The Edward N. & Della L. Thome Memorial Foundation Awards Program in Age-Related Macular Degeneration Research

2018 Grant Cycle

Catherine Bowes Rickman, Ph.D.
Associate Professor, Departments of Ophthalmology and Cell Biology
Duke University

"HDL - a Therapeutic Target for Age-related Macular Degeneration"

Scientific Abstract
There is strong evidence that lipid metabolism is a major pathway involved in the pathogenesis of age-related macular degeneration (AMD), a blinding disease that involves retinal pigmented epithelium (RPE) dysfunction. For cholesterol and lipid homeostasis, RPE cells utilize high-density lipoproteins (HDL). Apolipoprotein A-1 (ApoA-1) containing lipoproteins isolated from Bruch's membrane (BrM) of elderly human donor eyes have a unique protein composition, quite different from HDL isolated from plasma of the same individual. The most striking difference in these particles is the significantly higher concentration of ApoB and ApoE, which are known to bind to glycosaminoglycans (GAGs). Thus, their presence appears to promote LDL deposition onto BrM GAGs, initiating downstream effects such as reducing the free movement of molecules to and from the choriocapillaris, harmful oxidation of deposited proteins and lipids, complement activation and subsequent inflammatory responses that lead to RPE dysfunction/death. In this application we propose to test the hypothesis that HDL is a therapeutic target for AMD. We propose to: Aim 1: Identify conditions that promote "harmful" HDL production by RPE cells using polarized, primary RPE cell cultures; Aim 2: Test the efficacy of an ApoA-1 mimetic peptide to reduce lipid deposition in the eye, and resolve visual function loss and RPE damage in a multifactorial AMD mouse model [aged, humanized complement factor H H402 (CFH-H402:Cfh-/-) mouse on a high fat, high cholesterol diet]; and Aim 3: Compare the composition of plasma HDL (HDL proteome) in our AMD mouse model and controls to identify differentially occurring proteins that implicate disrupted pathways in the disease process and/or therapeutic targets that can be further interrogated.

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Tejala Desai, Ph.D.
Professor and Chair, Bioengineering and Therapeutic Sciences
University of California San Francisco

"Zero-order sustained release from a biodegradable thin film device for the treatment of macular degeneration"

Scientific Abstract

Over the past several years, our ophthalmology/bioengineering research group at UCSF has made progress in the development of nano-porous thin-film biopolymer devices for sustained intraocular delivery of large molecule, antibody-based retinal therapeutics, including ranibizumab (Lucentis) and aflibercept (Eylea). Employing novel nano-porous diffusion membranes, our proof-of-concept work has achieved linear drug release maintained over 4 months at 2-40 μg/day. Zero-order pharmacokinetics enables tight control of target drug concentrations, avoiding both initial bolus excess and late sub-therapeutic decline, while maximizing the small drug payloads necessitated by the size restrictions of the eye. Constructed from medically established polymer, poly(caprolactone) (PCL), the devices are bioerodible. Devices are fabricated from flexible thin films formed into cylindrical devices to fit within small-gauge needles for injection into the vitreous cavity. To address the challenges of drug stability with large molecule protein-based biologics, these cylindrical devices employ an internal reservoir of lyophilized drug, allowing customized formulation and avoiding chemical modification. The goal of this project is to complete the development of this technology toward clinical studies in patients with age related macular degeneration: 1) advance device production to generate devices capable of fitting with the bore of a 22-gauge needle, and produce two device variants with distinct and reproducible linear ranibizumab release rates; 2) optimize our lyophilized formulation to achieve drug stability through 6 months in a rabbit model; 3) assess the impact of repeated injection of cylindrical devices and determine any deleterious chronic impacts. This nanoporous thin film device has potential to maximize long-term vision outcomes, reducing treatment burden and ensuring continuous 6-month anti-VEGF therapy at the minimal effective concentrations.

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Phoebe Lin, M.D., Ph.D.
Associate Professor, Department of Ophthalmology
Oregon Health and Science University

"Alterations in the intestinal microbiota associated with advanced age-related macular degeneration"

Scientific Abstract
Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in the developed world. The advanced form of AMD is characterized by either atrophy of the retina/retinal pigment epithelium (geographic atrophy) or the development of choroidal neovascular membranes (CNVM) causing neovascular AMD (nvAMD). Important biological processes that are disrupted in AMD include innate immune pathways such as complement pathways and fatty acid metabolism pathways, both of which can be influenced by the commensal bacteria found normally in the gastrointestinal tract. The only current intervention to slow progression to advanced AMD is an oral supplement containing high doses of antioxidants, lutein/zeaxanthin, and minerals (AREDS2). These components can influence or be influenced by the intestinal microbiota. Given the role of the intestinal microbiota in altering the availability of the biochemicals that are important in AMD, as well as the importance of the intestinal microbiota in regulating the immune system, we wanted to test the hypothesis that the intestinal microbiome is involved in the pathogenesis of AMD.

Long term goals for this project over 5-10 years are to develop new therapeutics targeting the microbiota to treat AMD. Over the next 2 years, we propose to investigate the intestinal microbial differences in advanced AMD (specific aim 1) that are immunologically relevant, directly test intestinal bacterial and serum metabolites associated with advanced AMD (specific aim 2), and determine the microbial metabolites associated with the development of geographic atrophy vs. nvAMD (specific aim 3). We anticipate that we will find both novel bacterial and host metabolites that are associated with advanced AMD, as well as metabolites that are associated with sight-threatening consequences of this disease. In investigating the intestinal microbial metabolites associated with AMD as well as its complications, we will potentially identify novel effective therapeutic targets for this potentially blinding disease.

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Zongchao Han, M.D., Ph.D.
Assistant Professor, Department of Ophthalmology
University of North Carolina at Chapel Hill

"Developing novel nano antioxidants for the treatment of age-related macular degeneration"

Scientific Abstract
Age-related Macular Degeneration (AMD) is a multifactorial chronic disease caused by aging, chronic inflammation and innate immune dysregulation coupled with a genetic tendency. As a result, a single target may not be able to address the issues; the problems could potentially be resolved if a therapeutic agent had multi-targeted functionalities.

Nanoceria is a potent antioxidant that deactivates free radicals via oxidation–reduction reactions. Because of its autoregenerative properties, nanoceria has been widely used as a non-enzymatic antioxidant. However, its clinical implementation has been hampered by its poor water solubility and hence poor absorption, distribution, and targeted delivery. To generate an effective treatment for AMD, water solubility and biocompatible surface motifs are essential. We have begun to address these needs using nanoceria and have developed a water-soluble form, namely GCCNP, using chitosan derivation in plain water, which provides great stability and selective surface functionality. Our initial studies using both in vitro and in vivo of dry and wet AMD models showed that this water-soluble formulation has superior therapeutic effects over the suspension formulations for oxidative stress-related disorders.

In this application, we will develop strategies of delivering antioxidant nano-products for the treatment of AMD. New antioxidant GCCNP will be either directly injected or formulated as injectable hydrogels, where in the latter the nano-materials can be delivered in liquid and solidify into a hydrogel at the site of injection. We will 1) test safety and functionality of the treatment of in vitro cell models and 2) evaluate the therapeutic value of the particle and hydrogel implants in murine AMD models. We will test our hypothesis that newly developed water-soluble, biocompatible GCCNP and its hydrogels are capable of accumulating therapeutic levels of the particles to the target site of the pathological tissue for long-term neuroprotection, anti-inflammatory, and inhibition of angiogenesis.

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Martin Pera, Ph.D.
Professor, Department of Mammalian Genetics
The Jackson Laboratory

"Functional genomics analysis of the impact of disruption of extracellular matrix genes in early stages of AMD"

Scientific Abstract
An improved understanding of the key processes involved in the early stages of age related macular degeneration (AMD) pathogenesis would aid in identification of individuals at risk for disease progression, and provide new leads for therapeutic intervention. Damage to the retinal pigment epithelium (RPE) occurs early in the disease process, and is associated with disruption of Bruch's membrane, a critical barrier and exchange conduit between the retinal pigment epithelium and the choroid. Recent GWAS studies have identified a number of AMD risk alleles associated with extracellular matrix genes. However, the significance of these candidate alleles remains uncertain, because they have not been subjected to functional assessment. In this study, we will use the powerful combination of RPE derived from human pluripotent stem cells alongside mouse models to carry out functional genomic analysis of the activities of risk alleles in vitro and in vivo. We have established a pipeline for generation of mutant stem cell lines and the production and characterization of RPE. We will introduce the ECM variants into human pluripotent stem cells using CRISPR-Cas9 mediated targeting with homology directed repair, and assess effects on phenotype through analysis of gene expression, production of growth factors and extracellular matrix, assessment of specialized RPE functions including formation and maintenance of an intact epithelium, and cell migration and proliferation. Variants with strong effects will be studied in the mouse, to reveal whether they drive the emergence of pre-clinical and end-stage disease phenotypes. This combined approach will identify those ECM alleles that are most likely to predispose to disease, provide important insights into their mechanism of action at the molecular and cellular levels, and produce complementary models for screening of novel therapeutics in vitro and in vivo.

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Allen Taylor, Ph.D.
Professor of Biochemistry, Nutrition and Ophthalmology
Tufts University

"Repurposing FDA drugs to limit AMD"

Scientific Abstract
The high cost of human clinical intervention trials and dearth of animal models hampered development of drugs for dry AMD. This research will reveal new uses for 3 FDA-approved drugs that have not been previously exploited to combat early AMD, before it significantly compromises vision.
Every published study finds that non-diabetics who consume lower glycemia diets (measured by glycemic index) are protected against AMD onset and progression. We replicated the observation in multiple genotypes of mice in a 2-year test. Our analyses correlate established AMD features with visual function, retina structure, transcriptomics, proteomics, and metabolomics of tissues and plasma that will provide biomarkers of disease.
Findings to date suggest that drugs that lower glucose should limit risk for onset or progress of early AMD worldwide, where people are now consuming high glycemia diets that are more caloric. Surprisingly, drugs that lower glucose have not been assessed for their capacity to avoid AMD at its early stages. The drugs tested here work in different ways to limit AMD and the metabolic consequences of high glycemia diets. Aim 1: We hypothesize that the sodium-glucose cotransporter 2 inhibitor, empagliflozin will mitigate high glycemia by enhancing glucose excretion, thus attenuating hyperglycemia and systemic glycative damage we documented. It will also limit hyperlipidemia, reduce inflammation, RPE dystrophy, all with the result of thwarting AMD. Aim 2: The antihyperglycemic agent acarbose reduces glucose absorption. Aim 3: The PPARα activator fenofibrate, is used to treat diabetic retinopathy. It improves lipid metabolism, reduces inflammation, and activates Nrf2. The latter enhances anti-glycative (including glyoxalase) and anti-oxidative responses. We will test fenofibrate in WT and Nrf2-null mice. The latter appear to accelerate responses. By indicating phenotypes at earlier ages, our indicators and models will make trials shorter, cheaper, and allow for earlier diagnosis and intervention – before lesions affect vision.