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Scientific Abstracts > Emerging Technology

IGF-1 Nanoparticles Improve Functional Outcomes after Peripheral Nerve Injury

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Introduction

Extremity trauma often involves peripheral nerve injury (PNI), with a reported incidence of 20-30%. PNIs often result in persistent, debilitating motor and sensory deficits.(1). Following surgical repair of proximal trauma related PNIs, useful recovery of function is rare. Currently there are no clinically available therapeutics to address this problem. Poor outcomes following PNI result from the slow rate of axonal regeneration requiring excessive time to elapse prior to reinnervation, during which chronically denervated muscle and Schwann cells undergo progressive, irreversible atrophy .(2). Insulin-like growth factor 1 (IGF-1) carries promise as a therapeutic for PNI. IGF-1 is a potent mitogen that enhances axonal regeneration and reduces the deleterious effects of prolonged denervation on Schwann cells and myocytes. However, a safe, effective, and practical delivery strategy is needed as systemic IGF-1 treatment carries unacceptable risk including severe hypoglycemia, and local delivery of IGF-1 is limited by its short half-life .(3). The aim of this study was to develop a novel drug delivery system as a regenerative medicine-based solution to enhance nerve regeneration and functional recovery in the setting of PNI via a nanofiber fiber hydrogel composite (NHC) carrier to optimize in vivo retention of biodegradeable nanoparticles (NP) and then characterize its' efficacy in a rodent and non-human primate (NHP) peripheral nerve injury (PNI) model.

Materials and Methods

IGF-1 was encapsulated within biodegradable PEG-b-poly(e-caprolactone) NPs using a two-step flash nanocomplexation (FNC) and flash nanoprecipitation (FNP) process. The IGF-1 NPs were 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 IGF-1 NP/NHC drug delivery system was assessed in rodent and NHP forelimb PNI models. The IGF-1 NP/NHC was injected along the median nerve and within denervated muscle. In rodents, chronic denervation of the median nerve was induced before nerve repair. A range of IGF-1 doses (300, 900 and 1500 µg/mL) were investigated to evaluate dose-response relationships. In NHPs an acute median nerve repair model was used in which the median nerve was unilaterally transected and immediately repaired. The experimental NHP was treated with IGF-1 (300 µg/mL) and the control NHP was injected with 0.9% sodium chloride. The primary outcome measure in both models was stimulated grip strength testing used to assess functional recovery. Biointegration and the immune response of the NHC were characterized. Axonal regeneration, muscle atrophy, neuromuscular junction reinnervation were evaluated histologically.

IRB approval was obtained on 11/09/19 for a three year period.

Results/Case Report

IGF-1 was encapsulated into the nanoparticles with high uniformity, a high IGF-1 loading level (10–20%), and a high encapsulation efficiency (>80%). The IGF-1 NP/NHC provided sustained release of bioactive IGF-1 for 6 weeks in vitro and in vivo in both rodents and the NHP. The high, medium, and low dose IGF-1 treated rodents all demonstrated significantly improved functional recovery of 35% compared to untreated rodents ($p<0.05$), though there was no difference in recovery between the three doses of IGF-1. The IGF-1 treated NHP exhibited a 31.0% increase in functional recovery 71 weeks compared to the control NHP (Figure 1). The NHC minimized the inflammatory response by polarizing macrophages to the pro-regenerative M2 phenotype and upregulating production of anti-inflammatory cytokines. Collagen deposition between the NHC and flexor digitorum profundus (FDP) interface was decreased compared to collagen deposition in FDP in the control NHP (Figure 2). IGF-1 resulted in a two-fold increase in the number of regenerative axons compared to the saline treated control (5377 vs 2704, respectively) and reinnervation of glabrous skin.

Discussion

The NP/NHC preserves stability and bioactivity of IGF-1 during encapsulation, storage, and release. Our novel drug delivery system improved functional recovery by at least 30% in both rodents and NHP. Sustained, near-linear release of IGF-1 for 6 weeks was achieved and with this re-dosing schedule patient compliance will be much less problematic than with other approaches being investigated, requiring daily re-dosing. Clinical application of the IGF-1 NP/NHC drug delivery system as a therapeutic for PNI has potential since components of the delivery system are already utilized in FDA approved formulations. Additionally, the manufacturing method is scalable and easily tunable, making it well suited for future translation.

References

1. Noble J, Munro CA, Prasad VS, Midha R. Analysis of upper and lower extremity peripheral nerve injuries in a population of patients with multiple injuries. The Journal of trauma. 1998 Jul;45(1):116-22. Epub 1998/07/29.

2. Tuffaha SH, Budihardjo JD, Sarhane KA, Khusheim M, Song D, Broyles JM, Salvatori R, Means KR, Jr., Higgins JP, Shores JT, Cooney DS, Hoke A, Lee WP, Brandacher G. Growth Hormone Therapy Accelerates Axonal Regeneration, Promotes Motor Reinnervation, and Reduces Muscle Atrophy following Peripheral Nerve Injury. Plastic and reconstructive surgery. 2016 Jun;137(6):1771-80. Epub 2016/02/19.

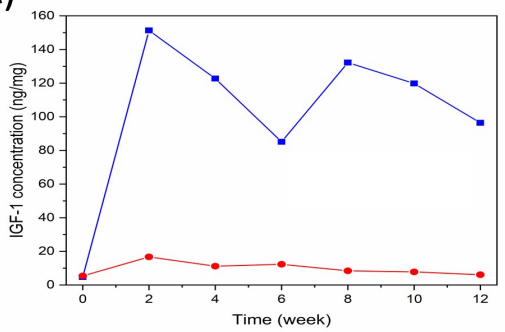
3. Mullis PE, Pal BR, Matthews DR, Hindmarsh PC, Phillips PE, Dunger DB. Half-life of exogenous growth hormone following suppression of endogenous growth hormone secretion with somatostatin in type I (insulin-dependent) diabetes mellitus. Clinical endocrinology. 1992 Mar;36(3):255-63. Epub 1992/03/01.

Disclosures

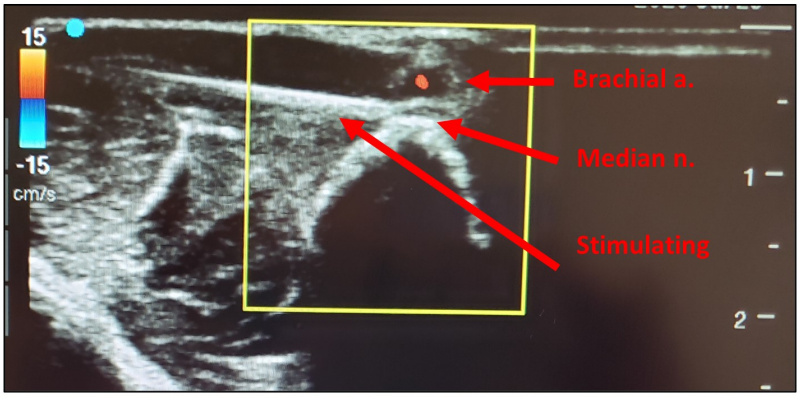
No

Tables / Images

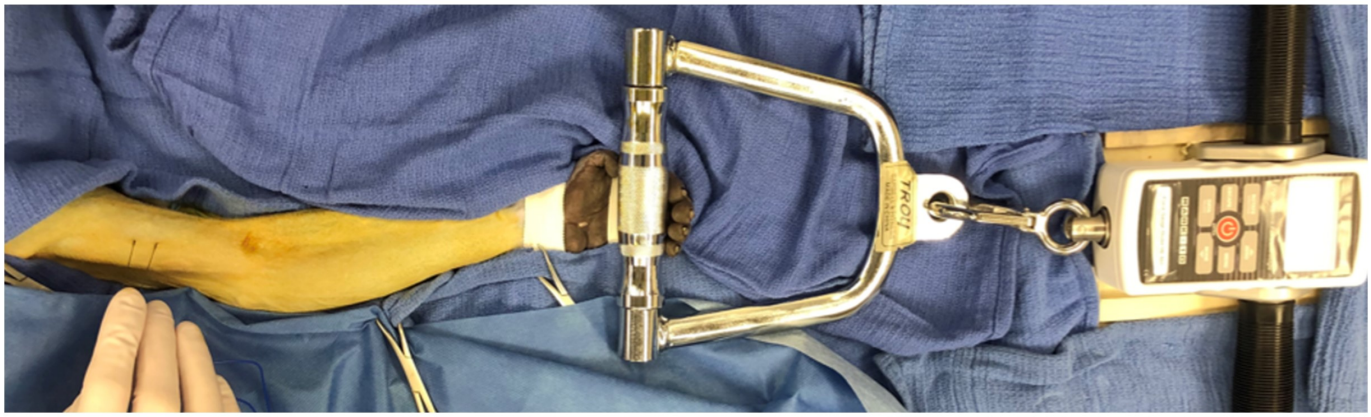
(A)


Experimental (IGF-1 NP, 300 µg/mL)
IGF-1 concentration (ng/mg)
Time (week)

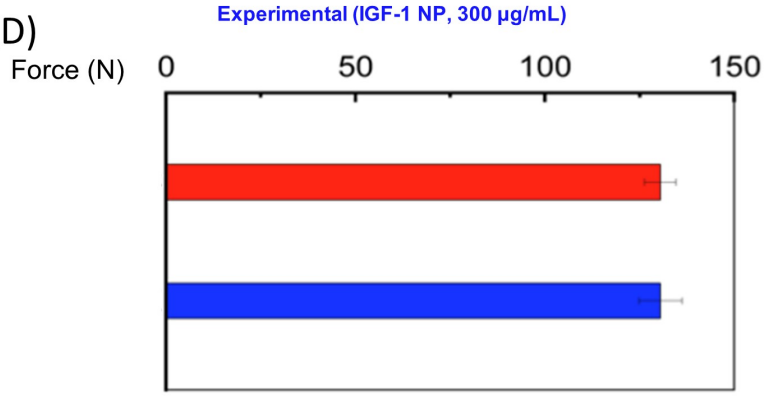
(B)


15
-15
cm/s
Brachial a.
Median n.
Stimulating
1
2

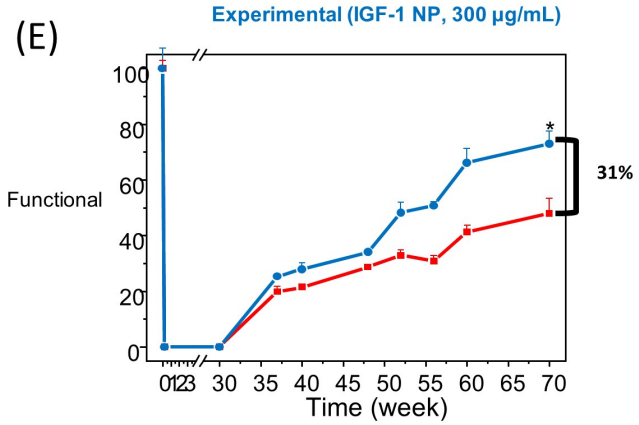
(C)



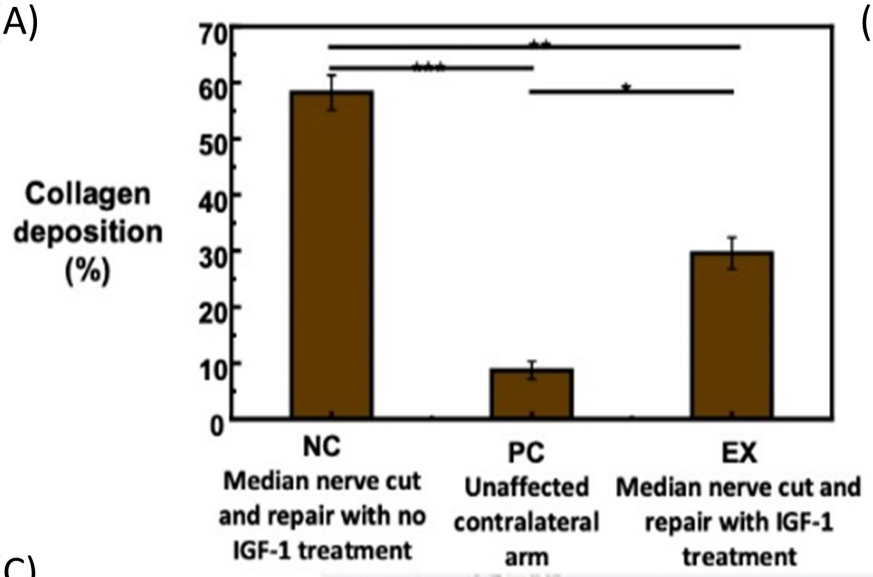
(D)


Experimental (IGF-1 NP, 300 µg/mL)
Force (N)
0
50
100
150

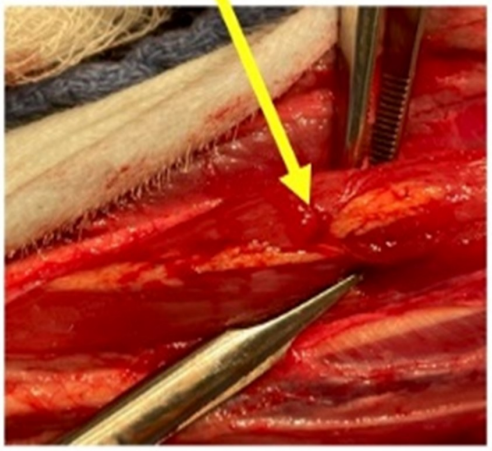
(E)


Experimental (IGF-1 NP, 300 µg/mL)
Functional
31%
Time (week)

(A)



(B) Composite in target muscle: Flexor digitorum superficialis (FDS)



(C)