**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 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.
Methods: A 30% dorsal burn and Achilles transection was performed in C57/BL6J mice. The tendon site tissues were harvested from baseline (t0) and day 7, 42 after induction. Samples were prepared for library generation on a 10x Genomics Chromium Controller, sequenced on a Illumina HiSeq 4000, and analyzed with Cell Ranger Software for pre-processing and alignment to the mm10 genome. DRG analyses and clusters were abstracted from NIH-GEO (GSE154659). Downstream analyses including unsupervised clustering downstream analyses were performed with Seurat.

Results: We first examined candidate neurotrophins and vascular signals in nerve (DRG), finding robust upregulation of Bdnf and Vegfa. In HO, the site of injury contains many cells that may potentially respond to these signals. Indeed, in sequencing data from the pre-HO anlagen, endothelium and smooth muscle cell populations express upregulation for receptors to the nerve-derived Vegfa via Flt1/VEGFR1. This population in addition to being sensitive to the VEGFA ligand, also demonstrates upregulation of Ngf, signifying a potential vasculo-neuro axis where a vascular signal induces endothelium/SMCs to produce neurotrophic signals. Completing the circuit, the original DRG cells and by logical extension, regenerating peripheral nerves, are highly enriched for the neurotrophin receptors: Ntrk1/TrkA (responsive to the SMC derived NGF), Ntrk2/TrkB (responsive to the nerve-autonomous BDNF), and Ntrk3/TrkC (partial combined NGF/BDNF response). This potentially signifies a feedforward loop where peripheral nerve induces angiogenesis which in return, promotes nascent nerve ingrowth in a cyclical process. Indeed, in targeted knockout of a local VEGFA source (VegfaPrrx1 mice), the injury site demonstrates parallel reduction in vascular density (77%) and reduction in nerve fiber frequency (62%) within the HO site.

Conclusions: These findings represent the first work characterizing the coordination between neurogenic and angiogenic transcription programs following extremity trauma. We demonstrate through NextGen sequencing, evidence of neuroangiogenic crosstalk following musculoskeletal/neural injury. This VEGFA/NGF axis involves vascular signaling as a potential source for additional proliferation of NGF expressing pericyte/SMCs. The presented data describe the potential nerve-driven regulation contributing to the formation of HO at the extremity that with antagonism or inhibition may lead to better treatments for aberrant extremity wound healing.

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Metacarpal Subsidence Following Trapeziectomy

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Purpose: It is controversial whether subsidence after trapeziectomy prognosticates pain, poor outcomes, and need for revision. The aim of this study was to investigate the degree of subsidence following trapeziectomy and whether subsidence contributes to poor outcomes.

Methods: An IRB approved retrospective review of all patients who underwent trapeziectomy for osteoarthritis of the first carpometacarpal (CMC) joint was conducted from 2003 to 2019. Patients with available radiographic imaging greater than three months postoperatively were included. Patients with arthritis of the metacarpophalangeal joint of the thumb, arthritis of radiocarpal, distal radioulnar, and midcarpal joints were excluded. Demographic information, pain scores, and revision procedures were recorded. Conolly-Rath patient function scores were determined. Subsidence was measured by the ratio of the difference between the trapezial space (TS = distance from base of thumb metacarpal to scaphoid) preoperatively and TS postoperatively over the TS preoperatively. Patients were divided as having a high degree of subsidence (≥50%) or low degree of subsidence (<50%). Pain scores (median and interquartile range) were compared before and after surgery, as well as between high and low subsidence groups using Mann-Whitney U tests. Age was compared between the two groups using an unpaired t-test. P value <0.05 was considered significant.

Results: One-hundred-eighty-six patients, who underwent 211 primary trapeziectomies, were included. The average age at the time of surgery was 61 years (range 18-86). Eighty-five percent of patients were female. Average follow-up was 38.2±31.9 months (range 3-146.5 months). Metacarpal subsidence was present in all patients after trapeziectomy (average 58.0±20.8%). There was no