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Outer Retina Reconstruction for Combat Afflictions (ORRCA)

Principal Investigator: GAMM, DAVID M
Institution Receiving Award: WISCONSIN, UNIVERSITY OF, MADISON
Program: VRP
Proposal Number: VR190043
Award Number: W81XWH-20-1-0655
Funding Mechanism: Focused Translational Team Science Award - Four Projects
Partnering Awards:
Award Amount: $4,967,689.00

View Technical Abstract

PUBLIC ABSTRACT

The human retina is an ultrathin, transparent, non-regenerating tissue composed of multiple layers of different cell types that work together to transmit visual information to the brain. Irreversible damage to the outermost layers of retina (i.e., the light-sensing photoreceptor (PR) layer and the underlying retinal pigment epithelium (RPE) layer) is a leading cause of untreatable visual disability in the deployed military population. Injury to the small, central area of the retina known as the macula is particularly devastating since it is responsible for the central, high-resolution, color vision that humans rely upon under normal lighting conditions.

Our application concentrates on two blinding macular injuries that currently have no treatments: (1) blunt force trauma (commotio retinae) and (2) laser trauma. Commotio retinae is a primary PR injury and permanent visual deficits are associated with PR death. It accounts for 12% to 18% of military eye injuries and affects the macula in 73% of cases. Military lasers are also a significant source of visual impairment, occurring either from accidental exposure or enemy action. Military targeting lasers can cause severe macular trauma (including RPE and PR loss) at 1km to 2 km, and optical aids including scopes and binoculars increase this range.

The critical challenge for our team is to reconstruct the central outer retina so as to improve macular function in Service men and women disabled by blunt force or laser injury (program title: Outer Retina Reconstruction for Combat Afflictions, or ORRCA). We propose to overcome this challenge using bioengineered outer retinal cell scaffolds, or "macular patches," containing PRs or RPE+PRs generated from human induced pluripotent stem cells (iPSCs). To overcome near-term barriers and achieve success in our challenge, ORRCA will combine first-hand knowledge of combat-related retinal injuries with state-of-the-art technologies and expertise in iPSCs, micro-fabrication and biomaterials, ophthalmology, and pig eye model systems. Four interrelated projects are proposed across two research sites: University of Wisconsin-Madison and the National Eye Institute (NEI). The four projects and their broad objectives are as follows:

(1) Production of RPE and PRs from human and pig iPSCs with incorporation into outer retina scaffolds. In collaboration with our industry partner, Opsis Therapeutics, we have already succeeded in generating RPE and PRs from human iPSCs in a quantity, purity, and manner suitable for human use. However, donor human cells may not be compatible within host animal model retinas. We will address this "Catch-22" using newly available pig iPSC lines and our extensive knowledge of iPSC differentiation. We will then optimize conditions for incorporating PR and RPE+PR cells into scaffolds and shipping the final scaffold products.

(2) Optimization of outer retina scaffold design and manufacture. Our current "ice cube tray" (ICT) scaffold is sufficient for the purposes of this challenge, but design and manufacturing process changes have been proposed by our engineering team to streamline production and enhance surgical handling and cell delivery.

(3) Development of protocols for controlled outer retina blunt force injury (commotio retinae) in the Yucatan pig. A notable gap in the development of therapies for commotio retinae is the lack of an animal model that also possesses human-like eye anatomy, such as the pig. In addition to developing a pig blunt injury model, we will refine a pig retinal laser model (developed by our NEI team) to mimic military laser injuries.

(4) Optimization of surgical techniques for the delivery of human and pig outer retina scaffolds and post-operative outcome testing in the blunt force and military laser injury Yucatan pig models. PR and combined PR+RPE loss are the largest challenges facing outer retina reconstruction efforts. We will optimize surgical procedures and monitor anatomic and functional effects after scaffold transplantation in our pig models to prepare for future human clinical trials,

a goal that is achievable within 10 to 15 years.

Generation of these scaffold products will allow precise, layered retinal cell replacement in areas of macular damage seen in commotio retinae and military laser burns, as well as other blinding outer retinal conditions that affect Service members and Veterans. Importantly, the outer retina scaffolds generated and tested via ORRCA also have the potential to treat blinding disorders that affect the civilian public, such as age-related macular degeneration, inherited macular disorders, and macular detachments that fail standard surgical treatment.

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