

Issue 20

Monday March 21 , 2011

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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## Drug treatment

**Jpn J Ophthalmol. 2011 Mar;55(2):123-7. Epub 2011 Mar 13.**

**Ranibizumab treatment administered as needed for occult and minimally classic neovascular membranes in age-related macular degeneration.**

Kang S, Roh YJ.

Department of Ophthalmology and Visual Science, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea.

**PURPOSE:** To report the clinical experience of intravitreal ranibizumab administered as needed for the treatment of neovascular age-related macular degeneration (AMD).

**METHODS:** We retrospectively reviewed the charts of 41 patients (41 eyes) with occult and minimally classic neovascular membrane in AMD. Patients received intravitreal injections (0.5 mg) of ranibizumab and were monitored monthly for 12 months. Forty-one eyes were retreated at the discretion of the treating physician on an as-needed basis after the first injection, instead of initially giving three monthly injections. The main outcomes measured were change in mean visual acuity and central retinal thickness, and the total number of injections received by patients during the 12 months.

**RESULTS:** At 12 months, the mean logarithm of the minimum angle of resolution (logMAR) visual acuity improved by 0.078 logMAR units ( $P = 0.046$ ) and the mean central retinal thickness decreased by 85.7  $\mu\text{m}$  ( $P < 0.001$ ). Thirty of 41 eyes (73.2%) avoided any loss of vision, and 20 eyes (48.8 %) showed improved visual acuity. A mean of 4.07 injections were given over the 12 months.

**CONCLUSIONS:** Ranibizumab administered on an as-needed basis may stabilize visual acuity in patients with neovascular AMD.

PMID: 21400056 [PubMed - in process]

**Drugs. 2011 Mar 5;71(4):455-63. doi: 10.2165/11206900-000000000-00000.**

**Ranibizumab: in macular oedema following retinal vein occlusion.**

Garnock-Jones KP.

Abstract

Ranibizumab (Lucentis®), a recombinant humanized IgG(1)  $\kappa$  isotype monoclonal antibody fragment, is

approved in the US for the treatment of macular oedema following retinal vein occlusion (RVO). It binds to the receptor-binding site of active forms of vascular endothelial growth factor-A, inhibiting its biological activity. In two large, well designed, phase III trials in patients with macular oedema following branch RVO (BRVO) or central RVO (CRVO), monthly intravitreal injections of ranibizumab 0.5 mg were associated with significantly greater improvement from baseline in mean best-corrected visual acuity letter score (measured on the Early Treatment Diabetic Retinopathy Study chart) in the study eye at 6 months (primary endpoint) than sham injections. Moreover, ranibizumab was significantly more effective than sham injections with regard to improvements in central foveal thickness at 6 months, as well as several other visual acuity measures. Ranibizumab was generally well tolerated in patients with macular oedema following CRVO or BRVO. Overall, the most common adverse events with ranibizumab were consistent with the adverse event profile previously reported in patients with age-related macular degeneration.

PMID: 21395358 [PubMed - in process]

**Nippon Ganka Gakkai Zasshi. 2011 Feb;115(2):122-33.**

**[Long-term efficacy and safety profile of pegaptanib sodium for age-related macular degeneration with choroidal neovascularization--evaluation of extended phase II clinical trial].**

**[Article in Japanese]**

Pegaptanib Sodium Multi-center Study Group.

Abstract

Long-term efficacy and safety profile of pegaptanib was evaluated for age-related macular degeneration (AMD) with choroidal neovascularization. Sixty-one AMD patients from phase II clinical trial were entered into an extended trial and followed up for more than 2 years. Pegaptanib sodium 0.3 mg was administered once every six weeks. Changes in visual acuity were evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The number of responders and adverse events were monitored. The mean change in visual acuity decreased by 10.3 letters for up to 199 weeks (62-199 weeks; mean 140 weeks) during follow-up. There were 77.4% responders at the beginning (54 weeks since the beginning of phase II trial) and 56.6% at the end of the extended trial. Adverse events were found in 57 of 61 patients (93.4%); 36 of the events (59.0%) were due to a preparation procedure, while 12 adverse events (19.7%), including retinal hemorrhage (3 events; 4.9%), anterior chamber inflammation (2 events; 3.3%), macular degeneration, floaters, photopsia, retinal vessel aneurysm, vitreous hemorrhage, ocular hypertension, arteriosclerosis obliterans and hypertension (1 event; 1.6%, respectively) were associated with pegaptanib sodium. Thus, the majority of adverse events was at least in part a result of the preparation procedure for injection. Based on the long-term efficacy and tolerability data of this trial, pegaptanib sodium appears to be beneficial for preventing the worsening of visual acuity caused by age-related macular degeneration with choroidal neovascularization.

PMID: 21400918 [PubMed - in process]

## Other treatment & diagnosis

**Invest Ophthalmol Vis Sci. 2011 Mar 11. [Epub ahead of print]**

**Fixation Control Before and After Treatment for Neovascular Age-Related Macular Degeneration.**

González EG, Tarita-Nistor L, Mandelcorn ED, Mandelcorn M, Steinbach MJ.

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Abstract

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**Purpose:** We studied changes in visual acuity, fixation stability, and location of the preferred retinal locus (PRL) after treatment for unilateral neovascular age related macular degeneration (AMD) for previously not treated eyes. Concomitant changes in fixation stability, preferred retinal locus, and visual acuity in the untreated fellow eye were also analyzed.

**Methods:** Pre and post-treatment tests of visual acuity, fixation stability (using a bivariate contour ellipse area, or BCEA), and PRL location in the treated and untreated eye were performed on 13 patients undergoing three monthly intravitreal injections of ranibizumab in one eye.

**Results:** For the treated eyes there were improvements in visual acuity ( $\Delta$ VA) and fixation stability ( $\Delta$ log(10) BCEA) but no changes in the location of the PRL. No significant changes in any of the three variables were found in the untreated eye.

**Conclusion:** For previously untreated eyes, the improvement in visual acuity following intravitreal ranibizumab injections is accompanied by improvement in fixation stability.

PMID: 21398288 [PubMed - as supplied by publisher]

**Nippon Ganka Gakkai Zasshi. 2011 Feb;115(2):147-50.**

**[A case of retinitis pigmentosa with retinal angiomatous proliferation].**

**[Article in Japanese]**

Nagao Y, Hiramoto Y, Takahashi K.

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**PURPOSE:** To report a first case of retinitis pigmentosa accompanied with retinal angiomatous proliferation (RAP).

**CASE:** A 60-year-old woman was diagnosed with retinitis pigmentosa. Fundus examination revealed intraretinal hemorrhage and exudates with retinal edema in the subfovea region OD. Indocyanine green angiogram revealed the presence of retino-choroidal anastomosis. These findings were compatible with the lesions observed in the form of RAP in age-related macular degeneration (AMD), which is resistant to photodynamic therapy with verteporfin and anti-vascular endothelial growth factor (VEGF) therapy.

**CONCLUSION:** A first case of retinitis pigmentosa accompanied with RAP presented. Although few clinical cases of retinitis pigmentosa accompanied with choroidal neovascularization have been reported, this is the first report of RAP combined with retinitis pigmentosa. Further research is required to examine the mechanism associating these two conditions.

PMID: 21400921 [PubMed - in process]

**Ophthalmic Physiol Opt. 2011 Mar 17. doi: 10.1111/j.1475-1313.2010.00819.x. [Epub ahead of print]**

**How does the presence and duration of central visual impairment affect reaching and grasping movements?**

Pardhan S, Gonzalez-Alvarez C, Subramanian A.

Vision and Eye Research Unit (VERU), Postgraduate Medical Institute, Anglia Ruskin University, Cambridge, UK Department of Optometry and Visual Science, City University, London, UK.

**Purpose:** To examine how subjects with central visual impairment (CVI) due to macular degeneration conduct reaching and grasping movements compared to those with normal vision and to determine whether

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these are influenced by the duration of the impairment.

**Methods:** Eighteen subjects with CVI and 9 subjects of a similar age but with normal vision were recruited. Subjects were required to pick up a cylindrical object and a motion analysis system recorded and reconstructed the reaching and grasping movements in 3-D. Subjects were also divided into two groups based on the duration of their vision loss: subjects with CVI of less/greater than 10 years duration.

**Results:** Subjects with CVI showed significant differences in some transport and grasping indices compared to age matched normal subjects ( $p < 0.05$ ) but not in all. More indices were correlated to contrast sensitivity (5) than to visual acuity results (2).

**Conclusions:** Subjects with CVI required extra time prior to starting the movement (as shown by longer onset time) and this was probably needed to localise the object and to perceive its dimensions. They spent more time after maximum grip aperture, indicating a need for a longer time to grasp the object. A possible reason is that visually impaired patients need to use more tactile information than normal subjects in order to fully execute grasping of the object. CVI that was of <10 years in duration affected more indices compared to CVI that was of long standing and may suggest adaptation to the visual impairment for this task.

PMID: 21410742 [PubMed - as supplied by publisher]

**Acta Ophthalmol. 2011 Mar 15. doi: 10.1111/j.1755-3768.2011.02141.x. [Epub ahead of print]**

### **The ocular pulse amplitude at different intraocular pressure: a prospective study.**

Knecht PB, Bosch MM, Michels S, Mannhardt S, Schmid U, Bosch MA, Menke MN.

Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland Department of Ophthalmology, Triemli Hospital Zurich, Zurich, Switzerland.

**Purpose:** To investigate changes in ocular pulse amplitude (OPA) during a short-term increase in intraocular pressure (IOP) and to assess possible influences of biometrical properties of the eye, including central corneal thickness (CCT) and axial length.

**Methods:** In a prospective, single centre study, OPA and IOP as measured by dynamic contour tonometry (DCT) were taken before baseline- and post-OPA (delta) intravitreal injection of 0.05 ml anti-vascular endothelial growth factor agents. Analysis was performed employing linear regression with baseline- and post (delta)-OPA differences as the dependent and post-IOP as well as delta IOP as the independent variable. A multilinear regression analysis with delta OPA as the dependent variable and baseline IOP, post -IOP, CCT and axial length as independent variables was conducted.

**Results:** Forty eyes of 40 patients were included. IOP and OPA increased significantly after injection (IOP mean increase  $\pm$  SD: 17.83  $\pm$  9.83 mmHg,  $p < 0.001$ ; OPA mean increase  $\pm$  SD: 1.39  $\pm$  1.16 mmHg,  $p < 0.001$ ). For every mmHg increase in IOP, the OPA showed a linear increase of 0.05 mmHg (slope 0.05, 95% CI: 0.02-0.09,  $p = 0.003$ ,  $r(2) = 0.20$ ). Multiple regression analysis with delta OPA as the dependent variable revealed a partial correlation coefficient of 0.47 ( $p = 0.003$ ) for post-IOP as the only significant contribution.

**Conclusion:** A clear positive relationship between OPA measurements and IOP levels was shown in a clinical routine setting using DCT focusing on baseline and postinterventional comparisons of OPA values after intravitreal injections in patients with exudative age related macular degeneration. When considering the OPA for diagnostic purposes, we recommend indication of corresponding IOP values.

PMID: 21401909 [PubMed - as supplied by publisher]

**Ophthalmic Surg Lasers Imaging. 2011 Mar-Apr;42(3):102-6. doi: 10.3928/15428877-20110316-01.**

**Non-mydriatic single-field fundus photography for the screening of retinal diseases in an executive health clinic.**

Tarabishy AB, Campbell JP, Misra-Hebert A, Seballos RJ, Lang RS, Singh RP.

**BACKGROUND AND OBJECTIVE:** To determine the accuracy and sensitivity of a single-field non-mydriatic digital fundus image interpreted by an ophthalmologist and performed within a primary care setting.

**PATIENTS AND METHODS:** Fundus photography using a digital non-mydriatic camera was performed on both eyes of 1,175 consecutive patients as part of an executive health program. All fundus images included a 45° field of the posterior pole capturing the optic nerve and macular area. Diagnostic findings were recorded and appropriate recommendations for follow-up were made. Patients were then contacted to see whether appropriate follow-up was successfully completed and chart reviews were performed to determine biomicroscopic findings.

**RESULTS:** Photographs were adequate in both eyes in 1,117 patients (95.1%). Examination findings were normal in both eyes in 951 (85.1%) patients. Abnormal findings were noted in either eye in 166 (14.9%) patients. The most common abnormal findings were macular degeneration (57/166, 34.3%), optic nerve cupping (45/166, 27.1%), hypertensive retinopathy (15/166, 9.0%), and choroidal nevi (10/166, 6.0%). In all patients with abnormal findings, routine follow-up ophthalmologic examination with an eye care specialist was indicated and none of the patients required urgent attention. Sensitivity was found to be 87% and stratification was performed based on the initial diagnosis. False-positive results were from confounding diagnoses rather than true false-positives.

**CONCLUSION:** Single-field non-mydriatic fundus photography is accurate and sensitive for screening retinal disease in a primary care setting.

PMID: 21410106 [PubMed - in process]

**Ophthalmic Physiol Opt. 2011 Mar 17. doi: 10.1111/j.1475-1313.2011.00820.x. [Epub ahead of print]**

**Influence of background on image recognition in normal vision and age-related macular degeneration.**

Bordier C, Petra J, Dauxerre C, Vital-Durand F, Knoblauch K.

INSERM, U846, Stem Cell and Brain Research Institute, Department of Integrative Neurosciences, Bron, France Université de Lyon, Lyon, France.

**Purpose:** The influence of background attenuation on the spatial frequency bandwidth requirements for image recognition was assessed in normal young and older groups and in a group with age-related macular degeneration (AMD). Bandwidth requirements were also assessed in the visual periphery of young normal observers.

**Methods:** In Experiment 1, each observer was presented with 20 series of images. Each series consisted of a sequence of progressively low-pass filtered images, presented in an order of increasing bandwidth, i.e., according to an ascending method of limits. For half of the series, the background of the base image was selectively darkened by 80% of its original luminance. Three measures were analyzed: (1) the critical bandwidth defined as the bandwidth in cycles/image (cpi) at which 50% of the images were recognized, (2) the minimal bandwidth, defined as the minimal bandwidth at which images were recognized and (3) the proportion of images recognized at full bandwidth. In Experiment 2, young normal observers were similarly tested in central vision and at 5.5° eccentricity (superior or inferior visual field). A third background attenuation condition was included, as well, in which the background was low-pass filtered.

**Results:** The critical bandwidth for image recognition was significantly reduced by darkening the image background for normal young and old and the AMD groups. This improvement was found to be contrast dependent for the darkened background. In addition, AMD observers tended to recognize more images at full bandwidth if the background was darkened. For normal young observers, making the background low-pass was ineffective in lowering the critical bandwidth in the fovea. Fewer images were recognized at full bandwidth at 5.5° eccentricity for a low-pass background and marginally fewer for a darkened background.

**Conclusions:** Selective attenuation of the image background can lead to reductions in the bandwidth requirements for image recognition in AMD. However, performance of young normal observers for images presented in the periphery was unlike AMD performance under the conditions investigated. These results have interesting implications for the design of image enhancement algorithms to aid low vision observers.

PMID: 21410743 [PubMed - as supplied by publisher]

**Acta Ophthalmol. 2011 Mar 17. doi: 10.1111/j.1755-3768.2011.02143.x. [Epub ahead of print]**

**Retinal stimuli can be restored after autologous transplant of retinal pigment epithelium and choroid in pigment epithelium tears.**

Caramoy A, Fauser S, Kirchhof B.

Department of Vitreo-Retinal Surgery, Center of Ophthalmology, University of Cologne, Cologne, Germany.

**Purpose:** To evaluate the functional and anatomical outcome of patients undergoing autologous transplant of retinal pigment epithelium (RPE) and choroid after RPE tear secondary to age-related macular degeneration (AMD).

**Methods:** Data from nine eyes of nine patients were analysed retrospectively. Examinations included fluorescein and indocyanine green angiography, fundus autofluorescence imaging, optical coherence tomography, microperimetry and determination of visual acuity (far and reading ability). Data regarding intraoperative and postoperative complications were recorded. Mean follow-up time was 18 months (range 4 months to 5 years).

**Results:** After surgery, far visual acuity improved or remained stable ( $\pm 3$  lines) in three of nine eyes and for the near visual acuity in three of nine eyes. Visual acuity decreased postoperatively at the last follow-up in four eyes mainly because of postoperative complications, i.e. retinal detachment due to proliferative vitreoretinopathy, retinal artery occlusion, pucker and fibrosis of the graft. In one case, retinal stimuli were restored over the scotoma as seen in microperimetry.

**Conclusion:** Autologous transplant of RPE and choroid is a therapy option for RPE tears. Retinal stimuli can be restored in selected cases. Numerous intra- and postoperative complications compromise the functional prognosis and outcome.

PMID: 21410906 [PubMed - as supplied by publisher]

## Epidemiology & pathogenesis

**Ophthalmic Epidemiol. 2011 Apr;18(2):83-90.**

**Statin use and the risk of age related macular degeneration in a large health organization in Israel.**

Shalev V, Srur M, Goldshtein I, Kokia E, Chodick G.

Maccabi Healthcare Services, Tel Aviv, Israel.

**Objective:** To investigate the association between persistent use of statins and the risk of age-related

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macular degeneration (AMD).

**Design:** A population-based retrospective cohort among adults who began statin therapy between 1998 and 2006 in a large health organization in Israel. The organization's central computerized databases were used to collect data on incident AMD cases diagnosed by ophthalmologists.

**Results:** A total of 108,973 individuals aged 55 or older were identified. During the study follow-up period 409,113 person-years, there were 2,732 incident AMD cases (6.68 per 1,000 person-years). The crude incidence density rate of AMD among patients at the lowest quintile of persistence with statins (7.18 per 1,000) was comparable to that of highest persistence quintile (7.13 per 1,000). After adjustment for potential confounders, patients in the highest quintile of persistence with statins had a hazard ratio of 0.99 (95% Confidence Interval: 0.78-1.26) for AMD compared with patients in the lowest proportion of days covered (PDC) quintile. In addition to age, AMD was found to associate with past smoking, asthma, diabetes and frequent visits to ophthalmologists or primary physicians prior to index date

**Conclusions:** Our study agrees with previous studies that showed no association between persistent use of statins and reduced risk of AMD. These results suggest that the early reports on a strong protective effect of statins against AMD development were probably a result of a small study effect.

PMID: 21401416 [PubMed - in process]

#### **FASEB J. 2011 Mar 16. [Epub ahead of print]**

##### **Transcriptional regulation of bone morphogenetic protein 4 by tumor necrosis factor and its relationship with age-related macular degeneration.**

Xu J, Zhu D, He S, Spee C, Ryan SJ, Hinton DR.

\*Neuroscience Graduate Program.

#### **Abstract**

Bone morphogenetic protein-4 (BMP4) may be involved in the molecular switch that determines which late form of age-related macular degeneration (AMD) an individual develops. BMP4 expression is high in retinal pigment epithelium (RPE) cells in late, dry AMD patients, while BMP4 expression is low in the wet form of the disease, characterized by choroidal neovascularization (CNV). Here, we sought to determine the mechanism by which BMP4 is down-regulated in CNV. BMP4 expression was decreased within laser-induced CNV lesions in mice at a time when tumor necrosis factor (TNF) expression was high (7 d postlaser) and was reexpressed in RPE when TNF levels declined (14 d postlaser). We found that TNF, an important angiogenic stimulus, significantly down-regulates BMP4 expression in cultured human fetal RPE cells, ARPE-19 cells, and RPE cells in murine posterior eye cup explants. We identified two specificity protein 1 (Sp1) binding sites in the BMP4 promoter that are required for basal expression of BMP4 and its down-regulation by TNF. Through c-Jun NH(2)-terminal kinase (JNK) activation, TNF modulates Sp1 phosphorylation, thus decreasing its affinity to the BMP4 promoter. The down-regulation of BMP4 expression by TNF in CNV and mechanisms established might be useful for defining novel targets for AMD therapy.-Xu, J., Zhu, D., He, S., Spee, C., Ryan, S. J., Hinton, D. R. Transcriptional regulation of bone morphogenetic protein 4 by tumor necrosis factor and its relationship with age-related macular degeneration.

PMID: 21411747 [PubMed - as supplied by publisher]

#### **Invest Ophthalmol Vis Sci. 2011 Mar 11. [Epub ahead of print]**

##### **Choriocapillaris Vascular Dropout related to Density of Drusen in Human Eyes with Early Age-Related Macular Degeneration.**

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Mullins RF, Johnson MN, Faidley EA, Skeie JM, Huang J.

Department of Ophthalmology and Visual Sciences, Carver College of Medicine;

**Purpose:** Age-related macular degeneration (AMD) is a common, potentially blinding disease characterized by the presence of extracellular deposits beneath the retinal pigment epithelium (RPE). Choroidal vascular changes have also been noted in AMD. In this study we examined the relationship between the choroidal vasculature and extent of drusen and other sub-RPE deposits, the key pathologic landmarks of AMD.

**Methods:** Sections of the maculas of 46 human eyes (21 early AMD and 25 age-matched control) were evaluated morphometrically. The cross sectional area of sub-RPE deposits, vascular density, number of CD45+ leukocytes, and number of "ghost vessels" were determined in a masked fashion and evaluated by regression analysis. In addition, the extramacular vascular density either directly beneath drusen or adjacent to drusen was evaluated in a separate set of donor eyes.

**Results:** The vascular density of the choriocapillaris showed a trend toward decreasing in association with AMD status. By linear regression analysis, vascular density was inversely associated with sub-RPE deposit density ( $r(2) = .22$ ,  $p < 0.01$ ). Number of ghost vessels was negatively correlated with vascular density ( $r(2) = .55$ ,  $p < 0.001$ ) and positively correlated with sub-RPE deposit density ( $r(2) = .57$ ,  $p < 0.001$ ). In morphological studies of extramacular solitary drusen, vascular density beneath drusen was found to be 45% lower than adjacent to drusen ( $p < 0.01$ ).

**Conclusions:** These findings support the concept that microvascular changes are related to the pathogenesis of AMD, and suggest that vascular endothelial cell loss occurs in association with sub-RPE deposit formation. Whether microvascular events are a cause or consequence of drusen or other deposit formation remains to be determined.

PMID: 21398287 [PubMed - as supplied by publisher]

## **Invest Ophthalmol Vis Sci. 2011 Mar 11. [Epub ahead of print]**

### **Characterization of conditioned media collected from aged vs. young human eye-cups.**

Kolomeyer A, Sugino I, Zarbin M.

University of Medicine and Dentistry of New Jersey, New Jersey Medical School, The Institute of Ophthalmology and Visual Science, Newark, New Jersey.

**Purpose:** To characterize secretion of in situ retinal pigment epithelium (RPE) from healthy-aged adult, age-related macular degeneration (AMD) adult, and fetal donor eyes, and to assess the impact on retina survival in vitro.

**Methods:** Conditioned medium (CM) was collected from adult and fetal donor eyes and analyzed for trophic factor composition by multiplex ELISA. Trophic factor receptor occupancy was calculated to evaluate differences in trophic factor concentrations. RPE trophic factor mRNA expression was quantified by real-time PCR. Retina-preserving activity of the collected CM was evaluated using degenerating porcine retina in vitro.

**Results:** Compared to CM from adult donors, AMD donor CM contained a significantly higher concentration of brain-derived neurotrophic factor (BDNF), while fetal donor CM contained significantly higher concentrations of hepatocyte growth factor (HGF) and pigment epithelium-derived factor (PEDF). We found no consistent correlation between trophic factor mRNA expression and protein secretion. Non-RPE components of the RPE-Bruch's membrane-choroid-sclera complex were a major contributor of vascular endothelial growth factor-A (VEGF-A). CM of fetal donors was significantly better than CM of adult or AMD donors at improving the survival of degenerating porcine retina.

**Conclusions:** RPE cells of adult and fetal eyes have significantly different trophic factor production

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capabilities, which correlated with changes in preservation of porcine retina. Combined with trophic factor receptor occupancy calculations, these data may implicate HGF and PEDF as key factors promoting the preservation of retinal structure and function.

PMID: 21398279 [PubMed - as supplied by publisher]

## Genetics

**J Mol Biol. 2011 Mar 9. [Epub ahead of print]**

### **Zinc binding to the Tyr402 and His402 allotypes of complement factor H: possible implications for age-related macular degeneration.**

Nan R, Farabella I, Schumacher FF, Miller A, Gor J, Martin AC, Jones DT, Lengyel I, Perkins SJ.

Department of Structural and Molecular Biology, Division of Biosciences Darwin Building, University College London, Gower Street, London WC1E 6BT, U. K.

#### Abstract

The Tyr402His polymorphism of complement factor H (FH) with 20 short complement regulator (SCR) domains is associated with age-related macular degeneration (AMD). How FH contributes to disease pathology is not clear. Both FH and high concentrations of zinc are found in drusen deposits, the key feature of AMD. Heterozygous FH is inhibited by zinc which causes FH to aggregate. Here, zinc binding to homozygous FH was studied. By analytical ultracentrifugation, large amounts of oligomers were observed with both the native Tyr402 and the AMD-risk His402 homozygous allotypes of FH and both the recombinant SCR-6/8 allotypes with Tyr/His402. X-ray scattering also showed that both FH and SCR-6/8 allotypes strongly aggregated at  $> 10 \mu\text{M}$  zinc. The SCR-1/5 and SCR-16/20 fragments were less likely to bind zinc. These observations were supported by bioinformatics predictions. Starting from known zinc-binding sites in crystal structures, 202 putative partial surface zinc binding sites were predicted in FH, most of which were in SCR-6. Metal site prediction web servers also suggested that SCR-6 and other domains bind zinc. Predicted SCR-6/8 dimer structures showed that zinc binding sites could be formed at the protein-protein interface that would lead to daisy-chained oligomers. It was concluded that zinc binds weakly to FH at multiple surface locations, most probably within the functionally-important SCR-6/8 domains, and this explains why zinc inhibits FH activity. Given the high pathophysiological levels of bioavailable zinc present in subretinal deposits, we discuss how zinc binding to FH may contribute to deposit formation and inflammation associated with AMD.

PMID: 21396937 [PubMed - as supplied by publisher]

**Ophthalmic Epidemiol. 2011 Apr;18(2):61-71.**

### **Prevalence of Chronic Ocular Diseases in a Genetic Isolate: The Norfolk Island Eye Study (NIES).**

Sherwin JC, Kearns LS, Hewitt AW, Ma Y, Kelly J, Griffiths LR, Mackey DA.

Centre for Eye Research Australia, University of Melbourne, Department of Ophthalmology, Royal Victorian Eye and Ear Hospital, Victoria, Australia.

**Purpose:** Over 40% of the permanent population of Norfolk Island possesses a unique genetic admixture dating to Pitcairn Island in the late 18(th) century, with descendants having varying degrees of combined Polynesian and European ancestry. We conducted a population-based study to determine the prevalence and causes of blindness and low vision on Norfolk Island.

**Methods:** All permanent residents of Norfolk Island aged  $\geq 15$  years were invited to participate. Participants completed a structured questionnaire/interview and underwent a comprehensive ophthalmic examination

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including slit-lamp biomicroscopy.

**Results:** We recruited 781 people aged  $\geq 15$ , equal to 62% of the permanent population, 44% of whom could trace their ancestry to Pitcairn Island. No one was bilaterally blind. Prevalence of unilateral blindness (visual acuity [VA]  $< 6/60$ ) in those aged  $\geq 40$  was 1.5%. Blindness was more common in females ( $P = 0.049$ ) and less common in people with Pitcairn Island ancestry ( $P < 0.001$ ). The most common causes of unilateral blindness were age-related macular degeneration (AMD), amblyopia, and glaucoma. Five people had low vision (Best-Corrected VA  $< 6/18$  in better eye), with 4 (80%) due to AMD. People with Pitcairn Island ancestry had a lower prevalence of AMD ( $P < 0.001$ ) but a similar prevalence of glaucoma to those without Pitcairn Island ancestry.

**Conclusions:** The prevalence of blindness and visual impairment in this isolated Australian territory is low, especially amongst those with Pitcairn Island ancestry. AMD was the most common cause of unilateral blindness and low vision. The distribution of chronic ocular diseases on Norfolk Island is similar to mainland Australian estimates.

PMID: 21401413 [PubMed - in process]

**Arch Ophthalmol. 2011 Mar;129(3):344-51.**

**Assessing susceptibility to age-related macular degeneration with genetic markers and environmental factors.**

Chen Y, Zeng J, Zhao C, Wang K, Trood E, Buehler J, Weed M, Kasuga D, Bernstein PS, Hughes G, Fu V, Chin J, Lee C, Crocker M, Bedell M, Salazar F, Yang Z, Goldbaum M, Ferreyra H, Freeman WR, Kozak I, Zhang K.

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**OBJECTIVES:** To evaluate the independent and joint effects of genetic factors and environmental variables on advanced forms of age-related macular degeneration (AMD), including geographic atrophy and choroidal neovascularization, and to develop a predictive model with genetic and environmental factors included.

**METHODS:** Demographic information, including age at onset, smoking status, and body mass index, was collected for 1844 participants. Genotypes were evaluated for 8 variants in 5 genes related to AMD. Unconditional logistic regression analyses were performed to generate a risk predictive model.

**RESULTS:** All genetic variants showed a strong association with AMD. Multivariate odds ratios were 3.52 (95% confidence interval, 2.08-5.94) for complement factor H, CFH rs1061170 CC, 4.21 (2.30-7.70) for CFH rs2274700 CC, 0.46 (0.27-0.80) for C2 rs9332739 CC/CG, 0.44 (0.30-0.66) for CFB rs641153 TT/CT, 10.99 (6.04-19.97) for HTRA1/LOC387715 rs10490924 TT, and 2.66 (1.43-4.96) for C3 rs2230199 GG. Smoking was independently associated with advanced AMD after controlling for age, sex, body mass index, and all genetic variants.

**CONCLUSION:** CFH confers more risk to the bilaterality of geographic atrophy, whereas HTRA1/LOC387715 contributes more to the bilaterality of choroidal neovascularization. C3 confers more risk for geographic atrophy than choroidal neovascularization. Risk models with combined genetic and environmental factors have notable discrimination power. **Clinical Relevance** Early detection and risk prediction of AMD could help to improve the prognosis of AMD and to reduce the outcome of blindness. Targeting high-risk individuals for surveillance and clinical interventions may help reduce disease burden.

PMID: 21402993 [PubMed - in process]

## Pre-clinical

**J Med Chem. 2011 Mar 11. [Epub ahead of print]**

### **Design, Synthesis, and Evaluation of Novel 3,6-Diaryl-4-aminoalkoxyquinolines as Selective Agonists of Somatostatin Receptor Subtype 2.**

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#### **Abstract**

Agonists of somatostatin receptor subtype 2 (sst(2)) have been proposed as therapeutics for the treatment of proliferative diabetic retinopathy and exudative age-related macular degeneration. An HTS screen identified 2-quinolones as weak agonists of sst(2), and these were optimized to provide small molecules with sst(2) binding and functional potency comparable to peptide agonists. Agonist 21 was shown to inhibit rat growth hormone secretion following systemic administration and to inhibit ocular neovascular lesion formation after local administration.

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**Neurobiol Aging. 2011 Mar 11. [Epub ahead of print]**

### **AAV5-mediated sFLT01 gene therapy arrests retinal lesions in Ccl2(-/-)/Cx3cr1(-/-) mice.**

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#### **Abstract**

To test the effects of adeno-associated virus encoding sFLT01 (AAV5.sFLT01) on the retinal lesions in Ccl2(-/-)/Cx3cr1(-/-) mice, a model for age-related macular degeneration (AMD), AAV5.sFLT01 was injected into the subretinal space of the right eyes and the left eyes served as controls. Histology found no retinal toxicity due to the treatment after 3 months. The treated eyes showed lesion arrest compared with lesion progression in the left eyes by fundus monitoring monthly and histological evaluation 3 months after treatment. Retinal ultrastructure showed fewer lipofuscin and better preserved photoreceptors after the treatment. A2E, a major component of lipofuscin, was lower in the treated eyes than in the control eyes. Molecular analysis showed that AAV5.sFLT01 lowered retinal extracellular signal-regulated kinase (ERK) phosphorylation and inducible nitric oxide synthetase expression, which suggested the involvement of reactive nitrogen species in the retinal lesions of Ccl2(-/-)/Cx3cr1(-/-). We concluded that local delivery of AAV5.sFLT01 can stabilize retinal lesions in Ccl2(-/-)/Cx3cr1(-/-) mice. The findings provide further support for the potential beneficial effects of sFLT01 gene therapy for age-related macular degeneration.

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**Graefes Arch Clin Exp Ophthalmol. 2011 Mar 12. [Epub ahead of print]**

### **Diurnal rodents as animal models of human central vision: characterisation of the retina of the sand rat *Psammomys obesus*.**

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**BACKGROUND:** Cone photoreceptor-based central vision is of paramount importance in human eyesight, and the increasing numbers of persons affected by macular degeneration emphasizes the need for relevant and amenable animal models. Although laboratory mice and rats have provided valuable information on retinal diseases, they have inherent limitations for studies on macular pathology. In the present study, we extend our recent analyses of diurnal murid rodents to demonstrate that the sand rat *Psammomys obesus* has a remarkably cone-rich retina, and represents a useful adjunct to available animal models of central vision.

**METHODS:** Adult *P. obesus* were captured and transferred to animal facilities where they were maintained under standard light/dark cycles. Animals were euthanised and their eyes enucleated. Tissue was either fixed in paraformaldehyde and prepared for immunohistochemistry, or solubilized in lysis buffer and separated by SDS-PAGE and subjected to western blot analysis. Samples were labelled with a battery of antibodies against rod and cone photoreceptors, inner retinal neurones, and glia.

**RESULTS:** *P. obesus* showed a high percentage of cones, 41% of total photoreceptor numbers in both central and peripheral retina. They expressed multiple cone-specific proteins, including short and medium-wavelength opsin and cone transducin. A second remarkable feature of the retina concerned the horizontal cells, which expressed high levels of glial fibrillar acidic protein and occludin, two proteins which are not seen in other species.

**CONCLUSION:** The retina of *P. obesus* displays high numbers of morphologically and immunologically identifiable cones which will facilitate analysis of cone pathophysiology in this species. The unusual horizontal cell phenotype may be related to the cone distribution or to an alternative facet of the animals lifestyle.

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**Biomacromolecules. 2011 Mar 14. [Epub ahead of print]**

**Photoresponsive PEG-Anthracene Grafted Hyaluronan as a Controlled-Delivery Biomaterial.**

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Abstract

Ophthalmic drug delivery to the posterior segment of the eye could benefit from a responsive controlled drug delivery system with light or laser inducible changes. For example, the delivery of age-related macular degeneration drugs requires invasive monthly injections making long-term photoresponsive drug delivery a desirable option. The feasibility of this may be facilitated by both the transparency of the eye and the advanced technology in ophthalmic lasers. Hyaluronic acid photogels that are compatible with retinal pigment epithelial cell lines are shown here to deliver a variety of small and large model drugs over the long term (months). Varying UV exposures resulted in decreases/increases or the turning off and on of delivery, potentially allowing the therapy to be tailored to suit the patient and the disease.

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**Exp Eye Res. 2011 Mar 14. [Epub ahead of print]**

**Optimization of laser-induced choroidal neovascularization in african green monkeys.**

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## Abstract

We developed and validated a new nonhuman primate model of laser-induced choroidal neovascularization (CNV) that addresses study design limitations prevalent in laser-induced CNV-based efficacy studies. Laser-induced Bruch's membrane disruption triggers CNV and has been widely utilized in animals to model neovascular ("wet") age-related macular degeneration (AMD). Despite widespread use of the approach, detailed assessment of experimental parameters and their influence on pathophysiological endpoints critical for disease modeling has been extremely limited and largely based on anecdotal observations. We evaluated laser power parameters and endpoint measures to optimize methods for CNV formation and quantification to facilitate drug efficacy screening in African green monkeys. Six laser spots of 350, 550, 750, 950 or 1500 mW laser power were positioned bilaterally 1.5 disc diameters from the fovea, within the macula. Fluorescein angiograms were collected 3-5 weeks later and scored by trained masked investigators using graded (I-IV) and densitometric methods. Histopathology assessments were also performed, including determination of CNV area. Test system sensitivity to angiogenesis inhibition was subsequently assessed by evaluating the effect of intravitreal bevacizumab (Avastin) pretreatment (one day prior to laser photocoagulation) on incidence of CNV. Grade III and grade IV lesions were considered clinically relevant, demonstrating early hyperfluorescence and late leakage within or beyond the lesion borders. By 4 weeks post-laser all treatment groups demonstrated evidence of grade III lesions with greatest incidence observed in lesions induced by 750 and 950 mW laser power (72.9% and 69.4% respectively). Grade IV lesions were confined to eyes receiving 550 mW laser power or higher, with highest incidence of grade IV lesions observed in eyes receiving 950 (19.4%) and 1500 mW (31%) laser spots, incidence peaking 4 weeks post-laser photocoagulation. Densitometric analyses of angiograms corroborated visual scoring. Bevacizumab completely abolished grade IV lesion development and significantly lowered lesion fluorescein signal intensity ( $P < 0.0001$ ) and CNV area ( $P = 0.038$ ) compared to vehicle-treated controls. Our studies demonstrate that laser power of 950-1500 mW and angiography analysis 4 weeks post-laser are optimal parameters to evaluate treatment effects on CNV induction following laser photocoagulation. Bevacizumab significantly attenuated CNV development, as determined by fluorescein angiography and histopathology assessments in this model, supporting the application of African green monkeys in preclinical modeling of CNV. Laser parameters and time points for therapeutic dosing and angiography endpoints are critical factors to the laser-induced CNV model and must be validated for robust assessment of efficacy. The newly optimized nonhuman primate model described will facilitate preclinical efficacy assessments of novel therapeutics for CNV.

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## Diet

**Arch Ophthalmol. 2011 Mar 14. [Epub ahead of print]**

### **Dietary {omega}-3 Fatty Acid and Fish Intake and Incident Age-Related Macular Degeneration in Women.**

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Schaumberg, Glynn, and Buring) and Aging (Dr Buring), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, the Department of Biostatistics, Harvard School of Public Health (Dr Glynn), and the Department of Ambulatory Care and Prevention, Harvard Medical School (Dr Buring), Boston, Massachusetts.

**OBJECTIVE:** To examine whether intake of  $\omega$ -3 fatty acids and fish affects incidence of age-related macular degeneration (AMD) in women.

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**DESIGN:** A detailed food-frequency questionnaire was administered at baseline among 39 876 female health professionals (mean [SD] age: 54.6 [7.0] years). A total of 38 022 women completed the questionnaire and were free of a diagnosis of AMD. The main outcome measure was incident AMD responsible for a reduction in best-corrected visual acuity to 20/30 or worse based on self-report confirmed by medical record review.

**RESULTS:** A total of 235 cases of AMD, most characterized by some combination of drusen and retinal pigment epithelial changes, were confirmed during an average of 10 years of follow-up. Women in the highest tertile of intake for docosahexaenoic acid, compared with those in the lowest, had a multivariate-adjusted relative risk of AMD of 0.62 (95% confidence interval, 0.44-0.87). For eicosapentaenoic acid, women in the highest tertile of intake had a relative risk of 0.66 (95% confidence interval, 0.48-0.92). Consistent with the findings for docosahexaenoic acid and eicosapentaenoic acid, women who consumed 1 or more servings of fish per week, compared with those who consumed less than 1 serving per month, had a relative risk of AMD of 0.58 (95% confidence interval, 0.38-0.87).

**CONCLUSION:** These prospective data from a large cohort of female health professionals without a diagnosis of AMD at baseline indicate that regular consumption of docosahexaenoic acid and eicosapentaenoic acid and fish was associated with a significantly decreased risk of incident AMD and may be of benefit in primary prevention of AMD.

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