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Testing the Preclinical Efficacy of Therapies for Proliferative Vitreoretinopathy

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Institution Receiving Award: SCHEPENS EYE RESEARCH INSTITUTE

Program: VRP

Proposal Number: VR150024

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Funding Mechanism: Technology/Therapeutic Development Award

Partnering Awards:

Award Amount: \$1,496,892.00

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PUBLIC ABSTRACT

The primary objective of this proposal is to address the lack of treatments for preventing the formation of retinal membranes following post-traumatic eye surgery, a condition known as proliferative vitreoretinopathy (PVR). Approximately 40%-60% of patients with an open injury to the eye globe will develop PVR, where cells grow uncontrollably beneath or on top of the retina, causing formation of contractile retinal membranes, retinal detachment, and permanent vision loss. Ocular trauma resulting from improvised explosive devices, blunt force, and projectiles is common in the Armed Forces; standard treatment currently involves surgery to repair retinal detachment and/or removal of foreign objects from the eye, most commonly metallic shrapnel, glass, or stone. Thus, PVR is a disease that is highly relevant for the military and military-related eye trauma.

Currently, the standard of care for the treatment of PVR is surgery to remove the contractile membranes that form on or under the retina; there are no specific therapeutic agents used for the prevention or treatment of PVR. Different pharmacological agents, such as anti-inflammatories, anti-proliferative agents, anti-growth factor, and antioxidants, have been tested as potential therapies for PVR, albeit without success. As PVR is a complex condition resulting from aberrant migration and proliferation of different cell types in the eye

where they do not belong, it is likely that multiple mechanisms contribute to the formation of PVR membranes. Thus, given the multifactorial nature of PVR, we propose that using pharmacological agents as combination therapies, rather than the traditional approach of monotherapy, will be more effective in the treatment of PVR.

In order to identify effective drug combinations for PVR treatment, we have developed a list of drug candidates that are already Food and Drug Administration (FDA)-approved for ocular use, or used in clinical trials for systemic/ocular therapy that target either cell proliferation, growth factors, or inflammation. The effect of drug combinations on cell migration, contractility, proliferation, death, and band formation will be tested using two novel cell culture models designed to mimic features of both early and late stages of PVR in vitro. Once promising drug candidates have been identified in vitro, we will examine the safety and efficacy of these drugs in vivo using a rabbit model of PVR.

We anticipate that by the end of this 3-year funding period, we will have identified ready-to-use drug combinations effective in preventing and/or treating PVR in both cell culture and animal model systems. As we are focusing on drugs that are already FDA-approved for use in the eye or found to be safe in ongoing clinical trials, this will rapidly decrease the time between preclinical evaluation and clinical trials; we anticipate that some of the drug combinations identified here could be ready for human testing at the completion of this 3-year study. It is hoped that the identification of new therapeutic agents for the prevention and treatment of PVR will provide a new standard of care, other than surgical intervention alone, for the treatment of this commonly occurring disease. This study will greatly benefit our Service men and women suffering from combat-related eye injuries, as well as civilians who experience PVR following ocular trauma. Moreover, the work proposed in this application will have a significant impact on the operational effectiveness of our Soldiers and has the potential to greatly improve the quality of life of civilians, Soldiers, and Veterans.

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