Targeting Metabolic Reprogramming for the Prevention and Treatment of Proliferative Vitreoretinopathy

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PUBLIC ABSTRACT
The overall goal of this proposal is to address the lack of treatment for proliferative vitreoretinopathy (PVR), a major cause of severe and irreversible visual loss in ocular trauma patients. The incidence of blindness from PVR is particularly high amongst active Service Members due to the combat-related risks of exposure to explosive devices, blast and projectiles.

PVR occurs when breaks and tears in the retina, caused by trauma-induced retinal detachment and perforating injuries, disrupt the retinal pigment epithelial cells (RPE), and place them in direct contact with the intraocular vitreous fluid. RPE are highly specialized cells residing under the retinal neurons and supporting visual function. Under normal conditions, RPE are quiescent, i.e., they do not divide or migrate. Upon activation by growth factors from the vitreous, RPE lose their epithelial phenotype and start proliferating and migrating uncontrollably. This leads to the formation of highly fibrotic intraretinal membranes closely adhering to the retinal tissue. The contraction of these membranes results in severe retinal damage (large retinal detachment, tears, and foldings) and rapid vision loss.

To date, the only treatment for PVR is the surgical removal of the membranes and reattachment of the retina. However, success of corrective surgery for PVR is low as invasive treatment and physical peeling of the membranes further damage the retina promoting recurrent PVR and low visual outcomes. The development of safe and efficient adjunctive medical treatments to PVR is therefore critical to reduce the prevalence of blindness following ocular injuries.

Targeting the key cellular processes involved in the dedifferentiation and activation of RPE cells is a promising strategy for the treatment of PVR. Our laboratory has identified that RPE activation during PVR induction is associated with pathological metabolic changes. Indeed, like most cells, RPE cells utilize precise metabolic pathways tailored to their functional state as levels of energy and metabolites needed by quiescent and active cells are vastly different. Using an in vitro model of early PVR, we found that RPE activation depends on a specific metabolic switch and that blockade of this switch inhibits RPE migration and contraction.

Based on our findings, we postulate that metabolism-targeting drugs can be particularly efficient at blocking PVR formation by limiting the production of metabolites required for RPE activation, membrane formation, and contraction. Our proposed approach combines a precise metabolic analysis of experimental and clinical PVR in order to guide the preclinical evaluation of novel metabolic drugs. To ensure the success of our project, we have assembled a team of scientists and clinicians experts in RPE metabolism, molecular mechanisms of retinal injury, and experimental and clinical PVR.

Completion of our proposal has strong potential to identify novel therapeutic targets, surrogate biomarkers, and strategies for efficient prevention or treatment of PVR through targeting of disease-associated metabolic pathways. We expect that our findings will provide the necessary validation for the subsequent evaluation of the selected metabolic drugs for clinical applications and have already established collaborations with drug delivery experts to facilitate translational development. Our proposed work will have an important beneficial impact on active Service members, Veterans, and civilians by reducing the risk of vision loss from ocular trauma thereby improving their quality of life and well-being.
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