DEPARTMENT OF DEFENSE - CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

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Protecting Neural Circuitry After Injury

Principal Investigator: TOWNES-ANDERSON, ELLEN
Institution Receiving Award: RUTGERS, NEW JERSEY, STATE UNIVERSITY OF
Program: VRP
Proposal Number: VR180129
Award Number: W81XWH-19-1-0819
Funding Mechanism: Investigator-Initiated Research Award
Partnering Awards:
Award Amount: $779,865.00

View Technical Abstract

PUBLIC ABSTRACT

Ocular injury is the fourth most common injury in 21st century combat. Improvised explosive devices are the most common cause of injury. Our proposal aims to improve the outcome of blast-related trauma to the retina of the eye.

Retinal detachment (RD) is an important complication of ocular trauma. Detachment causes a separation of the retina from the underlying retinal pigmented epithelium (RPE) and choroid, which provide nutrients and oxygen to the retina. This separation can lead to blindness. In combat, RD is one of the top three risks for blindness and occurs in 1% to 51% of ocular injuries depending on the combat arena. It is normally repaired by surgical re-apposition of the retina against the RPE, but studies have shown that normal vision is not restored in the majority of cases following this procedure.

We have discovered that RD increases the activity of a small molecule, RhoA, which results in contraction of the cellular cytoskeleton and breakdown of structural elements, the actin filaments. These changes lead to the breakage of the first synaptic connection in the visual pathway, which is the synapse between photoreceptors and bipolar neurons. Without this synapse there is no vision. We found, in animal models, that we can significantly reduce this synaptic damage by inhibiting Rho kinase (ROCK), an enzyme activated by RhoA. We want to pursue this finding and develop a therapy that can be used in combat to protect the injured retina and increase the chance of recovering visual function as the retina heals.

We have tested several ROCK inhibitors and found that netarsudil-M1, AR-13503, is the most potent inhibitor and can be used at the lowest concentrations. Its parent compound, netrasudil, has been approved by the FDA for use to lower intraocular pressure in glaucoma. The drug has now been formulated within a polymer to provide a continuous release over many weeks once placed in the vitreous cavity. We will apply this new sustained-release fiber with AR-13503 into eyes of pigs with RDs, along with soluble AR-13503 injections, with three research aims in mind: (1) To test how long the drug can provide protection to the injured retina; (2) To determine how long after an injury such as an RD we can apply the drug and still get rescue effects; and (3) To test whether applying a ROCK inhibitor before surgical reattachment, which may involve additional, more subtle, mechanical injury, can also be helpful to the retina and promote visual recovery. In these experiments, we will also apply an inhibitor to LIM kinase (LIMK), another RhoA sensitive molecule, to suppress pathological neural plasticity in the form of nerve cell sprouting. Like synaptic breakage, sprouting occurs with RD and retinal reattachment. We hope to help combatants, civilians in areas with active terrorism, and the general public who suffer sports injuries or other major traumas to the eye. Additionally, we have preliminary evidence suggesting that our drug applications can be helpful to the eye after traumatic brain injury (TBI) because the retina in patients with TBI shows pathology that is similar to RD. Moreover, we hypothesize that our pharmaceutical approach will help stabilize brain tissue itself after TBI.

Currently, we work on pigs because their eyes are very similar to human eyes. Over the next 2 years, we propose to get answers about the length of drug effectiveness, the timing of treatment, and the possible advantage of additional treatment at the time of retinal reattachment surgery in the porcine animal model of RD. These studies will be followed by safety studies before there can be clinical trials. However, because our drug is applied to the inside of the eye, with intravitreal injections, there should be little systemic risk. Moreover, the drug we will test has already been used to treat patients with eye disease (glaucoma) and found not to be harmful. In other words, we are using an existing drug in a new application. This approach will allow the possible application to humans to move more quickly.

In addition, we hope, from our work, to find out new information about how cone cells, which are responsible

for our color and high acuity vision, respond to injury. We have previously looked at rod cells, but to date, information on cone cells has been lacking. Also, we will test the use of LIMK inhibition, which has not previously been considered in nervous tissue repair and is a novel approach to protection of injured retina. On both fronts, we anticipate discovering potentially critical information about how photoreceptor cells respond to injury and their recovery.

Any improvement in restoration of visual function will have significant positive effects on the quality of life for military Service members, Veterans, and civilians. Of all the senses, vision is among the most important for maintenance of independent living and gainful employment.

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