DNA-Based Hydrogels for Peripheral Nerve Repair

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Peripheral neuropathy results from severe damage to the peripheral nerves (PNs) caused by combat-sustained traumatic injuries, autoimmune diseases, infections, chemotherapy, and toxin exposure. These injuries often lead to partial or total loss of sensory, motor, and autonomic functions and are associated with lifelong chronic pain, weakness, and limb paralysis. The increase in the number of PN injuries to the upper and lower limbs is correlated with the improvement of Warfighters' protective gears that significantly increased the survival rate of wounded Soldiers by protecting vital organs. The increase in the incidence of PN injuries poses major challenges for the military health system. Indeed, most patients in military hospitals and clinics for temporary and permanent disabilities suffer from some form of PN injury.

Today, repairing damaged PNs is one of the greatest challenges in military medicine. Despite tremendous progress in surgical techniques, complete PN repair usually requires multiple invasive procedures, and complete recovery remains rare. The limited regenerative capability of PNs and the wide variation in their architecture are the main factors reducing the efficiency of traditional therapeutic strategies. Nervous tissue engineering with biomaterials-based scaffolds that can replicate the complexity of the PN environment, including the spatial variation of mechanical and electrical properties, as well as the distribution of biochemical cues (e.g., growth factors and cytokines), represents an attractive alternative that could alleviate the issues of traditional therapies. These strategies have already proven successful in promoting neuronal cell survival and growth in vitro. However, while extremely promising, tissue engineering strategies have not yet enabled complete PN regeneration, primarily because the biomaterial scaffolds in common use rarely combine the critical mechanical, electrical, and biochemical features required for proper nervous tissue formation. Therefore, there is an unmet need to develop synthesis methods for biomaterial scaffolds that offer precise control over their mechanical and electrical properties, as well as the distribution of biochemical cues to faithfully mimic natural nervous tissue environment signaling.

Here, we propose to engineer electrically conductive DNA-based hydrogels with elastic modulus and electrical conductivity that can be finely controlled to match those of the PN tissue. We also propose to develop a novel bioprinting strategy to control the spatial distribution of neurotrophic factors known to promote PN regeneration, which will be patterned directly into the hydrogels to enable directed neurite growth toward functional tissue formation. To reach our objectives, we will follow two specific aims. First, we will leverage the unique properties of DNA molecules as building blocks to assemble a DNA-based hydrogel whose elastic moduli can be tuned to match those of PNs by varying the DNA motif concentration. These DNA hydrogels will be doped with conductive polymers, allowing electrical stimulation of neuronal cells to promote their growth. Next, we will develop a printing method to assemble these hydrogels with programmed gradients of

neurotrophic factors that can guide neurites across the hydrogel toward efficient PN regeneration with or without electrical stimulation. We will quantify the efficacy of our approach to promote directional neuronal axon growth in vitro with neuron-derived PC12 cells.

Our novel scaffolds could change the paradigm of treatment of PN injuries that affect the lives of many wounded Soldiers and Veterans, as well as millions of civilian patients every year worldwide, by reducing healing time and enabling rapid recovery of nerve functions to avoid the incapacitating consequences of PN injuries. In addition, the versatility of our strategy will also considerably advance knowledge on rational design of scaffolds for tissue engineering and regenerative medicine.