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

2023 Grant Cycle

John Hulleman, Ph.D.
Associate Professor, Larson Endowed Chair for Macular Degeneration
University of Minnesota Medical School

"Restoring RPE Basal Lamina Homeostasis for AMD Treatment"

Scientific Abstract
The canonical hallmark of dry age-related macular degeneration (AMD) is the formation of protein and lipid deposits (drusen) within Bruch's membrane. Additional sub-retinal pigment epithelium (RPE) accumulations located in the RPE basal lamina (RPE-BL), such basal laminar deposits (BLamDs), are early heralds of RPE stress and prognosticate impending pathogenic soft drusen formation as well as RPE atrophy. In many instances, BLamDs can trap membranous deposits and/or lipid droplets within the lamina and trigger inflammation/complement activation. An autosomal dominant mutation in one component of the RPE-BL, fibulin-3 (F3 or EFEMP1), causes massive drusen deposition in humans and the rare macular dystrophy, Doyne Honeycomb Retinal Dystrophy/Malattia Leventinese (DHRD/ML). In a high-throughput screen for small molecule regulators of F3, we discovered a compound that significantly reduces both intracellular and extracellular F3 levels in RPE cells. Upon follow up analysis, we were surprised to find that this compound also reduced the levels of additional proteins which are found in, or influence the formation of, BLamDs, including collagens, fibronectin, proteoglycans, and complement components. In this project, we will test the hypothesis that this small molecule can reduce sub-RPE basal deposit formation by readjusting multiple factors that influence RPE-BL protein homeostasis. We will test this hypothesis in diverse model systems, including primary porcine RPE cells (Aim 1A), DHRD/ML iPSC-RPE cells (Aim 1B), and also in the DHRD/ML mouse model of early AMD pathogenesis (Aim 2A, B). If we are successful in our endeavors, the small molecule that we identified may serve as a long-sought-after treatment for millions of individuals with AMD in the United States and worldwide.

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Yali Jia, Ph.D.
Professor of Ophthalmology and Biomedical Engineering
Oregon Health and Science University

"3D Imaging of neuronal dysfunction in AMD using a line-field OCT"

Scientific Abstract
Age related macular degeneration (AMD) is a leading cause of blindness, in part because geographic atrophy remains untreatable. Therapeutic research is currently stymied by a reliance on imaging technologies that are limited to revealing anatomy, and when morphological biomarkers like geographic atrophy present irreversible vision loss has occurred. For therapeutic research to effectively ameliorate the clinical burden of an aging population, a new generation of imaging technology that can interrogate the underlying, functional causes of vision loss is needed. Optical coherence tomography (OCT) is the best platform to meet this need. In this project, we will:
(1) Develop an ultrahigh spatiotemporal resolution OCT prototype that is capable of characterizing neuronal response to flicker stimulation. Cellular scale resolution is essential for achieving the promise of functional imaging because effective therapy development should be able interrogate different cell types in order to fully map AMD etiology to enable targeted treatments. Simultaneously, ultrafast scan volume acquisition is necessary in order to measure the initial response of any neuron to light stimulation (e.g., photoreceptors can hit peak response within 15 milliseconds of stimulation onset). Finally, OCT devices are capable of pairing this functional information with vascular and neural structural anatomy all from the same scan. We will accomplish this aim by using an innovative design based on line-field OCT and computational adaptive optics. This system will be translation-ready since its component cost will be similar to existing commercial systems.
(2) We will use this system to explore retinal function in non-human primate (NHP) models of AMD. As the only animal model that recapitulates key features of human physiology and AMD pathology, NHP models are critical to therapeutic research. We will investigate early stages of pathology to explore new biomarkers that could provide novel therapeutic endpoints to help prevent onset of advanced AMD.

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Konstantin Petrukhin, Ph.D.
Professor of Ophthalmic Science (in Ophthalmology)
Columbia University

"Pharmacological activation of lysosome-associated BK channels as a therapy for dry AMD"

Scientific Abstract
Despite high unmet medical need, there is no FDA-approved pharmacological therapy for dry AMD. Photoreceptor loss in dry AMD is secondary to RPE abnormalities. A crucial function of the RPE is the ability for degradation and processing of photoreceptor outer segments (POS). Efficient degradation of POS in the RPE depends on optimal lysosomal function. This function depends on effective fusion of lysosomes with phagosomes. In addition to suboptimal POS degradation, there is evidence that abnormal autophagy may also contribute to pathogenesis of dry AMD. The autophagy flux in the RPE is susceptible to stressors that impede the fusion of autophagosomes with lysosomes. Thus, the autophagy and phagocytic pathways are interconnected depending on the effective fusion of lysosomes with autophagosomes and phagosomes. BK channels, also known as maxi-K, Slo1 and KCa1.1 channels, are encoded by the KCNMA1 gene and characterized by large K+ conductance, sensitivity to voltage and Ca2+, and ubiquitous expression. The role of BK channels in lysosomal function relates to the induction the Ca2+ release from lysosomes which facilitates the SNARE-mediated fusion of lysosomes with autophagosomes and phagosomes. We hypothesize that BK channel openers (agonists) may facilitate fusion of lysosomes with autophagosomes and phagosomes increasing the efficiency of cargo degradation. Testing of efficacy for BK agonists may be optimally conducted in the mouse Lamp2 knock-out model. Genetic deficiency in lysosomal protein LAMP2 induces retinal changes that strongly resemble features of dry AMD. In humans, LAMP2 mutations cause inherited Danon disease which is associated with retinal and macular degeneration. LAMP2 deficiency manifests as retarded fusion between autophagic vacuoles or phagosomes and lysosomes leading to compromised lysosomal degradation. In the proposed study, we will identify a group of lysosome-specific BK channel agonist and assess their in vivo efficacy in the Lamp2 KO model.

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2023 Grant Cycle

Debasish Sinha, Ph.D.
Dr. Freda Derdeyn Bombas Professorship in Ophthalmology at the Wilmer Eye Institute
John Hopkins University School of Medicine

"Monoclonal antibody treatment for "dry" age-related macular degeneration"

Scientific Abstract
Age-related macular degeneration (AMD) is one of the leading causes of blindness in the elderly. With the human life span increasing, managing AMD is ever more important to the affected patient and to reduce the expensive public health problem that costs $30 billion/year. Despite this growing need, no definitive prevention or treatment is available for early atrophic/dry AMD. The current therapy for dry AMD is limited to intermediate stage disease with the AREDS2 formulation, which has very limited efficacy, with only a 25% decrease in progression, and a 19% risk reduction in vision decrease. One flaw in this treatment approach is that it only targets oxidative stress despite multiple known pathogenic contributors. The strategy proposed here for a possible therapy for atrophic AMD addresses this shortcoming with a novel target. We previously showed that Lipocalin-2 (LCN-2) is upregulated in the RPE from a mouse model with a dry AMD-like phenotype and in dry human AMD donor samples. Our recent data suggest that increased LCN-2 in the RPE potentiates dry AMD pathogenesis by inhibiting autophagy flux and deregulating iron homeostasis, resulting in inflammasome activation, oxidative stress, and ferroptosis in the RPE. We found that LCN-2 binds to ATG4B, which catalyzes LC3B processing (lipidation and delipidation) and forms a complex with both ATG4B and LC3B, thereby regulating autophagosome maturation. RPE cells that have increased LCN-2 exhibit decreased autophagy flux. This autophagy dysregulation led to abnormal iron homeostasis, causing elevated pro-oxidative stress iron levels. We also find that a monoclonal antibody (Clone #6 mAb) directed against LCN-2 rescues the autophagy/inflammasome/ferroptosis processes, along with improved retinal function in our dry AMD-like mouse model. Thus, the proposed therapy, by targeting multiple known pathogenic pathways, is both novel and holds high treatment potential for dry AMD because it targets several known dysregulated pathways.

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2023 Grant Cycle

Dimitra Skondra, M.D., Ph.D.
Associate Professor of Ophthalmology, Director of J. Terry Ernest Ocular Imaging Center
University of Chicago

"Harnessing the effects of diet-microbiome interactions to prevent and treat AMD"

Scientific Abstract
Pathobiology of age-related macular degeneration (AMD) is complex, involving an interplay between genetics and diet. The exact role of diet in AMD is still uncertain, but new evidence shows that gut retina axis and diet-induced gut microbiome changes play key role in AMD. A compelling picture is emerging that Mediterranean-type diet (MedD) slows AMD progression. However, the underlying AMD protective mechanism of MedD remains unknown. Recent data have revealed that MedD's beneficial effects on aging and several diseases are mainly mediated by the gut microbiome.

The goal of this innovative proposal is to study if MedD suppresses AMD via gut-retina axis modulation. In Aim 1, we plan to investigate if MedD suppresses choroidal neovascularization (CNV), the hallmark lesion of wet late-AMD and local inflammation compared to regular diet as well as western-style high fat diet (HFD) both as preventive measure and also as therapeutic intervention and will study the chorioretinal pathways involved. In Aim 2, we will study if MedD suppresses AMD via microbiome modulation. We will investigate how MedD alters microbial composition/functions and metabolites produced compared to ND and HFD. To investigate if MedD's protective effects are mediated by microbiome, we will study if AMD can be suppressed by colonizing germ-free mice with MedD -derived microbiota and will identify gut microbiome characteristics/metabolites, and their association with CNV features. In Aim 3, we will study if intervention with fecal material transplantation (FMT) with MedD-derived microbiota can suppress CNV as a preventive measure and also as therapeutic intervention. This innovative proposal will reveal new exciting diet-microbiome-metabolome-transcriptome associations providing a deeper understanding of both AMD pathobiology and MedD's protective effects. Our study could lead to the discovery of novel targets and open a completely new era of therapeutic strategies of AMD by harnessing the protective effects of MedD on gut-retina axis.