

## James & Esther King Biomedical Research Program

**Zhai, R. Grace**

*Department of Molecular and Cellular  
Pharmacology  
University of Miami*

*2007 Program*

*New Investigator (3-year project)*

**Project Title:** Mechanisms of Smoking-related Retinal Degeneration

**Project Summary:** Tobacco smoke is composed of about 4,000 active compounds, most of them toxic on either acute or long-term exposure. Although it has been widely recognized that cigarette smoking is highly irritating to the eyes of smokers as well as nonsmokers by passive exposure (secondhand smoking), the long-term effects of smoking on vision have largely been neglected or overlooked. Comparative studies on smokers and nonsmokers have found that smoking directly accelerates the progress of macular degeneration, a retinal degenerative disease that causes severe visual impairment and blindness. Macular degeneration is a leading cause of blindness in the western world. Unfortunately, currently there is no effective treatment for macular degeneration. The effect of smoking on the retina can be long-term, and even past smokers have a higher chance of developing macular degeneration. It is thought that the toxins in tobacco smoke affect eye tissues mainly through oxidative mechanisms; however, the details about how smoking causes and accelerates retinal degeneration are unclear. The research in our laboratory focuses on the molecular mechanisms of retinal degeneration using fruit flies as a model system. Similar to humans, fruit flies are diurnal, and they rely on color vision to navigate. More importantly, flies can easily be manipulated genetically and there are many genetic tools available publicly through the fly community ([www.flybase.org](http://www.flybase.org)). We have taken advantage of this model system and recently discovered a neural protective factor called NMNAT that protects the retina from degeneration under intense sunlight exposure. In this grant, we will first study the process of smoking-related retinal degeneration by examining the dose- and time-dependent effect of oxidative damage on the eye and therefore establish a causal link between the toxic compounds in tobacco smoke and retinal degeneration. Next, we will examine the protective effects of NMNAT in retinal degeneration. The results from this study will not only reveal the underlying cause for retinal degeneration but also provide a basis for designing treatment. Finally, we will isolate other genetic elements that work together with NMNAT in protecting neurons, establish models to select drug targets, and screen for small molecules that have eye protective effects. This study will help us understand the complex process of smoking-related retinal degeneration and reveal potential drug targets. The small-scale drug screen in this grant will be a test run for future, large-scale screening for the discovery of drugs and therapies for currently untreatable, smoking-related vision impairment.