NIH Award from the National Eye Institute

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- **Project:** Muller Cell Role in Retinal Diseases
- **Start Date:** August 1, 2009
- **Total Award Amount:** $685,911

How the results of this project will benefit society:
Retinal neurodegenerative diseases are characterized by progressive loss of rod and cone photoreceptors leading eventually to blindness. Recent investigations suggest that retinal disease pathogenesis might be influenced by changes in the activity of support cells, known as glial cells, that are associated with retinal neurons. The present proposal will examine the contribution of Muller (glial) cells in the pathogenesis of retinitis pigmentosa and age-related macular degeneration. Molecular characterization of activated Muller cells can be expected to lead to innovative, therapeutic treatments for photoreceptor degenerations, whose aim is to stimulate Muller cells to produce neuroprotective agents that prevent photoreceptor death, and to restore Muller cell’s neuron-supportive functions lost in the diseased retina.

The problem the project is trying to solve:
Muller cells, the predominant glial cells in the vertebrate retina, play an essential role in maintaining neuronal health and activity. Recent work on retinal glia has also shown that virtually every retinal disease is associated with “activation” of Muller cells. At present very little is known about what molecular changes occur following activation, and how activation impacts on Muller cell role in retinal homeostasis and retinal disease pathogenesis. The proposed studies are designed to answer these questions.

How this project will work:
These studies are made possible for the first time by the development of a method to purify Muller cells using Florescence Activated Cell Sorter. The proposal has three specific aims. The first specific aim is to determine the role of Muller cells in photoreceptor neuroprotection mediated by Ciliary neurotrophic factor (CNTF). CNTF appears to be the most effective and mutation-independent, neuroprotective agent that slows photoreceptor loss in inherited retinal degenerations. We propose to examine two ideas—whether CNTF-treated Muller cells release neuroprotective agents, which act to prevent photoreceptor loss or whether CNTF treatment leads to metabolic changes in Muller cells that promotes neuroprotection. The second specific aim is to determine gene expression changes induced in microglia by CNTF. These findings should help dissect Muller cell-microglia-photoreceptor interactions; thus, providing a molecular explanation for CNTF action as well as a rational basis for CNTF therapy. The third specific aim will utilize microarray data from FACS-sorted Muller cells to explore the functional changes in retinal degeneration 1 (rd1) mice, a mouse model of rapid retinitis pigmentosa. Alterations in normal Muller cell functions will be determined by biochemical, cell biological, and physiological assays. Molecular characterization of activated Muller cells can be expected to lead to innovative, therapeutic treatments for photoreceptor degenerations, whose aim is to stimulate Muller cells to produce neuroprotective agents that prevent photoreceptor death, and to restore Muller cell’s neuron-supportive functions lost in the diseased retina.

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