Project Title: A Novel Approach to Alleviating Aberrant Calcium Signaling Causing Retinal Cell Loss in Traumatic Optic Neuropathy

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Background: Visual impairments following concussion or blast-related injury are often due to optic nerve injury and degeneration of ganglion cells. Excessive intracellular Ca2+ ([Ca2+]i) levels, which in turn initiates degeneration and apoptotic cell death, characterizes injured ganglion cells. Recent findings in both the retina and elsewhere in the nervous system indicate that both L- and T-type Ca2+ channels are up-regulated in response to injury, and furthermore that Ca2+ channel antagonists in animal models of ocular injury enhance retinal ganglion cell survival.

Objective/Hypothesis: To provide fundamental information about Ca2+ signaling mechanisms following nerve injury and to support the development of novel approaches to save vision.

Hypothesis: Suppression of elevated [Ca2+]i following nerve injury enhances ganglion cell survival.

Specific Aims: The first two aims will gain fundamental knowledge of L- and T-type Ca2+ channel subunit expression and function in ganglion cells following optic nerve injury. The third aim seeks to determine the effectiveness of Ca2+ channel antagonists and molecular agents in regulating [Ca2+]i homeostasis and enhancing ganglion cell survival.

Study Design: Experiments will determine the expression and function of L- and T-type Ca2+ channels using qRT-PCR, immunohistochemistry, patch-clamp electrophysiology and Ca2+ imaging. Short- and long-term trauma-induced regulation of Ca2+ channel expression and function will be determined.

Relevance: Reduction of elevated [Ca2+]i via therapeutic regulation of Ca2+ channel activity is an important component of strategies for the treatment of retinal injury. Investigations will guide development of novel therapies to minimize or eliminate vision loss following optic nerve injury, and they will be directly beneficial to injured soldiers and veterans.