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**Treatment Strategies for Blinding Combat Retinal Injury Employing Combinatorial Therapeutics**

**Principal Investigator:** RADEKE, MONTE  
**Institution Receiving Award:** CALIFORNIA, UNIVERSITY OF, SANTA BARBARA  
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PUBLIC ABSTRACT
It can be argued that vision is our most important sense, and loss of vision has significant negative economic and quality of life impacts. Concussive and penetrating injuries to the eye often result in retinal detachment and tears and a subsequent loss of vision. Although less common in the civilian realm, trauma-related retinal injuries are quite prevalent among those with combat injuries. Additionally, the prognosis for visual recovery is three times worse for those with retinal injury resulting from fragmentary explosives, which comprise nearly 75% of combat injuries in recent military conflicts. Although most people probably associate explosive-related injuries with major whole body trauma, the number of penetrating eye injuries outnumbers those requiring amputation by two-fold.

Within minutes of retinal injury, a cascade of events begins that result in a burst of proliferation of non-neuronal cells that support visual function and death of the cells that detect light. This is followed days later by accumulation of scarring and remodeling of neuronal connections. The only effective treatment for retinal detachment is surgical reattachment, but even with surgery fewer than 40% of patients regain significant vision. Besides the general severity, the best predictor of surgical outcome is the delay between injury and reattachment, with the risk increasing significantly after 24 hours. Both of these factors likely contribute to the difference between visual outcomes between civilians and combatants given the preponderance of penetrating injuries and delays in surgical repair for injuries occurring on the battlefield.

The proposed project has both translational and discovery components directed at the development and testing of novel therapeutics and furthering our understanding of the molecular processes underlying retinal trauma. The translation component entails experiments directed at testing combinatorial therapeutics comprised of pharmacologics and biologics targeting the early phase of injury-induced retinal degeneration or secondary pathological scarring. More specifically, we will (1) investigate the use of a drug cocktail containing components that block proliferation and cell death that can be administered shortly after the initial trauma in order to stabilize the injury until a surgical repair can be made, and (2) investigate the use of a biologic-based therapeutic that enhances the patient's immune response in order to resolve or inhibit pathological scarring. These aims will utilize established animal models and efficacy will be evaluated based on anatomical and visual outcomes. The discovery component seeks to generate a molecular model of retinal wound responses with cell-type resolution for the purpose of identifying unrealized therapeutic targets and agents. These aims will utilize state-of-the-art genomics methods to measure changes in gene expression at the resolution of single cells and a cell culture model of retinal scarring. Information from the discovery-based analysis will be utilized for further development of multimodal therapeutic cocktails.

Prior attempts to develop a non-surgical treatment for retinal injury and aberrant wound responses have failed. In large part, we feel that this has been due to approaches that address single processes. Retinal injury and degeneration are complex multicellular processes; therefore, true success will likely only be achieved by accepting and addressing these complexities.
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