Nonviral Gene and Reprogramming-Based Cell Therapies for Peripheral Nerve Injury

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Institution Receiving Award: OHIO STATE UNIVERSITY, THE
Program: PRMRP
Proposal Number: PR211321P1
Award Number: W81XWH-22-1-0393
Funding Mechanism: Investigator-Initiated Research Award - Partnering PI Option
Award Amount: $790,159.00

PUBLIC ABSTRACT

This project will address the topic of Peripheral Neuropathy, focusing on the area of encouragement of "regenerative medicine-based solutions for peripheral nerve injury, such as gene therapy." Traumatic nerve injuries in the military typically result from high-velocity gunshot wounds or blast injuries that compromise multiple tissues. Although warfare has historically led to a large number of nerve injuries, the standard care for this condition has evolved very little throughout conflicts and continues to be a significant challenge for military surgeons. Moreover, the treatment of traumatic nerve injuries is often delayed in order to address additional complications from the injury, including hemorrhages, tissue necrosis and infections, among others. This, in turn, can result in severe long-term consequences, as the injured nerve and denervated muscle tissue continue to progressively deteriorate. The complications from peripheral nerve injuries are further compounded by lifelong chronic disabilities. Nerve injuries could result in pain, weakness, loss of sensation, and loss of independence, and as such have a significant impact in unit readiness and return-to-duty rates. Therefore, there is a clear need for the development of novel approaches that can be used to treat traumatic nerve injuries more promptly, and with simple-to-implement and versatile methodologies compatible with intervention across all levels of military medical care.

This application is focused on developing game-changing nanotechnologies that could be used to deliver simple to implement solutions, compatible with implementation at all levels of military medical care (e.g., from the battlefield to major military centers in the U.S.), for peripheral nerve injuries in the military. The proposed research will seek to develop novel nanotechnologies to repair or protect mangled nerves or muscle through a one-time intervention, lasting only a few milliseconds. The goal is to potentiate endogenous reparative mechanisms based on the novel concept of tissue nanotransfection (TNT)-driven reprogramming, which can either replace the current standard of care for nerve injuries in the military or delay progressive nerve damage until proper surgical intervention. TNT is a technology developed by the Principal Investigator, Gallego-Perez, which can be used to deliver therapeutic genes into tissues in a fast (e.g., it only takes a one-time intervention lasting ~100 milliseconds), benign (e.g., it does not cause tissue damage or deleterious side effects), and effective manner (e.g., superior performance to status quo gene delivery methodologies). The proposed studies will be conducted in preclinical animal models of nerve injury, and will be subdivided into 4 aims, as follows:

Aim 1: Develop optimized TNT strategies to generate new blood vessels to support the repair of nerve injury: Blood vessels are important for the repair and regeneration of mangled nerve tissue. At the

completion of these studies, we expect to have developed novel strategies to drive the formation of new blood vessels that can help injured nerve repair faster and more effectively.

Aim 2: Develop optimized TNT approaches to generate neurons in denervated skeletal muscle as a protective strategy: Nerve signals are important for the health of muscle tissue. Nerve injury can sometimes remove those nerve signals, which results in muscle atrophy. At the completion of these studies, we expect to have developed novel strategies to drive the formation of neurons in muscle tissue that can help to maintain muscle health until the nerve signals can be permanently restored.

Aim 3: Develop optimized TNT approaches to achieve localized immunoprotection in cellular nerve allografts: Large nerve defects could be repaired better with donor nerve graft tissue that still contains cells. However, since those cells, which are key to the success of the graft, can be rejected by the patient's immune system, the patient has to be subjected to extremely aggressive immunosuppression regimens, which can cause side effects. At the completion of these studies, we expect to have developed novel strategies to drive localized immunoprotection of the donor nerve graft tissue to help protect it from the patient's immune cells without the need for the use of aggressive immunosuppression drugs.

Aim 4: Evaluate the impact of an optimized combinatorial strategy of vasculogenic (Aim 1), neurogenic (Aim 2), and immunomodulatory (Aim 3) TNT on the repair of a long segmental PNI: Complex nerve injuries require the use of multimodal strategies aimed at solving multiple challenges at the same time. At the completion of these studies, we expect to have developed a combinatorial strategy that will lead to improved nerve tissue repair by combining the advantages of the strategies delineated in Aims 1-3.

Short term, the TNT technology may prove useful in nerve trauma cases where prolonged extraction issues to definitive care facilities arise given restrictive operation parameters or environments. This scenario is especially critical in missions focused within hostile countries lacking advanced medical care infrastructure. Delayed intervention in such cases would portend poor PNI outcomes with irreversible consequences and the propensity for developing lifelong disabilities that impact unit readiness and return-to-duty rates. Thus, a technology that could facilitate early intervention of mangled tissue would be essential to achieving successful salvage of nerves and end organs. Moreover, besides providing the means for delivering early care to PNI cases, TNT could also be implemented at higher echelons of medical care, where surgical reconstruction of PNIs with nerve grafts necessitates technologies that can improve graft vascularization or minimize the need for systemic immunosuppression. Long term, this technology may be able to cross varying operational platforms such as land, sea, and air via compact packaging of the material into an easily deliverable medical care kit that would allow for initiation of salvage operations potentially at the battlefield scene or locale of injury, as well as through the varying levels of care as currently supported by military treatment facilities. We believe that this technology can be pared down in the future into a compact, and readily deployable kit that can be used by an Army medic, Navy corpsman, Air Force PJ, general medical officer, or battalion surgeon within the field setting as well as within the advancing levels of medical care capabilities as the injured Service Member is extracted and his/her PNI is attended. The applications of this technology could go beyond the military population, as PNIs in general are also very prevalent in the civilian population.