Nutlin Analogues for the Prevention and Treatment of Proliferative Vitreoretinopathy in Ocular Trauma

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PUBLIC ABSTRACT

Objectives and Rationale: This research proposal specifically addresses the Fiscal Year 2013 Vision Research Program - Translational Research Award Focus Area: Developing treatments for proliferative vitreoretinopathy. It is estimated that as many as 15% of the military personnel who served in Iraq and Afghanistan sustained significant eye injuries. Blast injuries to the face and eyes produce extensive damage to ocular tissues causing retinal trauma and severe vision loss. In particular, retinal trauma is commonly associated with the development of a severe scarring response, proliferative vitreoretinopathy (PVR), which is highly destructive to the delicate retina and results in blindness. PVR is caused by an innate healing response following traumatic injury. Cells from under the retina are exposed to a new environment and begin to actively grow on the retinal surface creating membranes that cause traction and pull the retina off the back wall of the eye. The retina is like the film of the camera and it cannot function once pulled away from its normal position within the eye. Many drugs have been tested without success in attempts to treat PVR. The focus of this project is to test and validate a new therapeutic class of drugs for PVR that have been developed from a deeper understanding of the cellular and molecular genetics of the disease, to prevent and treat PVR and to achieve better visual outcomes in wounded warfighters.

The candidate drug molecules we are testing, Nutlin-3 analogues, are variants of a known drug currently in clinical trials for the treatment of cancer. Focal Point Pharmaceuticals and St. Jude Children's Research Hospital, our partners in this project, have the rights to commercially develop a panel of Nutlin-3-analogues to treat PVR and childhood eye cancers. The key objective of this proposal is to determine the efficacy of a panel of 12 novel Nutlin-3 drugs in the prevention and treatment of PVR.

Applicability and Impact of the Research: The key objectives of this proposal are to establish the dose toxicity and therapeutic efficacy for these compounds to prevent PVR. We will identify the most promising molecules and test them in tissue culture models and in a small animal model of the disease. We will examine alternative routes of administration including topical eye drops, periocular injections, and intraocular injection formulations in a small animal model to determine the optimal way to deliver the drugs and also measure systemic absorption and duration of action of the drugs. The animal model will permit us to examine the effects of the drugs both on established PVR disease in the eye and as a prophylactic regimen to prevent the development of PVR, for use as a protective drug in those patients at risk for developing PVR. This translational research project leverages both basic and clinical science evidence from our research studies that demonstrate that Nutlin-3 analogues may also improve the efficacy of other anti-proliferative drugs in the treatment of PVR and some cancers through a multidrug approach. The small animal studies in this project will serve as the initial preclinical assessment of therapeutic efficacy for a planned submission to the Food and Drug Administration for drug approval for human use within 36 months.

Military Benefit: Significant eye injuries are common in the military personnel who served in Iraq and Afghanistan. The benefit anticipated...
from successful completion of this project is the validation of the therapeutic potential of novel Nutlin-3 analogues for clinical use in the treatment of PVR and for the prevention of PVR caused by traumatic retinal and ocular injury. An effective therapeutic intervention to prevent and treat PVR would have a direct and significant impact upon the risk of blindness resulting from ocular trauma in military personnel and in patients with retinal detachments from any cause.