Targeted Treatment of Traumatic Optic Neuropathy Inspired by Neuroprotective Adaptations of Hibernation

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PUBLIC ABSTRACT
Objectives and Rationale: The primary objective of this research is to translate adaptive strategies used by hibernators to prevent vision loss associated with head injuries resulting in damage to the optic nerve. Currently there is no consensus on the appropriate treatment for traumatic optic neuropathy. Damage to the optic nerve is irreversible as the nerve fibers do not have the capacity to regenerate on their own, thus preservation of the ganglion cells and their axons under these adverse conditions by mimicking hibernation would represent a novel way to prevent vision loss.

The major obstacles to such an approach include optimizing the dose and timing of the prospective drugs inducing hibernation and their method of delivery for human use. This project is an interdisciplinary effort, bringing together a skilled group of scientists, with expertise across engineering, physiology, and medicine. The proposed studies will optimize the selected drugs to maximize the viability of ganglion cells following mechanical compression of the optic nerve, explore the feasibility of eyedrop delivery to facilitate safe compliance during the optimal therapeutic window, and to test the performance of the hibernation-inspired drugs and their topical eyedrop delivery in a real-world combat scenario using a simulated blast injury model.

Ultimate Applicability and Potential Impact of the Research: The proposed project exploits identified novel cellular pathways that protect the hibernating ground squirrel from optic nerve injury. This suggests that substantial improvements in the treatment of traumatic optic neuropathy can be gained by using hibernation-inspired treatment options that specifically target the RGC cells' response to injury and their interactions with the microenvironment before secondary mechanisms give rise to inflammation that lead to further RGC loss. We believe that this bioinspired approach is an important step in developing novel therapeutic candidates that promote RGC viability while selectively suppressing microglial activation and limiting systemic side effects. The insights gained from this research will help us better understand how to manipulate the adaptive strategies of hibernation to improve tissue and organ preservation strategies or methods to safely induce a hibernation-like state in humans to improve treatment of trauma or disease. We anticipate successful demonstration in animal models within the initial 3 years followed by clinical translation in 4-8 years.

Benefit to Service members, Veterans, and/or Their Family Members: Over 65% of all Service members that have suffered traumatic brain injury reported vision problems. Although the prevalence of traumatic optic neuropathy in the general population is relatively low (1:1,000,000), traumatic optic neuropathy from blast or blunt head trauma poses a growing and significant threat to the vision of military personnel, where the rate of incidents of TON is higher (20% of all military ocular trauma). TON patients frequently suffer profound vision loss, placing a significant socio-economic burden in both the short and long term. This requires the discovery of new and innovative treatment options to provide effective methods prevent ganglion cell death, loss of visual function, and promote recovery in alignment with the Department of Defense focus areas of eye injury or visual dysfunction related to military-relevant traumatic events (blast or blunt trauma). In order to improve TON treatment, significant advancements must be made in our understanding of the underlying molecular basis of cell death initiation and the inflammatory process that ensues following trauma to the optic nerve leading to ganglion cell death. Knowledge gained from the experiments proposed herein will enable the testing of novel, hibernation-inspired, targeted therapies that will preserve RGCs and maintain visual function.
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