Project Title: TrkB Activators for the Treatment of Traumatic Vision Loss
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Background: Pressure waves due to explosions can damage the neurons of the eye and visual centers in the brain, leading to visual function loss. There are currently few treatments for such injuries that can be deployed rapidly in the field to mitigate such damage. The researchers are developing small molecule activators of TrkB, the cognate receptor for brain-derived neurotrophic factor (BDNF). BDNF is neuroprotective in a number of degeneration models, including optic nerve crush and bright light-induced retinal degeneration. However, BDNF must be injected intraocularly or into the brain to be effective, as it does not cross the blood brain/retina barrier (BBB), making it impractical to deploy in the field. In contrast, the compounds the team is developing can be administered systemically and they readily cross the BBB. Following systemic injection, the drugs activate TrkB receptors in the retina and the brain. Treatment can continue for at least several months without toxicity. In preliminary studies, they have shown that they protect against retinal degenerations caused by exposure to toxic levels of light and by genetic aberrations.

Objective: The goal of this proposal is to develop effective, battlefield-deliverable treatments for traumatic blast-related retinal and visual system damage.

Hypothesis: They hypothesize that small molecule activators of TrkB will be useful for this purpose.

Specific Aims: 1. To examine the ability of TrkB activators to prevent retinal ganglion cell death and loss of visual function following optic nerve injury. 2. To examine the ability of TrkB activators to prevent traumatic blast-induced retinal damage and loss of visual function. 3. To examine the ability of TrkB activators to prevent traumatic blast-induced neuronal degeneration in visual pathways of the brain, including visual cortex.

Study Design: They will examine the ability of recently identified TrkB receptor agonists that reach the retina and brain following systemic injection to ameliorate the effects of traumatic injury to neurons in the retina and visual cortex of mice. They will inject mice with various doses of these drugs after optic nerve damage (aim 1), blast-induced unilateral ocular damage (aim 2), or blast-induced damage to the visual cortex (aim 3). Drugs will be administered at different time points after injury to assess effects of delayed treatment. Visual function will be assessed by measuring visual-evoked potentials (VEP), electro-retinograms (ERG), and optokinetic tracking (OKT). Neuronal damage will be assessed histologically at multiple time points after injury, counting retinal ganglion cells in aim 1, and with TUNEL and FluoroJade staining in aims 2 and 3.

Relevance: This study has the potential to develop therapeutics to prevent vision loss following blast injury. By treating soldiers on the battlefield or in clinics soon after traumatic injury, these treatments may rescue dying neurons and the associated loss of visual function.