DEPARTMENT OF DEFENSE - CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

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Strategies to Reduce Visual Pathway Damage Secondary to Brain Trauma

Principal Investigator: ROHRER, BAERBEL
Institution Receiving Award: MEDICAL UNIVERSITY OF SOUTH CAROLINA
Program: VRP
Proposal Number: VR190053
Award Number: W81XWH-20-1-0939
Funding Mechanism: Investigator-Initiated Research Award - Funding Level 1
Partnering Awards:
Award Amount: $388,700.00

View Technical Abstract

PUBLIC ABSTRACT

Explosive devices and blast trauma account for the majority of combat-related injuries, and Soldiers who survive often have debilitating injuries to unprotected areas. While eye injuries in the United States include ~50,000 diagnosed in the civilian population, ~17,000 injuries are seen in fixed military medical facilities. Many of the ocular injuries in the military population occur in both eyes and are typically caused by blast. Visual deficits are comparable in subjects exposed to blast or blunt trauma, which include bleeding, tears in the retina (tissue at the back of the eye containing the light-sensitive cells), detachments of the retina, ruptures of the blood supply to the retina, atrophy of the nerve that connects the retina to the brain, and deficits in contrast sensitivity and low-light visual acuity. Importantly, detection of visual deficits from blast injury is often delayed, which is thought to be due to ongoing secondary degenerations after the trauma that do not present until months later. Hence, identifying treatment strategies that are viable in a delayed setting, targeting the chronic phase of the disease, are of utmost importance. Thus, the overall goal of this project is to understand immunological changes that occur in the eye after blast trauma acutely and chronically, and to develop a strategy to target these changes in order to modulate the post-injury immune response and either reduce the amount of vision loss or aim to restore vision.

There are many kinds of treatments available for patients with traumatic brain injury. The initial treatment is aimed at stabilizing the individual, with acute treatment used to minimize the secondary injury. Much of the secondary injury is caused by changes in blood flow in both the affected organs/tissues as well as in tissues connected through joint blood supply or connected through nerves. These changes in oxygen supply cause so-called oxidative stress. An unavoidable consequence of oxidative stress is an inflammatory response, triggered in the affected organs, that increases the severity of the initial injury. We have found that following oxidative stress, immunological changes occur within the affected tissues such as the brain or the eye, and the cells express certain proteins and lipids on their cell membranes that are normally hidden in healthy tissue.

These normally hidden molecules are then recognized by naturally occurring circulating antibodies that initiate optic nerve and retina injury by activating the complement system, which is a collection of blood proteins that forms part of the immune system. Activating the complement system adds another tag to the affected cells, further damaging the cells. In this project, we propose to investigate the immunological changes that occur within the eye following traumatic brain injury in a mouse model. Based on this information, we further propose to characterize a strategy to reduce complement activation, with an inhibitor that is targeted to sites of complement activation. The studies will build on our preliminary data that shows that vision can be preserved in the mouse model when administered acutely at the time of injury. We will follow up this observation with a delayed administration, which will help us to determine how long we can wait, after the initial injury, to start the treatment regimen for the compounds to still ameliorate vision loss. Based on our preliminary data, we expect that by reducing complement activation, we will reduce the severity of the immune response, reduce the severity of cell loss in the eye, and prevent vision loss. A successful outcome of these studies will provide a novel approach to significantly improving vision outcome of patients with TBI with the potential for changing the standard of care.

The major relevant focus area for this proposal is the Vision Research Program – Investigator-Initiated Research Award, Level I.

All future individuals with TBI injuries will be potential beneficiaries of this research. In fact, individuals with other neurodegenerative consequences of TBI may also potentially benefit, since

neuroinflammation and complement activation is associated with many forms of secondary degenerations after trauma.

There is currently great interest in complement inhibitor therapeutics, and they have been shown to be safe in clinical trials. Furthermore, because we are investigating a targeted approach to delivering complement inhibition specifically to the eye and the brain, much lower doses of the inhibitor can be given while maintaining effectiveness.

While this is an Investigator-Initiated Research Award and not a grant for commercial development, our group is already planning for the next step. The targeted complement inhibitor based on the complement tag was licensed by a pharmaceutical company and was recently found to be safe and non-immunogenic in humans. With regard to time to achieve a patient-related outcome for the therapeutic approaches described herein, two of the applicants (BR and ST) have considerable experience in product commercialization, specifically with regard to targeted complement inhibitors. Investments for patent filing and prosecution costs relative to the technology at the center of this proposal have been secured, and the investors also have an option to license the technology.

A successful outcome to these studies will significantly increase our chances of attracting additional investment for the further development and the relatively rapid clinical application of our approach in TBI and vision restoration.

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