



US DEPARTMENT OF DEFENSE

BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Diagnostics and Biomarkers

Non-Invasive Immune Monitoring to Improve Outcomes in Composite Tissue Transplantation

Combat related amputations have led to greater than 1100 amputations from the Afghanistan and Iraq campaigns with facial injury occurring in one third of combat casualties. Composite tissue allograft (CTA) transplantation provides a unique opportunity to treat combat wounded, improve quality of life (QOL), and facilitate the return to active duty and occupation. Diagnosis of acute rejection (AR) remains dependent on non-specific clinical and pathological evidence. Therefore, novel concepts and innovative technologies are needed to non-invasively monitor AR that could be translated to long-term monitoring of chronic graft vasculopathy. Researchers at Walter Reed National Military Medical Center (WRNMMC) are actively studying non-invasive mechanisms for monitoring and recognizing AR following CTA transplantation. CTA transplants occur subsequent to disabling combat injuries involving hand, forearm, and craniofacial structures. Eighty-five percent of CTA transplant patients experience at least one AR phase during the first year following transplantation, and up to 60 percent undergo multiple AR episodes. The first phase of the study is to build a predictive model of graft rejection based on non-invasive imaging and immunological biomarkers in a swine CTA model. The resulting model will be validated in human patients during the second phase. The study team hypothesizes that non-invasive imaging modalities may be combined with immunological molecular markers to build a predicative Bayesian classifier model to allow for improved monitoring and diagnosis of rejection without the need for invasive tissue biopsies in advance of clinical signs of rejection or permanent tissue damage. A predicative model will help to identify potential novel monitoring and diagnostic tools and targets to improve treatment of CTA rejection. Imaging modalities employed include Raman Spectroscopy (RS), Infrared Thermography (IR) and visible reflectance spectroscopy (VRS) to examine compositional tissue changes, whole graft perfusion, and tissue oxygenation respectively. This study is funded by US Army Medical Research and Materiel Command (USAMRMC) in support of the Armed Forces Institute of Regenerative Medicine (AFIRM) II Cooperative Agreement.

The study employs a heterotopic hind-limb CTA swine model with three study groups: 1) AR, 2) standard immunosuppression, and 3) cycled immunosuppression. Daily digital, IR, and VRS images are collected following transplantation and the animals are monitored for rejection. At rejection, a skin biopsy is collected for RS analysis. To date, imaging studies have been completed on 15 pigs and identified potential imaging and spectroscopic markers of rejection and are currently analyzing chemokine/cytokine biomarkers. All metrics will be combined for Bayesian modeling analysis.

Concurrently, imaging of human patients will proceed at a partnering institute and skin biopsies will be collected. Once the final protocol amendment is processed by the Institutional Review Board (IRB) for Walter Reed Army Institute of Research (WRAIR), human samples and imaging data will be collected and imaging analysis will proceed.

