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High-Definition Axonal and Connective Tissue Imaging (HD-ACTI) in Porcine and Human Models of Traumatic Optic Nerve Injury

Principal Investigator: SCHNEIDER, WALTER
Institution Receiving Award: PITTSBURGH, UNIVERSITY OF
Program: VRP
Proposal Number: VR190139
Award Number: W81XWH-20-1-0774
Funding Mechanism: Investigator-Initiated Research Award - Funding Level 2
Partnering Awards:
Award Amount: $655,355.00

View Technical Abstract

PUBLIC ABSTRACT

Rationale: Combat Ocular Trauma (COT) is a significant cause of ocular morbidity in combat casualties. A retrospective non-comparative case series of traumatic registry data in OEF and OIF between 2002 through 2011 based on Joint Theatre Trauma Registry Data indicates that 10% of the 22,409 Service member (SM) injuries were COT. The nature of these injuries is variable and includes both open (intraocular foreign bodies, penetrating or perforating) and closed globe (anterior/posterior segment) trauma. Despite prophylactic measures, such as eye protection, COT can still result in ischemic, traumatic, or degenerative damage to the eye or optic nerve (ON). Vision restoration after traumatic ON (TON) injury remains a challenge with no clinical treatment. However, several teams from around the world have identified a number of molecular pathways and therapeutic approaches to enhance survival and regeneration of the ON in a broad swath of preclinical animal models.

Background: The scientific community to date has scarcely studied the effects of traumatic damage to the visual pathway in humans from the back of the eye, along the optic nerve, to the lateral geniculate nucleus (LGN) due to a lack of non-invasive diagnostic tools. This has impeded progress in accurate diagnosis, prognosis, and evaluation of potential therapeutic interventions. The development of new imaging technologies permits us now to address this gap in understanding. This project will work with porcine as well as human tissue (live and cadaver/harvested). It will also permit us to carry out mechanical stress tests of the tissue and conduct MR images of those tests. Specifically, the axonal tracts, bundles of axons (fascicles), myelin, vascular, and connective tissue will be examined and quantified. The pig eyeball and visual system is similar enough to human that results will carry over to human work.

Objectives: This work will address major gaps in the literature including (1) lack of high-resolution anatomical knowledge of how the axons of the ON traverse the distance from the eyeball to brain visual areas; (2) insufficient quantification of the tissue components of the optic nerve, and in particular, the importance of the role of connective tissue in injury and recovery; (3) MRI protocols for imaging the ON; and (4) understanding of the biomechanics of the ON.

Specific Aims: (1) Comprehensive ex vivo imaging analysis of ON fiber (fascicular, axonal, myelin, vascular) pathways of the porcine and human visual system, and evaluation of differential fiber and connective tissue composition and biomechanical properties. (2) Establish in vivo imaging correlates of anatomic and pathophysiologic changes in functional nerve conduction and structural connective tissue strength in fascicular, axonal, myelin, and vascular structures along the ON fiber pathways of the human and porcine visual system for reliable, reproducible, and longitudinal evaluation of fiber and connective tissue from ONH to LGN in humans on TRICARE MRI class clinical scanners.

Patient Diagnostic Deliverables: This project will provide MRI-based tools. These tools will be developed, validated, and calibrated in a porcine TON injury. This will lay the groundwork for development of a body of data that will identify patients for whom this technology will directly apply and provide those patients with a device to treat ON degeneration along with the proper procedure to provide the treatment (as tested in an animal model). This project will develop novel MR neuroimaging methods that would be usable at TRICARE hospitals to provide, for the first time, MR imaging to quantify the structural and functional integrity of the optic nerve non-invasively, localize pathology, and track treatment effectiveness in the tracts from the eyeball to the brain cortical areas (LGN and V1). For each of the fasciculi, scans will follow the path of the axons, and localize failures to transmit signals along the path. It will quantify the structural and function integrity of the axons. Sequential scans can track both the deterioration and healing of the tissue. It will aid research to discover new COT treatments.

Transition Strategy: Transition to TRICARE sites for clinical research studies can be swift. The HDFT technology for MR imaging of TBI and phantom calibration has been or is currently being implemented at major TRICARE sites (SAMMC, NMCSD, WRNMMC, Fort Belvoir). The imaging infrastructure required for this study already exists, and there is no requirement for regulatory approval for clinical research trials. HDFT has already been used to guide surgical planning in intracranial lesions. Once new methods are validated, the next stage would be clinical research trials expected to start in two years.

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