Maturation and Implantation of Engineered Retinal Tissue Grafts

Principal Investigator: RIZZOLO, LAWRENCE J
Institution Receiving Award: YALE UNIVERSITY
Program: VRP
Proposal Number: MR130036
Award Number: W81XWH-15-1-0029
Funding Mechanism: Vision Research Program - Translational Research Award
Partnering Awards:
Award Amount: $999,998.00

PUBLIC ABSTRACT

This proposal addresses war-related injury to the retina, the photosensitive portion of the eye, with the goal of developing treatments for these injuries. Additionally, these studies will benefit our Veterans who develop age-related macular degeneration (AMD), a leading cause of vision loss in the elderly. This encompasses two focus areas: vision restoration following traumatic injury and diseases of ocular structure. Despite differences in mechanism of injury, retinal damage inflicted in combat (e.g., laser or ionizing radiation) shares features with natural retinal degenerations like AMD. In each case, the same layers of the multilayered retina are injured. Advances in stem cell biology have led to clinical trials that explore the vision-restoring potential of stem-cell derived grafts for patients with retinal disease. Nonetheless, the biology of these retinal cell grafts is poorly understood. For example, in animal models of retinal degeneration, transplantation works in the earliest stage of disease, but fails when disease is advanced. This would provide very little benefit to patients with retinal degenerative diseases, and even less benefit to Soldiers who suffered retinal burns during military engagement. Further, the majority of transplant studies have focused on the retinal pigment epithelium (RPE) as the retinal cell to transplant. The reasoning is that AMD begins with a diseased RPE -- this is also true for the laser injury in the proposed study. Our proposal builds on this theory through use of a co-culture of RPE and retinal progenitor cells (RPC), which give rise to all neuronal cell types in the retina. Our rationale is that all of these cell types are needed when retinal disease is advanced. Thus, to overcome this challenge, we engineered a multilayered, multicellular retinal tissue from human stem cells. To allow these cells to thrive in co-culture, we will use a biodegradable scaffold that resembles a loosely woven fabric. We have previously shown that co-culture of RPE and RPC advances the maturation of each, and we will expand on these findings by asking: (1) Can externally added signaling factors further advance the maturation of the co-culture? If so, the tissue will provide an experimental platform to test putative therapeutic agents for healing retinal injury. (2) Second, would the engineered co-culture be more successful than monocultures of RPE in transplantation to repair advanced retinal disease?

Even though the eye represents a small percentage of the body surface, it is 50 times more likely to be injured than other body parts. Overall, 85% of Soldiers with non-fatal wounds can return to active duty, but only 25% of those with eye injury can do so. Notably, the incidence of ocular injuries has increased 30-fold since the Civil War, partly due to a rise in laser and other retinal injuries. Additionally, for our aging Veterans, like the general population, there is an increased risk for AMD, which is one of the most prevalent and disabling diseases in the elderly. The proposed research seeks to improve surgical approaches to advanced retinal disease and severe acute injury by using a pig model that closely resembles human eyes structurally and physiologically. This will enable translation of our findings from the research laboratory to the clinic or field hospital. However, the solution for war-related retinal injuries does not lie in surgical therapies alone. Our co-culture model will also allow us to test medical therapies that can stabilize Soldiers on the battlefield or field hospital until surgery can be done and that might augment or supplant surgery altogether.
If our studies are successful, the next steps would be to adapt our procedures to Good Manufacturing Practices for human use and apply to the Food and Drug Administration to certify the minipig model as an appropriate model for developing therapies for retinal disease. This would be a vast improvement over the existing rodent models because (unlike the pig) the rodent eye lacks a macula -- the structure that is essential for human vision. Laser and radiation injuries are ever increasing in modern warfare despite conventions that attempt to mitigate these dangers. These injuries impair vision by concentrating their harmful effects of the photosensitive layer of the retina. Further, the long-term consequences of impaired vision are devastating for Veterans and the families that care for them because they severely impede the normal activities of daily living.