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Other treatment & diagnosis

Eur J Pharm Biopharm. 2011 Nov 20. [Epub ahead of print]

A pharmacokinetic study of a combination of beta adrenoreceptor antagonists - In the isolated perfused ovine eye.

Mains J, Tan LE, Wilson C, Urquhart A.

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Scotland, United Kingdom.

Abstract

The treatment of posterior eye diseases, such as diabetic retinopathy and age-related macular degeneration, is of growing interest as the number of people affected by these conditions continues to rise. This study utilises the methods of cassette dosing and the perfused ovine eye model - to reduce animal usage and therefore animal time - to show that for a series of beta adrenoreceptor antagonists, lipophilicity is a key physicochemical property that governs drug distribution within the eye. Following intravitreal injection, lipophilic beta adrenoreceptor antagonists penetrate to the posterior eye, where they bind to the choroid and reside in the retina at greater concentrations than more hydrophilic beta adrenoreceptor antagonists, which preferentially penetrate to the anterior eye.

PMID:22120686 [PubMed - as supplied by publisher]

Pathogenesis

Curr Mol Pharmacol. 2011 Nov 24. [Epub ahead of print]

APE1/Ref-1Role in Redox Signaling: Translational Applications of Targeting the Redox Function of the DNA Repair/Redox Protein APE1/Ref-1.

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Abstract

The heterogeneity of most cancers diminishes the treatment effectiveness of many cancer-killing regimens.

Thus, treatments that hold the most promise are ones that block multiple signaling pathways essential to cancer survival. One of the most promising proteins in that regard is APE1, whose reduction-oxidation activity influences multiple cancer survival mechanisms, including growth, proliferation, metastasis, angiogenesis, and stress responses. With the continued research using APE1 redox specific inhibitors alone or coupled with developing APE1 DNA repair inhibitors it will now be possible to further delineate the role of APE1 redox, repair and protein-protein interactions. Previously, use of siRNA or over expression approaches, while valuable, do not give a clear picture of the two major functions of APE1 since both techniques severely alter the cellular milieu. Additionally, use of the redox-specific APE1 inhibitor, APX3330, now makes it possible to study how inhibition of APE1's redox signaling can affect multiple tumor pathways and can potentiate the effectiveness of existing cancer regimens. Because APE1 is an upstream effector of VEGF, as well as other molecules that relate to angiogenesis and the tumor microenvironment, it is also being studied as a possible treatment for age-related macular degeneration and diabetic retinopathy. This paper reviews all of APE1's functions, while heavily focusing on its redox activities. It also discusses APE1's altered expression in many cancers and the therapeutic potential of selective inhibition of redox regulation, which is the subject of intense preclinical studies.

PMID:22122463 [PubMed - as supplied by publisher]

Med Hypotheses. 2011 Nov 28. [Epub ahead of print]

Effective mobilisation of bone marrow-derived cells through proteolytic activity: A new treatment strategy for age-related macular degeneration.

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Abstract

Selective targeting of bone marrow-derived cells (BMCs) has been heralded as a promising avenue for age-related macular degeneration (AMD) therapeutics. Many researchers have demonstrated that the function of circulating BMCs is related to disease severity in patients with AMD. Transplanted BMCs are able to transdifferentiate into retina-specific cells to replace those lost due to damage or degeneration in the pathologic process of experimental models of AMD, which may provide beneficial effects in patients with AMD. However, a major barrier to transferring the use of BMCs into clinical practice is the limited quantity of BMCs in the peripheral circulation. Technology has not yet reached a stage where ex vivo-expanded BMCs can be routinely used for cell therapy. A feasible strategy to circumvent this issue of BMC scarcity is to increase the mobilisation of autologous BMCs from the patient's bone marrow into the blood circulation. Extensive studies have demonstrated that the SDF-1/CXCR4 axis is a key regulator for BMC mobilisation. Moreover, abrogation of the SDF-1/CXCR4 axis by proteolytic modification can efficiently increase BMC mobilisation. We speculate that BMC mobilisation by proteolytic enzymes may supply a sufficient amount of autologous cells to repair and regenerate injured and degenerated the retinal pigment epithelium (RPE), photoreceptors, or other retina-specific cells, which could prevent AMD progression. If the BMC mobilisation strategy is used to treat AMD, it may overcome the existing problems of transferring BMC-based therapy into the clinic and become a particularly feasible therapeutic approach for AMD.

PMID:22129485 [PubMed - as supplied by publisher]

J Interferon Cytokine Res. 2011 Dec 1. [Epub ahead of print]

Recombinant and Natural Human Interferons: Analysis of the Incidence and Clinical Impact of Neutralizing Antibodies.

Strayer DR, Carter WA.

Department of Clinical Research , Hemispherx Biopharma, Inc., Philadelphia, Pennsylvania.

Abstract

This review summarizes and analyzes the clinical outcomes following treatment of a wide range of diseases with recombinant interferons (r-IFNs) and/or natural interferons (n-IFNs). The investigation focuses on the frequency of neutralizing antibodies (NABs) directed against IFN, which are formed during treatment and their clinical impact. r-IFNs (α-2a, α-2b, β-1a, and β-1b) induced seroconversion with generation of NABs in 17.2% of patients studied. The highest incidence of NABs occurred in macular degeneration (61.4%) with the lowest in multiple sclerosis (14.7%). The incidence of antibodies induced against n-IFNs was very low (<0.2%) and was significantly less than that seen for r-IFNs (P<0.0001). Overall, the fraction of relapsed and refractory patients is statistically greater in NAB positive patients compared to NAB negative patients (<0.0001), whereas the percentage of responding patients is higher in the NAB negative cohort (P<0.001). Finally, we also analyzed relapsed and refractory NAB positive patients who switched treatment to n-IFN, such as leukocyte derived Alferon N Injection(®) (α-n3) or Wellferon(®) (α-n1). Overall, in 33/40 (82%) of these relapsed or refractory patients, switching to n-IFNs restored the clinical response. This result is consistent with serology studies showing that the NABs directed against r-IFNs do not effectively cross-react with n-IFNs.

PMID:22132684 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmic Res. 2011 Nov 26;47(4):171-188. [Epub ahead of print]

Epidemiology of Major Eye Diseases Leading to Blindness in Europe: A Literature Review.

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Abstract

The objective of this work was to study the epidemiology of major eye diseases leading to blindness in Europe through a systematic literature review. The literature search was performed using the Medline database (PubMed), with MeSH and free text search terms. Inclusion criteria for the studies were: (a) performed on a healthy population of Caucasian origin aged between 50 and 75 years; (b) diagnosed by ophthalmological examination in accordance with the International Classification of Diseases 10; (c) contained a detailed description of the sampling and diagnostic procedures and data resources; (d) sample size >500, and (e) published between 1990 and 2008. The results of 57 studies on the prevalence and incidence of age-related macular degeneration, diabetic retinopathy and glaucoma are reported, providing an up-to-date and comprehensive overview of these diseases in Europe from an epidemiological perspective.

PMID:22123077 [PubMed - as supplied by publisher]

J Epidemiol. 2011 Nov 26. [Epub ahead of print]

Prevalence of Eye Diseases and Causes of Visual Impairment in School-Aged Children in Western China.

Pi LH, Chen L, Liu Q, Ke N, Fang J, Zhang S, Xiao J, Ye WJ, Xiong Y, Shi H, Zhou XY, Yin ZQ.

Department of Ophthalmology, Children's Hospital, Chongqing Medical University.

Background: The present study investigated the prevalence of refractive error, visual impairment, and eye diseases in school-aged children in western China.

Methods: The survey was done in a representative county (Yongchuan District, Chongqing Municipality) of western China. Cluster random sampling was used to select children aged 6 to 15 years. We conducted door-to-door surveys and eye examinations including optometry, stereoscopic vision test, eye position and eye movement, slit lamp examination of the anterior segment, retinoscopy, and fundus examination after cycloplegia with 1% cyclopentolate.

Results: Among 3469 children, data were available for 3079 (88.76%). The prevalences of eye diseases were, in descending order, refractive error (20.69%; 637/3079), conjunctivitis (11.76%; 362/3079), amblyopia (1.88%; 58/3079), color vision defect (0.52%; 16/3079), keratitis (0.36%; 11/3079), strabismus (0.29%; 9/3079), cataract (0.23%; 7/3079), pathologic myopia (0.19%; 6/3079), and ocular trauma (0.13%; 4/3079). The prevalence of corneal leucoma, corneal staphyloma, optic neuropathy, macular degeneration, and myelinated nerve fibers was 0.03% (1/3079) for each. The prevalence of visual impairment was 7.70% (237/3079), and the major causes of visual impairment were uncorrected refractive error (86.08%; 204/237), amblyopia (9.70%; 23/237), pathologic myopia (1.27%; 3/237), congenital cataract (0.42%; 1/237), and others (2.11%; 5/237).

Conclusions: Among school-aged children in a less developed area of western China, refractive error was the most prevalent eye disorder, and uncorrected refractive error was the main cause of visual impairment.

PMID:22123227 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2011 Dec;25(6):421-33. Epub 2011 Nov 22.

Prevalence of eye diseases in South Korea: data from the Korea national health and nutrition examination survey 2008-2009.

Yoon KC, Mun GH, Kim SD, Kim SH, Kim CY, Park KH, Park YJ, Baek SH, Song SJ, Shin JP, Yang SW, Yu SY, Lee JS, Lim KH, Park HJ, Pyo EY, Yang JE, Kim YT, Oh KW, Kang SW.

Department of Ophthalmology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea.

PURPOSE: The aim of this study is to report on preliminary data regarding the prevalence of major eye diseases in Korea.

METHODS: We obtained data from the Korea National Health and Nutrition Examination Survey, a nation-wide cross-sectional survey and examinations of the non-institutionalized civilian population in South Korea (n = 14,606), conducted from July 2008 to December 2009. Field survey teams included an ophthalmologist, nurses, and interviewers, traveled with a mobile examination unit and performed interviews and ophthalmologic examinations.

RESULTS: The prevalence of visual impairment, myopia, hyperopia and astigmatism in participants over 5 years of age was 0.4 ± 0.1%, 53.7 ± 0.6%, 10.7 ± 0.4%, and 58.0 ± 0.6%, respectively. The prevalence of strabismus and blepharoptosis in participants over 3 years of age was 1.5 ± 0.1% and 11.0 ± 0.8%, respectively. In participants over 40 years of age, the prevalence of cataract, pterygium, early and late age-related macular degeneration, diabetic retinopathy and glaucoma was 40.2 ± 1.3%, 8.9 ± 0.5%, 5.1 ± 0.3%, 0.5 ± 0.1%, 13.4 ± 1.5%, and 2.1 ± 0.2%, respectively.

CONCLUSIONS: This is the first nation-wide epidemiologic study conducted in South Korea for assessment of the prevalence of eye diseases by both the Korean Ophthalmologic Society and the Korea Center for Disease Control and Prevention. This study will provide preliminary information for use in further

investigation, prevention, and management of eye diseases in Korea.

PMID:22131780 [PubMed - in process] PMCID: PMC3223710

Genetics

Ophthalmology. 2011 Nov 29. [Epub ahead of print]

Risk Alleles in CFH and ARMS2 Are Independently Associated with Systemic Complement Activation in Age-related Macular Degeneration.

Smailhodzic D, Klaver CC, Klevering BJ, Boon CJ, Groenewoud JM, Kirchhof B, Daha MR, den Hollander AI, Hoyng CB.

Department of Ophthalmology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

PURPOSE: Systemic complement activation is associated with age-related macular degeneration (AMD) and has mainly been attributed to a risk allele in the complement factor H (CFH) gene. Whether other important AMD genes also influence complement activation is unclear. In the present case-control study, complement activity and concentrations of complement components and their activation products are measured in AMD patients and in unaffected controls and correlated with genetic variants in the CFH, ARMS2, C3, CFI, and CFB genes.

DESIGN: Case-control study.

PARTICIPANTS: A cohort of 197 confirmed AMD patients and 150 unaffected age-matched controls were recruited prospectively for the study.

METHODS: Hemolytic complement assays (AP50, CP50, and LP50), complement components (C3, CFB, CFI, and CFH), and the activation products (C3d, C5a, and SC5b-9) were analyzed in serum or plasma. The DNA samples were genotyped for 5 single nucleotide polymorphisms (SNPs) previously associated with AMD in the CFH, ARMS2, C3, CFB, and CFI genes.

MAIN OUTCOME MEASURES: Complement concentrations and their associations with SNPs in the CFH, ARMS2, C3, CFB, and CFI genes.

RESULTS: The AMD patients had increased activation of the alternative complement pathway ($P = 0.003$) and elevated levels of complement activation components C3d ($P<0.0001$) and C5a ($P<0.0001$), CFB ($P<0.0001$), and an increased C3d/C3 ratio ($P<0.0001$) calculated as a measure of C3 activation. While the CFH risk genotype was significantly associated with the elevated C3d/C3 ratios obtained, in the absence of CFH risk alleles the ARMS2 risk genotype also showed significantly increased levels of complement activation ($P = 0.013$). Furthermore, the carriers of the CFB protective allele had lower CFB concentrations.

CONCLUSIONS: The current study found evidence showing that in AMD risk alleles in CFH and ARMS2 are independently associated with complement activation. Especially the C3d/C3 ratio seems to be a strong marker for AMD. The findings suggest that CFH and ARMS2 share a common pathway in the pathogenesis of AMD.

PMID:22133792 [PubMed - as supplied by publisher]

J Vis Exp. 2011 Nov 19;(57). pii: 3184. doi: 10.3791/3184.

Mouse Eye Enucleation for Remote High-throughput Phenotyping.

Mahajan VB, Skeie JM, Assefnia AH, Mahajan M, Tsang SH.

Department of Ophthalmology and Visual Sciences, University of Iowa.

Abstract

The mouse eye is an important genetic model for the translational study of human ophthalmic disease. Blinding diseases in humans, such as macular degeneration, photoreceptor degeneration, cataract, glaucoma, retinoblastoma, and diabetic retinopathy have been recapitulated in transgenic mice.(1-5) Most transgenic and knockout mice have been generated by laboratories to study non-ophthalmic diseases, but genetic conservation between organ systems suggests that many of the same genes may also play a role in ocular development and disease. Hence, these mice represent an important resource for discovering new genotype-phenotype correlations in the eye. Because these mice are scattered across the globe, it is difficult to acquire, maintain, and phenotype them in an efficient, cost-effective manner. Thus, most high-throughput ophthalmic phenotyping screens are restricted to a few locations that require on-site, ophthalmic expertise to examine eyes in live mice. (6-9) An alternative approach developed by our laboratory is a method for remote tissue-acquisition that can be used in large or small-scale surveys of transgenic mouse eyes. Standardized procedures for video-based surgical skill transfer, tissue fixation, and shipping allow any lab to collect whole eyes from mutant animals and send them for molecular and morphological phenotyping. In this video article, we present techniques to enucleate and transfer both unfixed and perfusion fixed mouse eyes for remote phenotyping analyses.

PMID:22126835 [PubMed - in process]

Nat Genet. 2011 Nov 28;43(12):1176-7. doi: 10.1038/ng.1012.

A rare variant in CFH directly links age-related macular degeneration with rare glomerular nephropathies.

Wright AF.

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Abstract

A careful analysis of risk haplotypes in relation to age-related macular degeneration (AMD) susceptibility has led to the identification of a rare, high-penetrance variant in the complement factor H (CFH) gene that is also causally associated with atypical hemolytic uremic syndrome (aHUS) and related glomerulopathies. This finding provides a convincing causal mechanism linking the two diseases and develops a paradigm for the genetic architecture of a common and complex disease.

PMID:22120053 [PubMed - in process]

Genet Epidemiol. 2011 Dec;35(8):745-54. doi: 10.1002/gepi.20622.

Sifting the wheat from the chaff: prioritizing GWAS results by identifying consistency across analytical methods.

Oldmeadow C, Riveros C, Holliday EG, Scott R, Moscato P, Wang JJ, Mitchell P, Buitendijk GH, Vingerling JR, Klaver CC, Klein R, Attia J.

School of Medicine and Public Health, University of Newcastle, Newcastle upon Tyne, United Kingdom; Hunter Medical Research Institute, John Hunter Hospital, New Lambton Heights, New South Wales, Australia. christoper.oldmeadow@newcastle.edu.au.

Abstract

The curse of multiple testing has led to the adoption of a stringent Bonferroni threshold for declaring genome-wide statistical significance for any one SNP as standard practice. Although justified in avoiding false positives, this conservative approach has the potential to miss true associations as most studies are drastically underpowered. As an alternative to increasing sample size, we compare results from a typical SNP-by-SNP analysis with three other methods that incorporate regional information in order to boost or dampen an otherwise noisy signal: the haplotype method (Schaid et al. [2002] Am J Hum Genet 70:425-434), the gene-based method (Liu et al. [2010] Am J Hum Genet 87:139-145), and a new method (interaction count) that uses genome-wide screening of pairwise SNP interactions. Using a modestly sized case-control study, we conduct a genome-wide association studies (GWAS) of age-related macular degeneration, and find striking agreement across all methods in regions of known associated variants. We also find strong evidence of novel associated variants in two regions (Chromosome 2p25 and Chromosome 10p15) in which the individual SNP P-values are only suggestive, but where there are very high levels of agreement between all methods. We propose that consistency between different analysis methods may be an alternative to increasingly larger sample sizes in sifting true signals from noise in GWAS. Genet. Epidemiol. 2011. © 2011 Wiley Periodicals, Inc. 35:745-754, 2011.

PMID:22125219 [PubMed - in process]

Diet

Mol Nutr Food Res. 2011 Nov 25. doi: 10.1002/mnfr.201100219. [Epub ahead of print]

A review of the evidence germane to the putative protective role of the macular carotenoids for age-related macular degeneration.

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Abstract

There is a consensus that age-related macular degeneration (AMD) is the result of (photo)-oxidative-induced retinal injury and its inflammatory sequelae, the latter being influenced by genetic background. The dietary carotenoids, lutein (L), zeaxanthin (Z), and meso-zeaxanthin (meso-Z), accumulate at the macula, where they are collectively known as macular pigment (MP). The anatomic (central retinal), biochemical (anti-oxidant) and optical (short-wavelength-filtering) properties of this pigment have generated interest in the biologically plausible rationale that MP may confer protection against AMD. Level 1 evidence has shown that dietary supplementation with broad-spectrum anti-oxidants results in risk reduction for AMD progression. Studies have demonstrated that MP rises in response to supplementation with the macular carotenoids, although level 1 evidence that such supplementation results in risk reduction of AMD and/or its progression is still lacking. Although appropriately weighted attention should be accorded to higher levels of evidence, the totality of available data should be appraised in an attempt to inform professional practice. In this context, the literature demonstrates that supplementation with the macular carotenoids is probably the best means of fortifying the anti-oxidant defences of the macula, thus putatively reducing the risk of AMD and/or its progression.

PMID:22121091 [PubMed - as supplied by publisher]