeons (RCS) rat characterized by a slower photoreceptor degeneration. Intravitreal STC-1 reduced the number of pyknotic nuclei in photoreceptors, delayed the loss of photoreceptor transcripts, and improved function of rod photoreceptors. Additionally, STC-1 upregulated UCP-2 and decreased levels of two protein adducts generated by reactive oxygen species (ROS). Microarrays from the two models demonstrated that STC-1 upregulated expression of a similar profile of genes for retinal development and function. The results suggested that intravitreal STC-1 is a promising therapy for various forms of RD including retinitis pigmentosa and atrophic age-related macular degeneration (AMD).

PMID: 28160614

Proc SPIE Int Soc Opt Eng. 2016 Feb 13;9706. Epub 2016 Mar 7.

Biophysical mechanism of transient retinal phototropism in rod photoreceptors.

Zhao X, Thapa D, Wang B, Gai S, Yao X.

Abstract: Oblique light stimulation evoked transient retinal phototropism (TRP) has been recently detected in frog and mouse retinas. High resolution microscopy of freshly isolated retinas indicated that the TRP is predominated by rod photoreceptors. Comparative confocal microscopy and optical coherence tomography (OCT) revealed that the TRP predominantly occurred from the photoreceptor outer segment (OS).

However, biophysical mechanism of rod OS change is still unknown. In this study, frog retinal slices, which open a cross section of retinal photoreceptor and other functional layers, were used to test the effect of light stimulation on rod OS. Near infrared light microscopy was employed to monitor photoreceptor changes in retinal slices stimulated by a rectangular-shaped visible light flash. Rapid rod OS length change was observed after the stimulation delivery. The magnitude and direction of the rod OS change varied with the position of the rods within the stimulated area. In the center of stimulated region the length of the rod OS shrunk, while in the peripheral region the rod OS tip swung towards center region in the plane perpendicular to the incident stimulus light. Our experimental result and theoretical analysis suggest that the observed TRP may reflect unbalanced disc-shape change due to localized pigment bleaching. Further investigation is required to understand biochemical mechanism of the observed rod OS kinetics. Better study of the TRP may provide a noninvasive biomarker to enable early detection of age-related macular degeneration (AMD) and other diseases that are known to produce retinal photoreceptor dysfunctions.

PMID: 28163347 PMCID: PMC5289741

J Med Chem. 2017 Feb 3. [Epub ahead of print]

Structure-based library design and fragment screening for the identification of reversible complement Factor D protease inhibitors.

Vulpetti A, Randl S, Rüdiger S, Ostermann N, Erbel P, MacSweeney A, Zoller T, Salem B, Gerhartz B, Cumin F, Hommel U, Dalvit C, Lorthiois E, Maibaum J.

Abstract: Chronic dysregulation of alternative complement pathway activation has been associated with diverse clinical disorders including age-related macular degeneration and paroxysmal nocturnal hemoglobinuria. Factor D is a trypsin-like serine protease with a narrow specificity for arginine in the P1 position, which catalyses the first enzymatic reaction of the amplification loop of the alternative pathway. In this paper, we describe two hit finding approaches leading to the discovery of new chemical matter for this pivotal protease of the complement system: in silico active site mapping for hot spots identification to guide rational structure-based design and NMR screening of focussed and diverse fragment libraries. The wealth of information gathered by these complementary approaches enabled the identification of ligands binding to different sub-pockets of the latent Factor D conformation and was instrumental for understanding the binding requirements for the generation of the first known potent non-covalent reversible Factor D inhibitors.

PMID: 28157311

Biochem Biophys Res Commun. 2017 Feb 1. [Epub ahead of print]

Activated microglia trigger inflammasome activation and lysosomal destabilization in human RPE cells.

Nebel C, Aslanidis A, Rashid K, Langmann T.

Abstract: Activation of the innate immune system plays a major role in retinal degenerative diseases including age-related macular degeneration (AMD). In this study, we investigated whether reactive microglia trigger and sustain NLRP3 inflammasome activation in human retinal pigment epithelium (ARPE-19) cells. Specifically, we analyzed the potential of cell culture supernatants from lipopolysaccharide (LPS)-stimulated human microglia in combination with the lysosomal destabilization agent Leu-Leu-O-Me (LLOMe) to activate the inflammasome in ARPE-19 cells. We found disorganization of ARPE-19 cytoskeletal structure after incubation with conditioned media of LPS-stimulated microglia and LLOMe and accumulation of lipid deposits in these cells using Nile Red staining. LC3-II, the active form of the autophagy marker microtubule-associated protein 1 light chain 3 beta (LC3B), was also elevated in ARPE-19 cells after inducing inflammasome activation. Finally, a significant increase of transcripts for IL-6, IL-8, IL-1 β , GM-CSF and CCL-2 was detected in ARPE-19 stimulated with both microglia-conditioned medium and

LLOMe. Our findings highlight a potential role of microglia in RPE inflammasome activation.

PMID: 28159556

Epidemiology

Eye (Lond). 2017 Feb 10. [Epub ahead of print]

Association between open-angle glaucoma and neovascular age-related macular degeneration: a case-control study.

Hu CC, Ho JD, Lin HC, Kao LT.

Purpose: To investigate the relationship between previously diagnosed open-angle glaucoma (OAG) and neovascular age-related macular degeneration (AMD) using a routine insurance dataset.

Methods: This study retrieved data from the Taiwan Longitudinal Health Insurance Database 2005. We found 3282 patients with neovascular AMD as cases and 13 128 sex- and age-matched subjects without neovascular AMD as controls. Conditional logistic regressions were performed to evaluate the association of neovascular AMD with previously diagnosed OAG among the sampled patients.

Results: Of the 16 410 sampled patients, 2.55% had previously diagnosed OAG, 5.06 and 1.92% for the cases and controls, respectively. The logistic regression analysis showed that the odds ratio (OR) of previously diagnosed OAG for cases was 2.45 (OR: 2.45; 95% confidence interval: 1.99-3.01) compared with the controls after adjusting for potential confounders. In addition, the adjusted ORs for previously diagnosed OAG were similar for patients with AMD in both genders (with an adjusted OR of 2.49 for males and 2.39 for females). Furthermore, it shows that OAG was significantly associated with neovascular AMD regardless of sex even after adjusting for monthly income, geographic region, urbanisation level, and comorbidities (with adjusted ORs of 2.49 for males and 2.39 for females).

Conclusions; This study demonstrated that patients with neovascular AMD had a higher odds of previously diagnosed OAG compared with those patients without neovascular AMD regardless of sex.

PMID: 28186508

Genetics

Hum Mol Genet. 2016 Nov 15;25(22):5027-5034.

Low-frequency coding variants in CETP and CFB are associated with susceptibility of exudative age-related macular degeneration in the Japanese population.

Momozawa Y, Akiyama M, Kamatani Y, Arakawa S, Yasuda M, Yoshida S, Oshima Y, Mori R, Tanaka K, Mori K, Inoue S, Terasaki H, Yasuma T, Honda S, Miki A, Inoue M, Fujisawa K, Takahashi K, Yasukawa T, Yanagi Y, Kadonosono K, Sonoda KH, Ishibashi T, Takahashi A, Kubo M.

PMID: 28173125

Stem Cells

Cells. 2017 Feb 2;6(1).

Stem Cell Therapies in Retinal Disorders.

Garg A, Yang J, Lee W, Tsang SH.

Abstract: Stem cell therapy has long been considered a promising mode of treatment for retinal conditions. While human embryonic stem cells (ESCs) have provided the precedent for regenerative medicine, the development of induced pluripotent stem cells (iPSCs) revolutionized this field. iPSCs allow for the development of many types of retinal cells, including those of the retinal pigment epithelium, photoreceptors, and ganglion cells, and can model polygenic diseases such as age-related macular degeneration. Cellular programming and reprogramming technology is especially useful in retinal diseases, as it allows for the study of living cells that have genetic variants that are specific to patients' diseases. Since iPSCs are a self-renewing resource, scientists can experiment with an unlimited number of pluripotent cells to perfect the process of targeted differentiation, transplantation, and more, for personalized medicine. Challenges in the use of stem cells are present from the scientific, ethical, and political realms. These include transplant complications leading to anatomically incorrect placement, concern for tumorigenesis, and incomplete targeting of differentiation leading to contamination by different types of cells. Despite these limitations, human ESCs and iPSCs specific to individual patients can revolutionize the study of retinal disease and may be effective therapies for conditions currently considered incurable.

PMID: 28157165

Diet, lifestyle and low vision

Ophthalmology. 2017 Jan 30. [Epub ahead of print]

Dietary Intakes of Eicosapentaenoic Acid and Docosahexaenoic Acid and Risk of Age-Related Macular Degeneration.

Wu J, Cho E, Giovannucci EL, Rosner BA, Sastry SM, Willett WC, Schaumberg DA.

PURPOSE: To evaluate the associations between intakes of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and the intermediate and advanced stages of age-related macular degeneration (AMD).

DESIGN: Prospective cohort study.

PARTICIPANTS: We followed 75 889 women from the Nurses' Health Study and 38 961 men from the Health Professionals Follow-Up Study who were at least 50 years old, from 1984 to 2012 and 1986 to 2010, respectively. Cohort participants are mostly white (≥95%).

METHODS: We assessed dietary intake by a validated food frequency questionnaire (FFQ) at baseline and every 4 years. We calculated cumulative average intakes of EPA and DHA from FFQs and also computed predicted erythrocyte and plasma scores directly from food intake using regression models. Cox proportional hazards models were used to compute the associations with AMD outcomes.

MAIN OUTCOME MEASURES: We confirmed 1589 incident intermediate and 1356 advanced AMD cases (primarily neovascular AMD) with a visual acuity of 20/30 or worse, owing primarily to AMD, by medical record review.

RESULTS: For intermediate AMD, the pooled hazard ratio (HR) between the 2 cohorts for DHA comparing the extreme quintiles of intake was 0.78 (95% confidence interval [CI], 0.66-0.92; P trend, 0.008) and for EPA + DHA was 0.83 (95% CI, 0.71-0.98; P trend, 0.03). The pooled HR for fatty fish, comparing ≥5 servings per week to almost never, was 0.61 (95% CI, 0.46-0.81; P trend, <0.001). For advanced AMD, the pooled HR for DHA was 1.01 (95% CI, 0.84-1.21; P trend, 0.75) and for fatty fish was 0.80 (95% CI, 0.59-1.08; P trend, 0.11). Secondary analyses using predicted erythrocyte and plasma scores of EPA and DHA yielded slightly stronger inverse associations for intermediate AMD and similar results for advanced AMD.

CONCLUSIONS: Higher intakes of EPA and DHA may prevent or delay the occurrence of visually

significant intermediate AMD. However, the totality of current evidence for EPA and DHA and advanced AMD is discordant, though there was no association with advanced AMD in the present study.

PMID: 28153441

Eye (Lond). 2017 Feb 3. [Epub ahead of print]

Assessment of the Apple iPad as a low-vision reading aid.

Morrice E, Johnson AP, Marinier JA, Wittich W.

Purpose: Low-vision clients frequently report having problems with reading. Using magnification, reading performance (as measured by reading speed) can be improved by up to 200%. Current magnification aids can be expensive or bulky; therefore, we explored if the Apple iPad offers comparable performance in improving reading speeds, in comparison with a closed-circuit television (CCTV) video magnifier, or other magnification devices.

Methods: We recruited 100 participants between the ages of 24-97 years, with low vision who were literate and cognitively capable, of whom 57 had age-related macular degeneration. To assess reading, participants read standardized iReST texts and were tested for comprehension. We compared reading speed on the Apple iPad (10 inch) with that of the CCTV, home magnification devices, and baseline measures.

Results: All assistive devices improved reading rates in comparison to baseline ($P < 0.001$, Hedge's $g > 1$), however, there was no difference in improvement across devices ($P > 0.05$, Hedge's $g < 0.1$). When experience was taken into account, those with iPad experience read, on average, 30 words per minute faster than first time iPad users, whereas CCTV experience did not influence reading speed.

Conclusions: In our sample, the Apple iPad was as effective as currently used technologies for improving reading rates. Moreover, exposure to, and experience with the Apple iPad might increase reading speed with that device. A larger sample size, however, is needed to do subgroup analysis on who would optimally benefit from each type of magnification device.

PMID: 28157222

Int J Vitam Nutr Res. 2017 Feb 10:1-5. [Epub ahead of print]

Bioactivity of Carotenoids - Chasms of Knowledge.

Bohn T.

Abstract: Carotenoid dietary intake, especially within fruits/vegetables and their plasma levels have been associated in many epidemiological studies with a reduced risk of several chronic diseases, including type-2 diabetes, cardiovascular diseases, several types of cancer, and age-related macular degeneration. However, intervention trials with isolated carotenoids (as supplements) have fallen short of fulfilling the hopes that were placed in these lipophilic pigments, often producing no positive or even adverse effects, such as increased lung cancer rate or total mortality. More recent studies have suggested that certain metabolites, and not necessarily the native compounds may be (the most) biologically active ones, such as certain apocarotenals (originating following enzymatic cleavage) and other more polar compounds, acting as more suitable electrophiles to react with transcription factors such as nuclear factor kappa-B (NF- κ B) and nuclear factor (erythroid-derived 2)-like 2 (Nrf2). In addition, it appears that questions of dosing are likewise crucial, as may be interactions of non-provitamin A carotenoids and their derivatives with retinoic acid receptors (RAR) or retinoid X receptors (RXR). Furthermore, our picture on carotenoid metabolism may be incomplete, as our knowledge on e. g. the interaction with the microbiota is virtually nil. In this

position article, it is aimed to highlight some of the discrepancies that appear to trouble carotenoid-related research, and point out some of the existing gaps in our knowledge.

PMID: 28186459

J Pharm Pharmacol. 2017 Feb 3. [Epub ahead of print]

Anti-apoptotic effects of *Curcuma longa* L. extract and its curcuminoids against blue light-induced cytotoxicity in A2E-laden human retinal pigment epithelial cells.

Park SI, Lee EH, Kim SR, Jang YP.

OBJECTIVES: The purpose of the study was to investigate the protective effect of the *Curcuma longa* L. extract (CLE) and its curcuminoids against blue light-induced cytotoxicity in human retinal pigment epithelial (RPE) cells loaded with A2E. A2E has been concerned in age-related macular degeneration (AMD).

METHODS: To perform this study, A2E-accumulated ARPE-19 cells were exposed to blue light to induce cytotoxicity. The cytotoxicity and apoptotic gene expression levels were evaluated using a lactate dehydrogenase (LDH) assay and real-time PCR analysis, respectively.

KEY FINDINGS: *Curcuma longa* L. extract was found to exert a protective effect in a dose-dependent manner. At a concentration of 15 μ m, curcumin, demethoxycurcumin and bisdemethoxycurcumin exerted significant protective effects against blue light-induced cytotoxicity. Treatment with CLE and curcuminoids meaningfully reduced the mRNA levels of c-Abl and p53, which was known to be augmented in apoptotic RPE cells. Demethoxycurcumin and bisdemethoxycurcumin were found to inhibit p38 expression, which is increased in blue light-irradiated A2E-accumulated RPE cells.

CONCLUSIONS: *Curcuma longa* L. extract and its curcuminoids provided significant protection against photooxidative damage and apoptosis in the RPE cells. Our results suggest that curcuminoids may show potential in the treatment of AMD.

PMID: 28155996

Oxid Med Cell Longev. 2017;2017:6469138. Epub 2017 Jan 5.

Nutritional and Lifestyle Interventions for Age-Related Macular Degeneration: A Review.

Carneiro Â, Andrade JP.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. In this narrative review, we will summarize the nutritional interventions evaluated in numerous observational studies and a few randomized clinical trials. The AREDS and AREDS2 studies demonstrated that supplements including vitamins C and E, beta-carotene, and zinc may reduce the progression to advanced AMD, in some patients, by 25% in five years. This is one of the few nutritional supplements known to have beneficial effects in any eye disease. Lutein/zeaxanthin supplementation may have beneficial effects in some individuals whereas omega-3 fatty acids supplementation needs to be further investigated and supported by more evidence. Genetic factors may explain the different patterns of response and explain differences found among individuals. More importantly, a combination of lifestyle behaviors such as the avoidance of smoking, physical activity, and the adoption of a healthy dietary pattern like the Mediterranean diet was associated with a lower prevalence of AMD. The adoption of these lifestyles may reduce the prevalence of the early stages of AMD and decrease the number of individuals who develop advanced AMD and consequently the onerous and climbing costs associated with the treatment of this disease.

PMID: 28154734 PMCID: PMC5244028

Occup Ther Health Care. 2017 Feb 3:1-11. [Epub ahead of print]

Effects of Simulated Low Vision on Postural Adjustment to Changes in Center of Mass in Older Adults.

Copolillo A, Christopher A, Lyons A.

Abstract: This study examined how instrumental activities of daily living (IADL) performed by older adults under low-vision simulation conditions affect postural adjustments to changes in center of mass (COM). Ten participants with normal vision performed seven activities under two conditions, normal vision, and simulated macular degeneration (MD). Postural adjustment to changes in COM and time to complete activities were recorded. Low vision was compared to normal vision using Wilcoxon signed rank and t tests. Differences between the two conditions were statistically significant for postural adjustments to change in COM and time. Postural adjustments and time to perform IADLs are greater under simulated low vision conditions versus normal vision. These preliminary findings support research with older adults with MD, who may be at risk when making movement transitions like descending or ascending stairs, stepping in and out of a tub, stooping, or reaching from one surface to another.

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