The proposed research is aimed at restoring vision after injury to the optic nerve. As in most pathways of the central nervous system (CNS), nerve fibers (axons) that course through the optic nerve do not regenerate if injured, resulting in a lifelong loss of vision. Our laboratory has discovered ways to greatly enhance the ability of retinal ganglion cells (RGCs), the neurons that convey visual information from the eye to the brain, to regenerate their axons after injury. However, these cells continue to die over time. Our objectives are to understand the cellular and molecular mechanisms that cause RGCs to die after axonal injury, develop treatments to counteract these mechanisms, and combine these treatments with our current strategies for enhancing regeneration. The goal of this work is to achieve sufficient levels of regeneration to restore meaningful levels of visual functioning. We will test the hypothesis that RGC death is due to the activation of a particular type of inflammatory cell, and that either these cells or others kill RGCs by producing superoxide and nitric oxide to form peroxynitrite, a highly toxic molecule. We will also investigate whether RGC death is associated with the liberation of free zinc ions, a mechanism that was recently shown to result from the action of peroxynitrite and to lead to the death of other brain cells following injury to their axons. Finally, we will investigate whether our current methods for activating neurons’ intrinsic growth state, when combined with neuroprotective methods discovered in the proposed studies, will strongly augment regeneration and help restore visual functioning. This outcome would be of great benefit for victims of battlefield injuries that include the optic nerve, and are also likely to be relevant for treating injuries in other parts of the nervous system. In view of the total absence of visual recovery that normally occurs, we believe that the benefits of the proposed intraocular treatments greatly outweigh the risks, if any. The interim outcome of these studies will be greatly improved levels of optic nerve regeneration in an animal model. With a concerted effort, the results of these studies could be translated into clinically usable treatments after another 3 years. At a basic level, the proposed research should substantially increase our understanding of why RGCs die after their nerve fibers are injured, and are likely to lead to unprecedented levels of functional recovery. Our results may also likely to be applicable to other types of CNS injury.