Novel Use of Clinical Drugs to Prevent the Major Eye Injury-Associated Complication

Principal Investigator: TAMIYA, SHIGEO
Institution Receiving Award: LOUISVILLE, UNIVERSITY OF
Program: DMRDP
Proposal Number: DM090475
Funding Mechanism: Applied Research and Advanced Technology Development Award
Partnering Awards:
Award Amount: $424,264.00

PUBLIC ABSTRACT

Rationale and Objective of the Proposed Research: Ocular injuries have been shown to account for more than 10% of total battlefield injuries. Proliferative vitreoretinopathy (PVR) has been identified as the main cause of poor visual outcome following ocular injuries. PVR is essentially a scarring that happens in the back of the eye in response to an injury that can lead to tractional retinal detachment and loss of vision. Abnormal retinal pigment epithelial (RPE) cells have been shown to play a major role in the formation of PVR. Abnormal changes that occur to RPE cells include changes in cell shape and behavior as well as increased proliferation. Past studies that have tested drugs targeting cell proliferation as potential therapeutic agents for PVR had limited success. We have discovered that chemicals that inhibit the function of tyrosine kinases, a group of enzymes involved in regulating a variety of cell functions, can prevent abnormal changes that occur to the RPE cells in vitro. The tyrosine kinase inhibitors (TKIs) not only prevented cell proliferation but also changes to cell shape and behavior. This suggests that TKIs works differently from the previous tested anti-proliferation drugs.

The major objective of this project is to evaluate Food and Drug Administration (FDA)-approved TKIs, which are currently used to treat other diseases such as leukemia, as a therapeutic agent to prevent PVR formation. We will conduct research to evaluate efficacy of FDA-approved TKIs using a cell culture model in vitro for their effect to prevent abnormal RPE changes and then in vivo for their efficacy to reduce the incidence of retinal detachment using a pig model of experimental PVR.

Applicability of the Research: A majority of patients with PVR have poor visual function. Unfortunately, it is difficult to regain the visual function once PVR has developed. Therefore, prevention of PVR is important for patients who are at risk of PVR development. These patients include soldiers and civilians that have had ocular injuries in combat zones. PVR has been reported as the most common complication following open globe injuries, comprising 20%-30% of postoperative failure. In addition, PVR prevention will also benefit patients having corrective surgery for retinal detachment. Ten percent of the patients who have undergone this surgery are affected by PVR. By demonstrating that TKIs can prevent PVR, the project will help these patients who are at risk of developing PVR.

All drugs evaluated in the project have FDA approval for use in human patients. Therefore, once proven effective to prevent PVR in vivo, we expect clinical trials for TKIs to prevent PVR to start within 3 years of completion of this project.

It should be noted that while this project only focuses on PVR, tyrosine kinases are involved in other scar-forming complications. Therefore, ultimately TKIs may be used to prevent other scar-forming complications.

The Contribution of This Study in Advancing the Field of Research: We believe that preventing RPE cells from acquiring abnormal cell shape and behavior in addition to preventing proliferation is important in preventing PVR. Past studies have examined each change individually and thus could not link the changes. By determining how TKIs prevents both abnormal cell behavior as well as proliferation, the information obtained from the project could allow us to understand the molecular cause for each mechanism as well as how each change are linked.