determine aesthetic outcomes. The present pilot suggests that symmetric nail size may be an area of importance for creating the sense of aesthetic success. Incorporation of this data into surgical counseling may assist the patient and medical team focus on surgical-decision making priorities.

2

Sensorimotor Myoelectric Control Using Surface Based Regenerative Peripheral Nerve Interface (RPNI)

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Purpose: Although advanced prosthetic devices have the potential to allow fine-motor movements and extract somatosensory signals via sensitive pressure sensors, an ideal interface to integrate the human nervous system with the prosthetic doesn’t exist. Furthermore, the requirement for the implantation of indwelling electrodes and prohibitive costs limits the application of current technologies. The Regenerative Peripheral Nerve Interface (RPNI) was developed as a stable biologic interface on the notion of providing physiologic end-organ targets for regenerating axons by implantation of a residual nerve into an autogenous free muscle graft. Despite providing intuitive motor control, RPNI sensory feedback is limited and also relies on implantable electrodes for myoelectric signal transmission. To address these challenges, we investigated the placement of RPNIs underneath the defatted skin in rats to capture myoelectric signals using surface electrodes. This strategy simultaneously provides sensory feedback through the sensory reinnervation of the overlying skin.

Methods: Utilizing six male F344 rats, the right tibial nerve was transected distally in the thigh before entering the leg’s posterior compartment. Subsequently, the left side extensor digitorum longus (EDL) muscle was harvested and co-apted with the proximal segment of the tibial nerve for RPNI fabrication. The RPNI was placed and secured in between the biceps femoris muscle near the skin while the side opposite to the nerve coaptation was facing the dermis. The overlying skin was defatted and fixed on top of the superficial RPNI (S-RPNI). At two months post-surgery, functional motor reinnervation was evaluated by electrical stimulation of the tibial nerve and compound muscle action potentials (CMAPs) were recorded using surface electrodes. Sensory feedback was assessed by electrical and mechanical stimulation of the skin to respectively record sensory nerve action potentials (SNAPs) and sensory afferent signals. The S-RPNI construct and its overlying skin were subsequently harvested and processed for immunohistochemistry and whole-mount immunostaining.

Results: Recording muscle CMAPs from the skin was readily feasible in all animals, showing robust signals with minimal noise distortion (366 µV ± 86.3). Electrical stimulation of the skin on the lateral thigh, which is not innervated by the tibial nerve normally, resulted in classic tri-phasic SNAP generation in this nerve. Brushing the overlying skin using a cotton swab generated synchronized monomorphic afferent signals. Sensory reinnervation of the skin was shown using IHC. Whole-mount staining of the muscle component showed regenerated muscle with new neuromuscular junctions (NMJs) and spatial segregation of sensory fibers toward their end-target organ.

Conclusion: Superficially placed RPNI is a viable and an alternate methodology that is simple to implicate and has the potential to transmit simultaneous, real-time, and independent sensory and motor signals between the residual nerve and the prostheses.

3

IGF-1 Hydrogel-based Nanofiber Drug Delivery System to Improve Nerve Regeneration and Functional Recovery After Peripheral Nerve Repair

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**Purpose:** Insulin-like growth factor 1 (IGF-1) is a potent mitogen with the potential to enhance axonal regeneration and minimize muscle atrophy and Schwann cell senescence following prolonged denervation after peripheral nerve injury. IGF-1 is a small protein with a half-life of 5 min, making local delivery a challenge. Our group has demonstrated over 6 weeks of sustained release of bioactive IGF-1 encapsulated within biodegradable nanoparticles (NP) and subsequently developed a nanofiber fiber hydrogel composite (NHC) carrier to retain IGF-1 NPs at target tissue locally for the duration of drug release. The aim of this study was to further characterize and refine the IGF-1 NP-NHC drug delivery and then investigate its efficacy in both rodent and non-human primate (NHP) median nerve injury models.

**Methods:** IGF-1 was encapsulated in biodegradable PCL NPs and then embedded within the NHC composed of hyaluronic acid and PCL nanofibers. Release kinetics and biocompatibility were evaluated and optimized both in vitro and in vivo. The drug delivery system was assessed using a chronic denervation median nerve injury rat model and an acute median nerve repair NHP model. IGF-1NP/NHC was injected along the median nerve and within denervated muscle. In rodents, a range of IGF-1 doses (300, 900 and 1500 μg/mL) were investigated to evaluate dose-response relationships. Axonal regeneration, muscle atrophy, neuromuscular junction reinnervation and recovery of grip strength were assessed.

**Results:** The refined NP-NHC delivery system provided sustained release of bioactive IGF-1, in vivo, for at least 42 days by serial ELISA. IGF-1 treated rodents demonstrated a 35% increase in functional recovery (stimulated grip strength) compared to untreated rodents, with no differences observed between the different concentrations of IGF-1 that were evaluated. Median nerve histomorphometry demonstrated a significantly greater total number of axons at each concentration of IGF-1 compared to untreated rodents (p<0.0001). IGF-1 treated rodents also demonstrated a greater percentage of reinnervation of neuromuscular junctions by 17% (from 14% to 31%). In addition, the IGF-1 treated non-human primate demonstrated a 31% increase in functional recovery compared to the untreated animal (N=1 per group).

**Conclusion:** The IGF-1 NP/NHC delivery system provided sustained delivery for over 42 days in rodents and NHP. IGF-1 improves motor functional recovery by enhancing axonal regeneration and neuromuscular junction reinnervation while limiting denervation-induced muscle and Schwann cell atrophy in rodents. Our NHP pilot study has established a used pre-clinical model with robust functional analysis that will serve as a platform for a formal NHP study prior to clinical testing. The components of the NP-NHC delivery system are already used in FDA approved formulations, which will facilitate clinical translation.

4

**Peripheral Nerves Engage in Reciprocal Neuro- and Angiogenic Crosstalk With SMCs in Extremity Trauma**

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**Purpose:** Existing literature describes the interdependence between neurotrophic and vascular signals in the central nervous system. We hypothesize a similar crosstalk important to extremity healing involving the peripheral nervous system and angiogenic cells. Nerves are difficult to capture via axons found in the periphery alone. Thus, we have interrogated from publicly available single-nuclei transcriptomic data of peripheral nerve soma (dorsal root ganglia), injured by physical transection or chemically induced pain. We present a combined analysis of extremity polytrauma (burn/tenotomy HO model) and peripheral nerve (post-injury/pain DRG model) to determine if there is expression of vascular signals by nerves and reciprocal neurotrophic signals by cells local to the injury site.