**Project Title:** Pharmalogical Treatment for Combat Traumatic Optic Neuropathy  
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**Background:** Traumatic optic neuropathy (TON) is a frequent cause of significant visual loss after a combat-related frontal head trauma. In TON, the injury of the optic nerve originates from concussive forces to the head. The injury-induced edema of the canalicular portion of the optic nerve leads to neural compression that triggers the development of an intracanalicular compartment syndrome.

**Objective:** Reduction of swelling by inhibiting injury-induced edema in the intracanalicular portion of the optic nerve is a sound strategy for the prevention of TON-related loss of vision. B-3(+) is an abandoned fluorenone drug that has demonstrated significant efficacy in preventing mortality in the animal models of concussive brain injury. B-3(+) acts as a chloride transport inhibitor capable of significantly reducing insult-induced astrocyte swelling in a number of experimental systems.

**Hypothesis:** Given the efficacy of B-3(+) in animal models of traumatic brain injury and assuming that mechanisms of neuronal damage in the canalicular portion of the optic nerve are likely to be analogues to those of the rest of the CNS, the researchers hypothesize that intravitreally administered B-3(+) may be used as a treatment for traumatic optic neuropathy associated with combat-related traumatic brain injury.

**Specific Aims:** The overall goal of this project is to establish pre-clinical efficacy for B-3(+) in the animal model mimicking the optic nerve damage typical for TON and to confirm a negligible systemic B-3(+) exposure after an intravitreal injection. In order to accomplish this goal, they will conduct in vitro B-3(+) titrations in cultured optic nerve astrocytes in order to select the optimum dose range for in vivo testing (Specific Aim 1), establish drug efficacy in the animal model of optic nerve damage (Specific Aim 2), and evaluate the level of systemic exposure in response to intravitreal injections of the efficacious doses (Specific Aim 3).

**Study Design:** Calcein quenching will be used to monitor relative cell volume changes in cultured optic nerve astrocytes to document the ability of B-3(+) to inhibit insult-induced astrocyte swelling and to establish the EC90 concentration that will guide the in vivo testing. Intravitreal administration of B-3(+) at the EC90 concentration will be used to establish compound efficacy in the animal model of the optic nerve damage using the quantification of fluorogold-labeled ganglion cells as an analytical technique. Published HPLC protocol will be used to determine B-3(+) concentrations in circulation after intravitreal injection in order to confirm negligible systemic exposure after the intraocular drug administration.

**Relevance:** If successful, these studies could result in human clinical trials in the near future and could help treat a problem caused by trauma for which there is currently no therapy available.