Extremity Trauma Rehabilitation and Treatment

Stem Cell Based Neurotrophic Enhancement of an Aligned Nanofiber Scaffold for Nerve Repair

Peripheral nerve trauma is a challenging complication of wartime injuries and often leads to significant disability and dysfunction. Current wartime combat operations have resulted in many injuries to Service Member's limbs as a result of explosive blasts. What many of these injuries have in common is that they significantly affect the peripheral nerves involved in these areas. Certain cells collected from traumatized muscle tissue were found to behave similarly to stem cells, normally found in bone marrow, which are known to help regenerate tissue by either direct differentiation or secreted trophic factors. These cells with tissue/bio-engineered microenvironment could become useful in treating injured Service Members suffering from peripheral nerve injuries by reinserting them back into the injured areas so that missing nerve connections can be regenerated and finally return to functional level recovery quickly. Researchers at the Uniformed Services University of the Health Sciences (USUHS) are conducting a study to test the hypothesis that mesenchymal progenitor cell (MPC) derived from traumatized muscle and seeded within a biodegradable scaffold consisting of aligned nanofibers are capable of providing neurotrophic enhancement of nerve regeneration by generating a biochemical bridge that promotes axonal growth and migration of cells. This study is funded by the Peer Reviewed Orthopedic Research Program (PRORP) and managed by the Congressionally Directed Medical Research Program (CDMRP). The study team identified a population of MPCs from war-traumatized muscle tissue (Figure 1). The morphology and cell surface epitope profiles of MPCs are similar to those of bone marrow-derived mesenchymal stem cells (MSCs), which are the resident osteoprogenitor cells from the marrow stroma. Traumatized muscle-derived MPCs are also capable of giving rise to colony-forming-unit-fibroblasts, an indicator of a clonogenic, multipotent cell population. The MPCs appeared to be a distinct population of progenitor cells with characteristic similarities to bone marrow-derived MSCs, with some notable differences between the MPCs and MSCs, which likely reflect their different tissue of origin and in vivo function, and both cell types converge on the osteogenic differentiation pathway under appropriate induction. MPCs are also capable of differentiating into two other mesenchymal lineages, adipocytes and chondrocytes. In addition, they may also be useful in the development of tissue engineering strategies of regenerative medicine. In the first ten months of this project, researchers at USUHS have developed methods to fabricate a nanofiber-based scaffold with the appropriate geometry and have verified the alignment of the nanofibers along the longitudinal axis of the graft. In addition, the device has been optimized to have sufficient mechanical strength for surgical handling and suture retention. During this study, researchers seeded these grafts with the human MPCs in vitro, and evaluated the effect of the cell/scaffold composite on the cells responsible for nerve regeneration using rat sciatic nerve transection defect model of nerve injury (Figure 2). MPCs appear to be a promising cell type for cellular therapy to enhance tissue regeneration, and may be

useful as an autologous cell type at the point-of-care. They express several factors that are known to enhance neuron function after injury and this research provides further evidence indicating that these cells may be useful to promote peripheral nerve regeneration. The MPCs appear to exhibit neurotrophic function when exposed to factors that are up regulated by nerve injury, suggesting that the MPCs may be induced to perform their neurotrophic function in situ. The research outcomes described demonstrates preliminary evidence of human MPC enhancing nerve regeneration at the early time point (two-week) in a well-established rodent peripheral nerve transection model. The nature of the nerve growth and the neurotrophic activity of the MPC will be further elucidated upon completion of the ongoing research tasks.

FIGURE 1: Workflow how to isolate Mesenchymal Progenitor cells (MPCs) from trauma blast injured tissue.

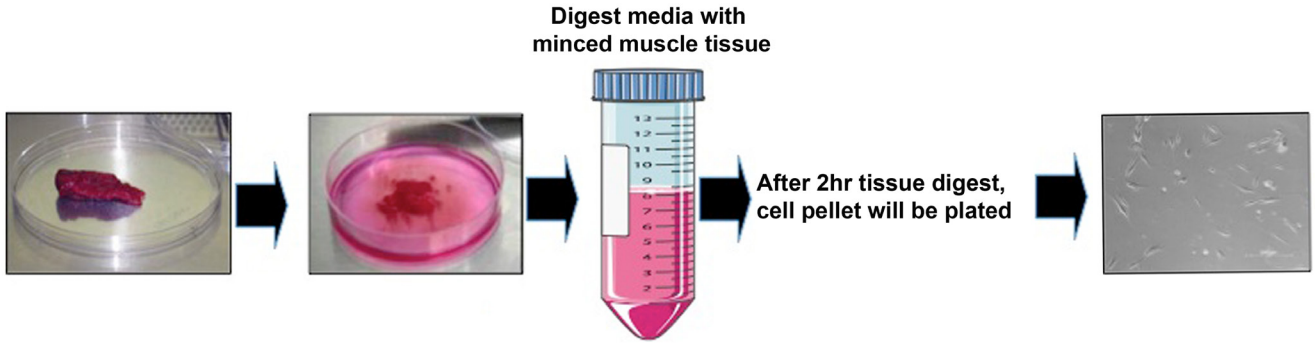

FIGURE 2: Schematic of the prepared MPCs loaded nerve conduits and implantation in the rat sciatic nerve transection model.