

James & Esther King Biomedical Research Program

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2007 Program
Bridge (1-year project)

Project Title: Wnt Signaling and Neuroprotection in the Retina

Project Summary: Age-related macular degeneration (AMD) is the leading cause of vision loss in the USA, affecting approximately 8 million people. AMD interferes with everyday activities, including driving, reading, watching television, and recognizing faces of family and friends. Vision deficits also lead to impaired mobility, disorientation, loss of independence, and are associated with a high incidence of clinical depression. Cigarette smoking is the largest environmental risk factor for AMD, increasing the risk by two- to threefold. Furthermore, a recent study in *The British Journal of Ophthalmology* showed that people living with a smoker double their risk of developing AMD. Smoking is implicated in the dry and wet forms of AMD. Vision loss in both forms of AMD is due to death of photoreceptors, the light sensitive cells in the retina. There is no cure, and even therapies that halt blood vessel leakage in wet AMD do not reverse photoreceptor death. Therefore, there is an urgent need for therapies to protect photoreceptors. Our goal is to develop treatments that preserve photoreceptors in AMD in order to enable patients to retain their sight. We recently discovered that molecules called "Wnts" can rescue retinas grown in the lab from a smoking-related tissue injury called oxidative damage. We believe that protective Wnt molecules are normally increased during retinal injury but are not at high enough levels to save photoreceptors. In this study, we will test the hypothesis that delivering extra Wnt molecules protects photoreceptors in a living animal. We will use mice that have a genetic predisposition to photoreceptor death. These mice have oxidative damage to photoreceptors as a consequence of the genetic mutation and allow us to focus on photoreceptor rescue without any complicating smoking-related changes to the vascular system. We will inject Wnt molecules into the mouse retina with a thin needle using the same procedure used in humans, and we have perfected the injection procedure. We will then use several measurements to test whether the photoreceptors in the injected mice have been rescued, compared to the uninjected mice that will have photoreceptor death. Electrical recordings will test if the photoreceptors are functioning normally. If there is less photoreceptor death after injecting the Wnts, it will indicate that Wnt molecules protect photoreceptors in the mice, which will support our hypothesis. Additional experiments will use retinas grown in a culture dish in the lab to identify the specific cell types and mechanisms that control Wnt-mediated protection. By determining whether Wnt molecules are a potential therapy for halting photoreceptor death in AMD, these studies will reveal new directions for treating this tobacco-related blinding disease.