Prospectus

Computational Macrophage Quantification and Phenotype Response Model
(Technical Topic)

User Configuration and Barriers to Care for Female Veterans diagnosed with Post-Traumatic Stress Disorder
(STS Topic)

By

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Sociotechnical Problem Frame

Individuals in the military suffer extensive traumatic injuries on the battle field, among which, those affecting the musculoskeletal system are most prevalent. In particular, explosive devices used during wars cause severe skeletal muscle tissue loss, especially in the extremities. When the degree of tissue loss exceeds the endogenous regenerative capacity of skeletal muscle, permanent cosmetic and functional deficits result. This unrecoverable state is referred to as volumetric muscle loss (VML). There are few current treatment options for restoration of VML injuries. To address this problem, we seek to develop new tissue engineered technology to improve muscle regeneration in individuals suffering from this condition.

When designing a tissue-engineered therapeutic that will be implanted into the body, it is important to consider the body's response to the foreign object. In addition, one must understand the physiological mechanisms that occur in response to the therapy in order to assess and improve its effectiveness. Both of these areas can be explored by analyzing the influence that the tissue-engineered treatments have on the modulation of macrophage phenotype at early timepoints after injury creation and biomaterial implantation. Macrophages are immune cells that are attracted to areas of injury to induce an initial inflammatory response. ("Macrophage," n.d.) It is well established that macrophages play an important role in the regenerative process (Chazaud et al., 2009), however there is currently no standardized method for quantifying macrophages in tissue samples. For this project, I will be designing an automated method of macrophage quantification, and then will use this program to create and validate a computational model that can predict the macrophage response to skeletal muscle regenerative technology. This will provide insight about the biocompatibility and efficacy of these treatments, which is important in order to gain approval for use in the clinic.

This technical solution, however, fails to account for social aspects, such as ideas about the user for which this product is being created. When designing a medical treatment, a designer's prior ideas about the user must be closely analyzed to ensure that the product reflects the identity and needs of the actual user. Failure to address both the technical and social aspects of this problem will lead to a treatment that has certain biases concerning the user's identity, and consequently is not available for use by all VML patients. In order to create an effective product to improve muscle regeneration, both technical and social factors must be considered. First, I will discuss the technical process of developing an automated quantification method for macrophage profile and the design of a model of macrophage modulation in response to tissue-engineered treatments. Then, I will use the STS Framework of User Configuration to investigate a case in which certain biases were imbedded in a medical treatment -- the treatment options designed for veterans at the Veteran Health Administration (VHA) diagnosed with post-traumatic stress disorder. This will provide an example of the negative effects that could result by not taking the social aspects into consideration when developing a treatment. By acknowledging both the technical and social needs of this issue, I will be able to provide a more complete solution to the problem that was presented.

Technical Problem Frame

VML injuries are often observed in those in war after explosive blast trauma. There are few current treatment options for restoration of VML injuries. The current standard of care involves physical rehabilitation, orthotics, or the placement of free or rotational flaps of muscle onto the site of large skeletal muscle defects. These procedures have proved ineffective in replacing lost skeletal muscle tissue and restoring function. (Garg et al., 2015) A report detailing the wounding patterns in recent US conflicts found that 54% of combat wounds were located in the extremities, which often involve severe musculoskeletal injury. (Owens et al., 2008) These injuries contribute the most to the long-term disability of service members (Corona et al., 2015), and the lack of effective therapies presents a significant need for a regenerative solution that will restore the function of skeletal muscle. This problem is currently being addressed in the laboratory of Dr. George Christ at the University of Virginia, through work with biomaterials that are designed to increase skeletal muscle regeneration. In order to develop effective solutions, the physiology of skeletal muscle regeneration and wound healing must be better understood. Specifically, macrophages are a major player with extremely important roles in functional regeneration of muscle; analysis of macrophage phenotype over time will provide significant information to aid in understanding the process of macrophage recruitment to injury site. After *in vivo* testing is conducted on animal models in the laboratory, treated muscles can be sectioned and stained for CD68 and CD163, which are macrophage markers that allow for visualization of the M1 and M2 macrophage phenotypes. Quantifying the number and types of macrophages over time provides insight to the effectiveness of the treatment.

Currently, there is no standardized approach for quantifying macrophages. A common method is to manually count cells through the microscope, or produce digital images of the stained sections and manually count and mark the cells on ImageJ. While this method does prove effective in some ways, there are several draw backs. Manual counting of each macrophage is a tedious and time-consuming process. In addition, this method relies heavily on human judgement and has the potential to introduce error in the results due to human bias and inter-user variability. By creating an automated method for macrophage quantification, lab personnel will save large amounts of time and receive more accurate results for use as evidence for efficacy and safety.

Due to the novelty of these treatments, no model of the macrophage response after treatment currently exists. Computational models of skeletal muscle do exist, but there are several drawbacks or missing components that do not render them effective for predicting macrophage response to the tissue-engineered treatments described. This is due – in part – to a lack of existing data in this field, specifically for skeletal muscle regeneration after VML. This project will address this gap in knowledge through the development of a more comprehensive model of macrophage response after injury and biomaterial implantation. I will be conducting a two-step design process. First, I will use MATLAB and ImageJ imaging software to develop a computational method that is able to quantify macrophages in digital pathology slides, and distinguish between inflammatory macrophages and regenerative macrophages. Then, I will create a system of differential equations that models the change in macrophage profile over time at early timepoints after injury creation and biomaterial implantation. This project will provide a quicker and more accurate way of analyzing macrophage profile, and will create a computational macrophage model that can be utilized to accurately predict macrophage response based on injury severity and treatment. This model will allow for a more comprehensive understanding of the immune response, biocompatibility, and efficacy of the treatments when paired with *in vivo* work, and will give researchers the option to see the effects of fine-tuning the treatments before conducting tests in animals. Macrophage quantification data using the automated program will be compared to counts done manually by lab personnel to confirm its accuracy. The macrophage profile model will be validated using data from *in vivo* studies conducted in the laboratory on rodents with 20% of their tibialis anterior muscle mass removed as a simulation of the VML injury.

STS Problem Frame

Due to the strong link between combat exposure and posttraumatic stress disorder (PTSD), a mental health problem developed by some individuals after experiencing or witnessing a life-threatening event (PTSD Basics - PTSD, n.d.), treatment services for PTSD are an extremely important element of veteran health care. Veterans diagnosed with PTSD can seek counseling or treatment through the VHA. Provided services include mental health assessment and testing, psychotherapy such as Cognitive Processing Therapy, family therapy, group therapy for special needs and special residential or inpatient care programs (PTSD Treatment, 2020). It is the understanding of the VHA that these current services are adequate for meeting the care needs of veterans with this specific mental health diagnosis, however, there have been studies that indicate female veterans with PTSD or depressive symptoms have experienced barriers to VHA health and unmet medical needs (Lehavot et al., 2013). As women's participation and roles in the military continue to expand and the female veteran population increases, failure to explore the design of the VHA's PTSD care programs will result in continued unmet medical needs for female veterans.

By considering the social factors in this case, one can attempt to determine if certain ideas about the patient population using this care played a role in the creation of the treatment program. One can gain a better understanding of how these assumptions about the users affected the treatment design by investigating how the PTSD treatment programs were created. Drawing on the STS framework of User Configuration, I argue that the VA's PTSD program embedded biases about their patients' gender into the design, and consequently does not provide female veterans equal quality of care.

User configuration allows for a better understand the relationship between users of a technology and the technology itself. It is based on the idea that engineers or designers embed certain ideas and assumptions about the user into the technology's design and as a result the users' interaction with the technology are constrained. This framework can be used to better understand if these configured users reflect the identity of the actual users (Oudshoorn & Pinch, 2003). User configuration will allow me to determine if ideas about the users' genders were imbedded in the design of the VHA's PTDS program. To further investigate this idea and support this claim, I will analyze evidence from a study that examined unmet medical needs and barriers to health among women veterans who screened positive for lifetime PTSD or current depressive symptoms, and document the top reasons as to why female veterans were not satisfied with their care. In addition, I will investigate the sex differences in trauma and PTSD (Olff, 2017; Tolin & Foa, 2006), which takes into account the increased likelihood of female veterans to have experienced sexual assault and sexual harassment compared to male veterans.

Conclusion

The technical report proposed will provide a new method of macrophage quantification, and create a system of equations to model the macrophage profile in response to tissue-engineered treatments administered *in vivo*. This technical fix will provide more accurate and less time-consuming macrophage analysis methods, and provide information necessary for developing an effective tissue-engineered solution to increase skeletal muscle regeneration after VML injury. When developing this medical solution, it is important to keep in mind ideas about the user of the device. Implicit biases can be imbedded in the product deeming it unusable for some groups, an example of which can be seen in the case of barriers to care and unmet medical needs of female veterans diagnosed with PTSD. The STS paper will use the concept of user configuration to analyze how implicit bias was imbedded in the design of the PTSD care program, and will emphasize the importance of considering how the ideas designers have about users have a large impact on the product being developed. It will show the potential consequences that can be faced if the user is not considered when designing the regenerative treatment for VML injuries.

Word Count: 1840

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