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

2020 Grant Cycle

Laura Ensign, Ph.D.
Marcella E. Woll Professor of Ophthalmology
Johns Hopkins University

"Novel Gel-forming Eye Drop for Treatment of Age-related Macular Degeneration"

Scientific Abstract

Injectable therapies for blocking VEGF have provided impressive initial benefits to patients with neovascular age-related macular degeneration (nAMD), but long-term outcomes have been disappointing. The short duration of action requires that injections be repeated every 1-2 months. Life circumstances often make it difficult or impossible to return to the clinic as frequently as is required for injections. One solution is to develop a treatment that can be self-administered by patients so that treatment can continue even when patients are unable to return to their retina specialist. Patients are able to apply drops to their eyes, but thus far it has not been possible to deliver adequate amounts of drug to the retina by topical eye drops. We have engineered a novel thermosensitive gelling eye drop (OcuGel) that is liquid at room temperature and spreads to cover the surface immediately and uniformly, and then gels to trap the medication in place against the ocular surface to provide enhanced absorption. The thin gel film is unnoticeable and optically clear. Our preliminary data shows that daily topical dosing of OcuGel containing a small molecule drug with potent anti-angiogenic properties strongly suppressed ssed d (in)1 sp.pogly(g)(ly)r oglyic Si n ((g1))(i(d s)13c growth. This is a key finding, posterior ocular tissues effectively in large animals with eyes more similar in size to that of humans. Here, we propose further characterization and preclinical testing of OcuGel for treatment of nAMD that includes characterization of the gel material properties and drug delivery mechanism, pharmacokinetics, efficacy in large animals, and ocular surface safety.

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Patsy Nishina, Ph.D.
Professor
The Jackson Laboratory

"Mouse Models Bearing Human AMD GWAs Alleles"

Scientific Abstract
Despite the significant progress made toward understanding the genetic basis of AMD, we still are at early stages of developing therapeutic strategies from this knowledge. Part of the problem is the lack of animal models in which we can directly determine the contribution of the different GWA variants and we can do invasive, longitudinal studies to detect early biomarkers for the disease to use as surrogate end-points in drug development. Another part of the problem is having robust animal models that recapitulate the multigenic nature of the disease in which therapeutic strategies can be tested. In this application, we are directly testing the contributions of GWAs variants, ARMS2A69S and CETPD442G to development of AMD-like features under different modifiable conditions known to increase AMD risk. These variants were selected because their effect on AMD risk has not been resolved in large GWA studies and understanding whether they mediate pathological effects is critical for developing effective therapeutics. We will also be studying these single variants on different genetic backgrounds and in combination with other variants that may interact with them in order to build complex models that more accurately reflect what might be occurring in the highly genetically heterogeneous human population. Our long term goal, beyond the scope of this proposal, is to place the variants generated/characterized in this study on a high risk susceptible collaborative cross background strain that bears as many of the AMD GWAs that affect gene expression (derived by eQTL analysis of retinal tissue in mouse) to reflect human AMD transcriptomic profiles for the 54 AMD GWAs genes. All models generated will be available for distribution so that they can serve as resources for studying gene and environmental interactions that may affect AMD (by combining different alleles under different environmental challenges), and for testing therapeutic interventions.

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David Wu, M.D., Ph.D.
Assistant Professor of Ophthalmology
Massachusetts Eye and Ear Infirmary

"Metabolic Regulation of the Outer Retinal Blood Barrier and Age-related Macular Degeneration"

Scientific Abstract

The Outer Blood-Retinal Barrier (OBRB), spanning the choriocapillaris, Bruch's membrane, and the retinal pigment epithelium (RPE), undergoes pathognomonic changes in Age-related Macular Degeneration (AMD). How these are linked with the earliest known AMD changes, the loss of the perifoveal rod photoreceptors, remains unknown. There is growing awareness that photoreceptors and RPE are mutually dependent members of a tightly regulated metabolic ecosystem. Photoreceptors metabolize glucose from RPE by aerobic

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