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MD Research News

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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

Ophthalmologica. 2013 Oct 15. [Epub ahead of print]

Polypoidal Choroidal Vasculopathy Exudation and Hemorrhage: Results of Monthly Ranibizumab Therapy at One Year.

Kokame GT, Yeung L, Teramoto K, Lai JC, Wee R.

Division of Ophthalmology, Department of Surgery, University of Hawaii John A. Burns School of Medicine, Hawaii, USA.

Purpose: To evaluate the efficacy and safety of monthly intravitreal injections of ranibizumab in patients with polypoidal choroidal vasculopathy (PCV) and active exudation or hemorrhage.

Methods: A prospective, single practice, open label trial of monthly intravitreal ranibizumab (0.5 mg) injections for PCV in 13 eyes of 13 patients who completed the 1-year study. The primary outcome measure was stabilization of vision (loss of <15 ETDRS letters). Secondary outcome measures included incidence of ocular and systemic adverse events, changes in subretinal hemorrhage, central foveal thickness, and polypoidal complexes on indocyanine green angiography at 1 year.

Results: No patient lost ≥15 letters in visual acuity at 1 year. Three patients (23%) gained ≥15 letters at 12 months. Subretinal hemorrhage resolved in 9/9 eyes (100%). Macular edema improved in 5/5 eyes (100%). Subretinal fluid completely resolved in 4/9 eyes (44%), decreased in 2/9 eyes (22%), and increased in 3/9 eyes (33%). Polypoidal complexes decreased in 5/13 eyes (38%).

Conclusion: Continuous monthly intravitreal ranibizumab decreases leakage and hemorrhage in eyes with exudative and hemorrhagic complications of PCV. Branching vascular networks persisted, and polypoidal complexes decreased in only 5/13 (38%) eyes with continuous antiangiogenic therapy at 1 year.

PMID: 24135557 [PubMed - as supplied by publisher]

Mol Pharm. 2013 Oct 16. [Epub ahead of print]

Nanoparticles in Porous Microparticles Prepared by Supercritical Infusion and Pressure Quench Technology for Sustained Delivery of Bevacizumab.

Yandrapu SK, Upadhyay AK, Petrash JM, Kompella UB.

Abstract: Nanoparticles in porous microparticles (NPinPMP), a novel delivery system for sustained delivery of protein drugs, was developed using supercritical infusion and pressure quench technology, which does

not expose proteins to organic solvents or sonication. The delivery system design is based on the ability of supercritical carbon dioxide (SC CO2) to expand poly(lactic-co-glycolic) acid (PLGA) matrix but not polylactic acid (PLA) matrix. The technology was applied to bevacizumab, a protein drug administered once a month intravitreally to treat wet age related macular degeneration. Bevacizumab coated PLA nanoparticles were encapsulated into porosifying PLGA microparticles by exposing the mixture to SC CO2. After SC CO2 exposure, the size of PLGA microparticles increased by 6.9 fold. Confocal and scanning electron microscopy studies demonstrated the expansion and porosification of PLGA microparticles and infusion of PLA nanoparticles inside PLGA microparticles. In vitro release of bevacizumab from NPinPMP was sustained for 4 months. Size exclusion chromatography, fluorescence spectroscopy, circular dichroism spectroscopy, SDS-PAGE, and ELISA studies indicated that the released bevacizumab maintained its monomeric form, conformation, and activity. Further, in vivo delivery of bevacizumab from NPinPMP was evaluated using noninvasive fluorophotometry after intravitreal administration of Alexa Flour 488 conjugated bevacizumab in either solution or NPinPMP in a rat model. Unlike the vitreal signal from Alexa-bevacizumab solution, which reached baseline at 2 weeks, release of Alexa-bevacizumab from NPinPMP could be detected for 2 months. Thus, NPinPMP is a novel sustained release system for protein drugs to reduce frequency of protein injections in the therapy of back of the eye diseases.

PMID: 24131101 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2013 Oct 11. [Epub ahead of print]

Prospective Comparison of Low-Fluence Photodynamic Therapy Combined with Intravitreal Bevacizumab versus Bevacizumab Monotherapy for Choroidal Neovascularization in Age-Related Macular Degeneration.

Datseris I, Kontadakis GA, Diamanti R, Datseris I, Pallikaris IG, Theodossiadis P, Tsilimbaris MK.

OMMA Eye Institute , Athens , Greece .

Purpose: To evaluate combination treatment with reduced-fluence photodynamic therapy (RDPDT) with Verteporfin and intravitreal bevacizumab, compared to bevacizumab alone, for choroidal neovascularization (CNV) in age-related macular degeneration.

Methods: This was a prospective, randomized comparative study comprising 95 patients with CNV. 49 patients received RDPDT (25 J/cm2) followed by intravitreal bevacizumab 1.25 mg one hour later, while 46 received intravitreal bevacizumab alone. Patients were followed for 12 months at four-week intervals with visual acuity (VA) assessment and Optical Coherence Tomography (OCT) of the macula. Bevacizumab re-injections were performed as needed.

Results: On average, patients were re-injected 4.45 times in the combination group and 6.96 times in the bavacizumab group ($p < 0.001$). At 12 months, VA improved by 8.64 letters in the bevacizumab group and by 8.37 letters in the combination group ($p = 0.922$).

Conclusion: Adding a reduced-fluence PDT arm in combination with bevacizumab offers similar results to those of intravitreal bevacizumab alone with significantly reduced number of injection repetitions.

PMID: 24117412 [PubMed - as supplied by publisher]

Ocul Immunol Inflamm. 2013 Oct 16. [Epub ahead of print]

Subretinal Fibrosis and Uveitis: A Spectral Domain OCT Study of Its Evolution and the Minimal Therapeutic Effect of the Off-label Treatment with Ranibizumab.

Symeonidis C, Dastiridou A, Konidaris V, Brazitikos P, Androudi S.

2nd Department of Ophthalmology, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital , Thessaloniki, Macedonia , Greece .

Purpose: The subretinal fibrosis and uveitis (SFU) syndrome is a rare multifocal posterior uveitis characterized by progressive subretinal fibrosis and significant visual loss.

Methods: Slit-lamp examination, dilated fundoscopy, fluorescein angiography, Spectral Domain-Optical Coherence Tomography (SD-OCT) and laboratory testing were employed.

Results: A 52-year-old male presented with bilateral (best-corrected visual acuity: 2/10) visual loss. Clinical examination revealed bilateral anterior uveitis with posterior synechiae and posterior uveitis. Medical workup revealed no pathologic findings. Treatment included 1 gr intravenous prednisone followed by oral prednisone, immunosuppresive therapy and three ranibizumab injections in the right eye with no improvement. One year later, there was significant subretinal fibrosis. In the second year follow-up, the picture was slightly worse, with persisting bilateral macular edema and fibrosis.

Conclusions: This is the first SFU syndrome report monitored with SD-OCT. This novel imaging modality can localize the lesion level, guide the therapeutic approach and may prove helpful in assessing disease prognosis.

PMID: 24131103 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Clin Experiment Ophthalmol. 2013 Oct 3. doi: 10.1111/ceo.12247. [Epub ahead of print]

Nanosecond-laser application in intermediate AMD - 12-month results of fundus appearance and macular function.

Guymer RH, Brassington KH, Dimitrov P, Makeyeva G, Plunkett M, Xia W, Chauhan D, Vingrys A, Luu CD.

Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye & Ear Hospital, East Melbourne, Australia.

BACKGROUND: A novel, ultra-low energy nanosecond laser (Retinal Rejuvenation Therapy, 2RT) has been developed with the aim to slow progression of early age-related macular degeneration (AMD). The safety, changes in fundus characteristics and macular function in a cohort of participants with bilateral intermediate AMD is reported.

DESIGN: Prospective non-randomised, pilot intervention study.

PARTICIPANTS: Subjects with bilateral intermediate AMD (n=50, aged 50-75 years).

METHODS: Ultra-low energy laser pulses applied in 12 spots around the macula of one eye (0.15mJ to 0.45mJ), using 400um diameter spot, 3 nanosecond pulse length, 532nm wavelength and energy titrated to each patient.

MAIN OUTCOME MEASURES: Best corrected visual acuity, drusen area and macular sensitivity (flicker perimetry) at baseline and at 3, 6 and 12 months post-laser.

RESULTS: Treatment was painless with no clinically visible lesions. No participant developed choroidal neovascularization, whilst two with thin central retinal thickness at baseline developed atrophy at 12-month follow-up. Drusen area was reduced in 44% of treated eyes and 22% of untreated fellow eyes, with changes in drusen and function not being coincident. Improvement in flicker threshold within the central 3° was observed in both the treated and untreated fellow eyes at 3 months post-laser. Of the 11 eyes at greatest risk of progression (flicker defect >15dB), 7 improved sufficiently to be taken out of this high-risk category.

CONCLUSIONS: A single unilateral application of nanosecond laser to the macula produced bilateral improvements in macula appearance and function. The nanosecond 2RT laser warrants ongoing evaluation as an early intervention for AMD.

PMID: 24118741 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Oct 18. [Epub ahead of print]

Comparison of spectral-domain and high-penetration OCT for observing morphologic changes in age-related macular degeneration and polypoidal choroidal vasculopathy.

Sayanagi K, Gomi F, Ikuno Y, Akiba M, Nishida K.

Department of Ophthalmology, Osaka University Medical School, Osaka, Japan.

BACKGROUND: We compared the visibility of retinal and choroidal pathologies using high-penetration optical coherence tomography (HP-OCT) with a long-wavelength light source (1,050 nm) and conventional spectral-domain OCT (SD-OCT) in age-related macular degeneration (AMD).

METHODS: One hundred and forty-six eyes were included: 63 eyes with AMD, 79 eyes with polypoidal choroidal vasculopathy (PCV), and four eyes with retinal angiomatous proliferation. The SD-OCT and HP-OCT images were compared using the grading criteria to grade the visibility of the retinal changes, the line corresponding to the retinal pigment epithelium (RPE), and the chorioscleral interface (CSI). In 132 eyes with a pigment epithelial detachment (PED), we graded the structures inside the PED, Bruch's line, and the CSI. We compared the visibility of those changes in eyes with subretinal hyperreflective changes due to a subretinal hemorrhage (SRH) (n = 17) or a hemorrhage inside the PED (HPED) (n = 12).

RESULTS: HP-OCT provided superior visibility of the following structures compared to SD-OCT ($P < 0.01$): the CSI, structures inside the PED, Bruch's line inside the PED, the CSI inside the PED, SRH, type 1 CNV, polyps, and HPED. There were no significant differences between the two OCT devices in the scores for the RPE line, retinal morphology, or type 2 CNV and/or fibrin.

CONCLUSION: HP-OCT visualizes morphologies beneath the RPE better than SD-OCT, and is equivalent to SD-OCT for visualizing morphologies above the RPE.

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Retina. 2013 Oct 16. [Epub ahead of print]

SUITABILITY AND REPEATABILITY OF A PHOTOSTRESS RECOVERY TEST DEVICE, THE MACULAR DEGENERATION DETECTOR (MDD-2), FOR DIABETES AND DIABETIC RETINOPATHY ASSESSMENT.

Loughman J, Ratzlaff M, Foerg B, Connell P.

*Department of Optometry, School of Physics, College of Sciences and Health, Dublin Institute of Technology, Dublin, Ireland; †African Vision Research Institute, Faculty of Health Sciences, University of KwaZulu Natal, Durban, South Africa; and ‡Department of Ophthalmology, Mater Misericordiae University Hospital, Dublin, Ireland.

BACKGROUND: Diabetic retinopathy can result in impaired photostress recovery time despite normal visual acuity and fundoscopic appearance. The Macular Degeneration Detector (MDD-2) is a novel flash photostress recovery time device. In this study, we examine the repeatability of the MDD-2 in normal and diabetic subjects.

METHODS: One hundred and ninety one (90 women, 101 men) subjects were recruited and divided into 1 of the 3 study groups (normal controls, n = 40; diabetes no retinopathy, n = 98; nonproliferative diabetic retinopathy, n = 53). Photostress recovery time was measured three times in the study eye using the MDD-2, each measurement separated by a 5-minute interval.

RESULTS: Repeated measures analysis of variance revealed no statistically significant learning or fatigue effects on intrameasurement repeatability for any group. Photostress recovery time measures were broadly similar and typically not statistically significantly different between study groups. The coefficient of repeatability reached clinically acceptable levels once the initial photostress recovery time measure, which demonstrated increased variability and latency compared with all subsequent measures, was excluded.

CONCLUSION: The MDD-2 seems to provide repeatable photostress recovery time measurements among naive diabetic subjects. The device does not, however, seem capable of differentiating normal and nonproliferative diabetic eyes, and would not be suitable for inclusion in diabetic retinopathy screening protocol.

PMID: 24136407 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Oct 17. pii: iovs.13-12433v1. doi: 10.1167/iovs.13-12433. [Epub ahead of print]

Cone Structure Imaged with Adaptive Optics Scanning Laser Ophthalmoscopy in Eyes with Non-Neovascular Age-related Macular Degeneration.

Zayit-Soudry S, Duncan JL, Syed R, Menghini M, Roorda A.

Ophthalmology, UCSF, 10 Koret Way, K131, San Francisco, CA, 94143-0730, United States.

Purpose: To evaluate cone spacing using Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO) in eyes with non-neovascular age related macular degeneration (AMD), and to correlate progression of AOSLO-derived cone measures with standard measures of macular structure.

Methods: AOSLO images were obtained over 12-21 months from 7 patients with AMD including 4 eyes with geographic atrophy (GA) and 4 eyes with drusen. AOSLO images were overlaid with color, infrared and autofluorescence fundus photographs and spectral domain optical coherence tomography (SD-OCT) images to allow direct correlation of cone parameters with macular structure. Cone spacing was measured for each visit in selected regions including areas over drusen (n=29), at GA margins (n=14), and regions without drusen or GA (n=13) and compared to normal, age-similar values.

Results: AOSLO imaging revealed continuous cone mosaics up to the GA edge and overlying drusen, although reduced cone reflectivity often resulted in hyporeflective AOSLO signals at these locations. Baseline cone spacing measures were normal in 13/13 unaffected regions, 26/28 drusen regions and 12/14 GA margin regions. Although standard clinical measures showed progression of GA in all study eyes, cone spacing remained within normal ranges in most drusen regions and all GA margin regions.

Conclusion: AOSLO provides adequate resolution for quantitative measurement of cone spacing at the margin of GA and over drusen in eyes with AMD. Although cone spacing was often normal at baseline and remained normal over time, these regions showed focal areas of decreased cone reflectivity. These findings may provide insight into the pathophysiology of AMD progression.

PMID: 24135755 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Oct 17. pii: iovs.13-12617v1. doi: 10.1167/iovs.13-12617. [Epub ahead of print]

Intrasession Test-Retest Variability of Microperimetry in Age-related Macular Degeneration.

Wu Z, Ayton LN, Guymer RH, Luu CD.

Centre for Eye Research Australia, University of Melbourne, 1/32 Gisborne Street, Royal Victorian Eye and Ear Hospital, East Melbourne, VIC, 3002, Australia.

Purpose: To determine the intrasession test-retest variability of microperimetry in participants with age-related macular degeneration (AMD). Methods: This study consisted of two separate groups of subjects who have not performed microperimetry previously. In Group 1, 30 AMD and 14 control participants performed three microperimetry examinations of a selected eye within one session (Test 1 and 2 - first pair, Test 2 and 3 - second pair). Follow-up examination at six months was available in 20 AMD participants in Group 1, who performed two microperimetry examinations. In Group 2, 71 AMD participants performed a short practice examination, then two microperimetry examinations of the right eye (Test 1 and 2; first pair) and two of the left eye (Test 3 and 4; second pair). Results: There was a significant improvement in average point-wise sensitivity (PWS) between the first pair of examination in both groups ($P < 0.001$), but not in the subsequent pair ($P \geq 0.774$). This improvement was not observed at the follow-up visit in the subset of AMD participants in Group 1 ($P = 0.433$). The PWS coefficient of repeatability (CoR) for the second pair of examinations was ±4.12 dB and ±4.37 dB for AMD participants for Group 1 and 2 respectively. Conclusions: A significant increase in threshold between the first and second test, but not in the subsequent tests, was found for participants who had not performed microperimetry previously. Intrasession test-retest variability can therefore be minimised by discarding the first examination to avoid the influence of a learning effect.

PMID: 24135753 [PubMed - as supplied by publisher]

Pathogenesis

Angiogenesis. 2013 Oct 13. [Epub ahead of print]

In vitro and ex vivo retina angiogenesis assays.

Rezzola S, Belleri M, Gariano G, Ribatti D, Costagliola C, Semeraro F, Presta M.

Department of Molecular and Translational Medicine, University of Brescia, Viale Europa 11, 25123, Brescia, Italy.

Abstract: Pathological angiogenesis of the retina is a key component of irreversible causes of blindness, as observed in proliferative diabetic retinopathy, age-related macular degeneration, and retinopathy of prematurity. Seminal studies in the early 1980 s about the angiogenic activity exerted by mammalian retinal tissue extracts on the chick embryo chorioallantoic membrane and the later discovery of vascular endothelial growth factor (VEGF) accumulation in eyes of patients with diabetic retinopathy paved the way for the development of anti-angiogenic VEGF blockers for the treatment of retinal neovascularization. Since then, numerous preclinical and clinical studies about diabetic retinopathy and other retinal disorders have opened new lines of angiogenesis inquiry, indicating that limitations to anti-VEGF therapies may exist. Moreover, the production of growth factors other than VEGF may affect the response to anti-VEGF approaches. Thus, experimental models of retinal angiogenesis remain crucial for investigating novel anti-angiogenic therapies and bringing them to patients. To this aim, in vitro and ex vivo angiogenesis assays may be suitable for a rapid screening of potential anti-angiogenic molecules before in vivo validation of the putative lead compounds. This review focuses on the different in vitro and ex vivo angiogenesis assays that have been developed over the years based on the isolation of endothelial cells from the retina of various animal species and ex vivo cultures of neonatal and adult retina explants. Also, recent observations have

shown that eye neovascularization in zebrafish (Danio rerio) embryos, an in vivo animal platform experimentally analogous to in vitro/ex vivo models, may represent a novel target for the identification of angiogenesis inhibitors. When compared to in vivo assays, in vitro and ex vivo models of retina neovascularization, including zebrafish embryo, may represent cost-effective and rapid tools for the screening of novel anti-angiogenic therapeutics.

PMID: 24121991 [PubMed - as supplied by publisher]

Free Radic Biol Med. 2013 Oct 10. pii: S0891-5849(13)00637-0. doi: 10.1016/j.freeradbiomed.2013.10.006. [Epub ahead of print]

Independent roles of methionine sulfoxide reductase A in mitochondrial ATP synthesis and as antioxidant in retinal pigment epithelial cells.

Dun Y, Vargas J, Brot N, Finnemann SC.

Department of Biological Sciences, Center for Cancer, Genetic Diseases, and Gene Regulation, Fordham University, Bronx, NY 10458, USA.

Abstract: The antioxidant enzyme methionine sulfoxide reductase A (MsrA) is highly expressed in the retinal pigment epithelium (RPE), a support tissue for neighboring photoreceptors. MsrA protein levels correlate with sensitivity of RPE in culture to experimental oxidative stress. To investigate whether and how MsrA affects RPE functionality regardless of oxidative stress, we tested the effects of acute silencing or overexpression of MsrA on the phagocytosis of photoreceptor outer segment fragments (POS), a demanding, daily function of the RPE that is essential for vision. Endogenous MsrA localized to mitochondria and cytosol of rat RPE in culture. RPE cells manipulated to express higher or lower levels of MsrA than control cells showed no signs of cell death but increased or decreased, respectively, POS binding as well as engulfment. These effects of altered MsrA protein concentration on phagocytosis were independent of the levels of oxidative stress. However, altering MsrA expression had no effect on phagocytosis when mitochondrial respiration was inhibited. Furthermore, ATP content directly correlated with MsrA protein levels in RPE cells that used mitochondrial oxidative phosphorylation for ATP synthesis but not in RPE cells that relied on glycolysis alone. Overexpressing MsrA was sufficient to increase specifically the activity of complex-IV of the respiratory chain, while activity of complex-II and mitochondrial content were unaffected. Thus, MsrA likely enhances ATP synthesis by increasing complex-IV activity. Such contribution of MsrA to energy metabolism is independent of its function in protection from elevated oxidative stress but contributes to routine but vital photoreceptor support by RPE cells.

PMID: 24120970 [PubMed - as supplied by publisher]

Int J Biochem Cell Biol. 2013 Oct 9. pii: S1357-2725(13)00305-1. doi: 10.1016/j.biocel.2013.09.016. [Epub ahead of print]

CD46: The 'multitasker' of complement proteins.

Yamamoto H, Fara A, Dasgupta P, Kemper C.

Division of Transplant Immunology and Mucosal Biology, MRC Centre for Transplantation, King's College London, Guy's Hospital, London SE1 9RT, UK; The Urology Centre, Guy's and St. Thomas' NHS Foundations Trust, London SE1 9RT, UK.

Abstract: Complement is undeniably quintessential for innate immunity by detecting and eliminating infectious microorganisms. Recent work, however, highlights an equally profound impact of complement on the induction and regulation of a wide range of immune cells. In particular, the complement regulator CD46 emerges as a key sensor of immune activation and a vital modulator of adaptive immunity. In this review,

we summarize the current knowledge of CD46-mediated signalling events and their functional consequences on immune-competent cells with a specific focus on those in CD4+ T cells. We will also discuss the promises and challenges that potential therapeutic modulation of CD46 may hold and pose.

PMID: 24120647 [PubMed - as supplied by publisher]

PLoS One. 2013 Oct 9;8(10):e76766.

Topical Application of PPADS Inhibits Complement Activation and Choroidal Neovascularization in a Model of Age-Related Macular Degeneration.

Birke K, Lipo E, Birke MT, Kumar-Singh R.

Department of Ophthalmology, Tufts University School of Medicine, Boston, Massachusetts, United States of America.

Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness among the elderly. AMD patients have elevated levels of membrane attack complex (MAC) in their choroidal blood vessels and retinal pigment epithelium (RPE). MAC forms pores in cell membranes. Low levels of MAC result in an elevation of cytokine release such as vascular endothelial growth factor (VEGF) that promotes the formation of choroidal neovascularization (CNV). High levels of MAC result in cell lysis and RPE degeneration is a hallmark of advanced AMD. The current standard of care for CNV associated with wet AMD is intravitreal injection of anti-VEGF molecules every 4 to 12 weeks. Such injections have significant side effects. Recently, it has been found that membrane pore-forming proteins such as α-haemolysin can mediate their toxic effects through auto- and paracrine signaling and that complement-induced lysis is amplified through ATP release followed by P2X receptor activation. We hypothesized that attenuation of P2X receptor activation may lead to a reduction in MAC deposition and consequent formation of CNV. Hence, in this study we investigated topical application of the purinergic P2X antagonist Pyridoxalphosphate-6-azophenyl-2',4'-disulphonic acid (PPADS) as a potential treatment for AMD. We found that 4.17 µM PPADS inhibited formation of HUVEC master junctions and master segments by 74.7%. In a human complement mediated cell lysis assay, 104 µM PPADS enabled almost complete protection of Hepa1c1c7 cells from 1% normal human serum mediated cell lysis. Daily topical application of 4.17 mM PPADS for 3 days attenuated the progression of laser induced CNV in mice by 41.8% and attenuated the deposition of MAC at the site of the laser injury by 19.7%. Our data have implications for the future treatment of AMD and potentially other ocular disorders involving CNV such as angioid streaks, choroidal rupture and high myopia.

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Angiogenesis. 2013 Oct 16. [Epub ahead of print]

A peptide derived from TIMP-3 inhibits multiple angiogenic growth factor receptors and tumour growth and inflammatory arthritis in mice.

Chen YY, Brown NJ, Jones R, Lewis CE, Mujamammi AH, Muthana M, Seed MP, Barker MD.

Department of Oncology, Medical School, University of Sheffield, Beech Hill Road, Sheffield, S10 2RX, UK.

Abstract: The binding of vascular endothelial growth factor (VEGF) to VEGF receptor-2 (VEGFR-2) on the surface of vascular endothelial cells stimulates many steps in the angiogenic pathway. Inhibition of this interaction is proving of value in moderating the neovascularization accompanying age-related macular degeneration and in the treatment of cancer. Tissue inhibitor of metalloproteinases-3 (TIMP-3) has been shown to be a natural VEGFR-2 specific antagonist-an activity that is independent of its ability to inhibit metalloproteinases. In this investigation we localize this activity to the C-terminal domain of the TIMP-3

molecule and characterize a short peptide, corresponding to part of this domain, that not only inhibits all three VEGF-family receptors, but also fibroblast growth factor and platelet-derived growth factor receptors. This multiple-receptor inhibition may explain why the peptide was also seen to be a powerful inhibitor of tumour growth and also a partial inhibitor of arthritic joint inflammation in vivo.

PMID: 24129822 [PubMed - as supplied by publisher]

J Control Release. 2013 Oct 11. pii: S0168-3659(13)00838-9. doi: 10.1016/j.jconrel.2013.10.008. [Epub ahead of print]

Sustained Delivery of a HIF-1 Antagonist for Ocular Neovascularization.

Iwase T, Fu J, Yoshida T, Muramatsu D, Miki A, Hashida N, Lu L, Oveson B, Lima E Silva R, Seidel C, Yang M, Connelly S, Shen J, Han B, Wu M, Semenza GL, Hanes J, Campochiaro PA.

Department of Ophthalmology, Baltimore, MD; Department of Neuroscience, Baltimore, MD.

Abstract: Doxorubicin (DXR) and daunorubicin (DNR) inhibit hypoxia-inducible factor-1 (HIF-1) transcriptional activity by blocking its binding to DNA. Intraocular injections of DXR or DNR suppressed choroidal and retinal neovascularization (NV), but also perturbed retinal function as demonstrated by electroretinograms (ERGs). DXR was conjugated to novel copolymers of branched polyethylene glycol and poly(sebacic acid) (DXR-PSA-PEG3) and formulated into nanoparticles that when placed in aqueous buffer, slowly released small DXR-conjugates. Intraocular injection of DXR-PSA-PEG3 nanoparticles (1 or 10 μg DXR content) reduced HIF-1-responsive gene products, strongly suppressed choroidal and retinal NV, and did not cause retinal toxicity. In transgenic mice that express VEGF in photoreceptors, intraocular injection of DXR-PSA-PEG3 nanoparticles (10 μg DXR content) suppressed NV for at least 35 days. Intraocular injection of DXR-PSA-PEG3 nanoparticles (2.7 mg DXR content) in rabbits resulted in sustained DXR-conjugate release with detectable levels in aqueous humor and vitreous for at least 105 days. This study demonstrates a novel HIF-1-inhibitor-polymer conjugate formulated into controlled-release particles that maximizes efficacy and duration of activity, minimizes toxicity, and provides a promising new chemical entity for treatment of ocular NV.

PMID: 24126220 [PubMed - as supplied by publisher]

Nat Protoc. 2013 Nov;8(11):2197-2211. doi: 10.1038/nprot.2013.135. Epub 2013 Oct 17.

Laser-induced choroidal neovascularization model to study age-related macular degeneration in mice.

Lambert V, Lecomte J, Hansen S, Blacher S, Gonzalez ML, Struman I, Sounni NE, Rozet E, de Tullio P, Foidart JM, Rakic JM, Noel A.

1] Department of Ophthalmology, University Hospital (CHU), Liège, Belgium. [2] Laboratory of Tumor and Development Biology, GIGA-Cancer, University of Liège, Liège, Belgium.

Abstract: The mouse model of laser-induced choroidal neovascularization (CNV) has been used extensively in studies of the exudative form of age-related macular degeneration (AMD). This experimental in vivo model relies on laser injury to perforate Bruch's membrane, resulting in subretinal blood vessel recruitment from the choroid. By recapitulating the main features of the exudative form of human AMD, this assay has served as the backbone for testing antiangiogenic therapies. This standardized protocol can be applied to transgenic mice and can include treatments with drugs, recombinant proteins, antibodies, adenoviruses and pre-microRNAs to aid in the search for new molecular regulators and the identification of novel targets for innovative treatments. This robust assay requires 7-14 d to complete, depending on the treatment applied and whether immunostaining is performed. This protocol includes details of how to induce

CNV, including laser induction, lesion excision, processing and different approaches to quantify neoformed vasculature.

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Invest Ophthalmol Vis Sci. 2013 Oct 17. pii: iovs.13-12546v1. doi: 10.1167/iovs.13-12546. [Epub ahead of print]

Bone Marrow Transplantation Transfers Age-Related Susceptibility To Neovascular Remodeling In Murine Laser-Induced Choroidal Neovascularization.

Espinosa-Heidmann DG, Malek G, Mettu PS, Caicedo A, Saloupis P, Gach S, Dunnon A, Hu P, Spiga MG, Cousins SW.

Ophthalmology, Georgia Health Sciences University, Augusta, GA, 30912, United States.

Purpose: Neovascular remodeling (NVR), the progression of small capillaries into large-caliber arterioles with perivascular fibrosis, represents a major therapeutic challenge in neovascular age-related macular degeneration (AMD). NVR occurs after laser-induced choroidal neovascularization (CNV) in aged but not young mice. Additionally, bone marrow-derived cells, including macrophages, endothelial precursor cells, and mesenchymal precursor cells, contribute to CNV severity. In this study, we investigated the impact of aged bone marrow transplantation (BMT) on the degree of fibrosis, size, and vascular morphology of CNV lesions in a mouse model of laser-induced CNV.

Methods: Young (2-months) and old (16-months) mice were transplanted with GFP-labeled bone marrow isolated from either young or old donors. Laser CNV was induced one month following transplant and eyes were analyzed via choroidal flatmounts and immunohistochemistry one month post-laser. The identity of cells infiltrating CNV lesions was determined using specific markers for the labeled transplanted cells (GFP+), macrophages (F4/80+), perivascular mesenchymal-derived cells (SMA+), and endothelial cells (CD31+).

Results: BMT from aged mice transferred susceptibility to NVR into young recipients. Inversely, transplantation of young marrow into old mice prevented NVR, preserving small size and minimal fibrosis. Mice with NVR demonstrated a greater relative contribution of marrow-derived SMA+ perivascular mesenchymal cells as compared to other cells.

Conclusions: Our findings indicate that the status of bone marrow is an important determining factor of neovascular severity. Furthermore, we find that perivascular mesenchymal cells, rather than endothelial cells, derived from aged bone marrow may contribute to increased CNV severity in this murine model of experimental neovascularization.

PMID: 24135751 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2013 Oct 10. pii: S0161-6420(13)00693-3. doi: 10.1016/j.ophtha.2013.07.053. [Epub ahead of print]

Prediction of Age-related Macular Degeneration in the General Population: The Three Continent AMD Consortium.

Buitendijk GH, Rochtchina E, Myers C, van Duijn CM, Lee KE, Klein BE, Meuer SM, de Jong PT, Holliday EG, Tan AG, Uitterlinden AG, Sivakumaran TS, Attia J, Hofman A, Mitchell P, Vingerling JR, Iyengar SK, Janssens AC, Wang JJ, Klein R, Klaver CC.

Department of Ophthalmology, Erasmus Medical Center, Rotterdam, The Netherlands; Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands.

PURPOSE: Prediction models for age-related macular degeneration (AMD) based on case-control studies have a tendency to overestimate risks. The aim of this study is to develop a prediction model for late AMD based on data from population-based studies.

DESIGN: Three population-based studies: the Rotterdam Study (RS), the Beaver Dam Eye Study (BDES), and the Blue Mountains Eye Study (BMES) from the Three Continent AMD Consortium (3CC).

PARTICIPANTS: People (n = 10 106) with gradable fundus photographs, genotype data, and follow-up data without late AMD at baseline.

METHODS: Features of AMD were graded on fundus photographs using the 3CC AMD severity scale. Associations with known genetic and environmental AMD risk factors were tested using Cox proportional hazard analysis. In the RS, the prediction of AMD was estimated for multivariate models by area under receiver operating characteristic curves (AUCs). The best model was validated in the BDES and BMES, and associations of variables were re-estimated in the pooled data set. Beta coefficients were used to construct a risk score, and risk of incident late AMD was calculated using Cox proportional hazard analysis. Cumulative incident risks were estimated using Kaplan-Meier product-limit analysis.

MAIN OUTCOME MEASURES: Incident late AMD determined per visit during a median follow-up period of 11.1 years with a total of 4 to 5 visits.

RESULTS: Overall, 363 participants developed incident late AMD, 3378 participants developed early AMD, and 6365 participants remained free of any AMD. The highest AUC was achieved with a model including age, sex, 26 single nucleotide polymorphisms in AMD risk genes, smoking, body mass index, and baseline AMD phenotype. The AUC of this model was 0.88 in the RS, 0.85 in the BDES and BMES at validation, and 0.87 in the pooled analysis. Individuals with low-risk scores had a hazard ratio (HR) of 0.02 (95% confidence interval [CI], 0.01-0.04) to develop late AMD, and individuals with high-risk scores had an HR of 22.0 (95% CI, 15.2-31.8). Cumulative risk of incident late AMD ranged from virtually 0 to more than 65% for those with the highest risk scores.

CONCLUSIONS: Our prediction model is robust and distinguishes well between those who will develop late AMD and those who will not. Estimated risks were lower in these population-based studies than in previous case-control studies.

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