Clinical Translation of a Keratin Biomaterial Hydrogel for Nerve Repair

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Statement of Purpose: Peripheral nerve injuries requiring surgery occur in approximately 3% of trauma patients. Large peripheral nerve defects can be surgically repaired by autograft (the clinical "gold-standard", although the patient must undergo two surgeries and experience donor site morbidity) or implantation of a nerve guidance conduit. Many investigators have published the general finding that an appropriate conduit filler can modestly improve functional recovery in preclinical models. However, none of these technologies have advanced to pivotal preclinical studies or clinical trials. Human hair keratins (HHK) are the main structural element of hair fibers, and we have developed a conduit filler based on a HHK biomaterial hydrogel and extensively tested it in several preclinical models.

Methods: Human hair was obtained from a commercial vendor and keratin proteins were oxidized, extracted and lyophilized. The lyophilized powder was re-hydrated with sterile PBS to form a 15% weight/volume hydrogel. HHK hydrogel-filled conduits were compared to saline-filled conduits and sural nerve autografts in a mouse 4mm and a rabbit 2cm tibial nerve transection model. After several weeks, the nerves were tested by electrophysiology using a Sierra Wave electrodiagnostic system (Cadwell Laboratories, Kennewick, WA), harvested and analyzed by histomorphometry. In the non-human primate study, 10 cynomolgus macaques underwent unilateral (n=4) or bilateral (n=6) transection and repair of a 1cm median nerve defect with an HHK-filled or saline-filled conduit. Baseline and monthly dexterity measurements are performed with a puzzle feeder designed to evaluate pinch grasp while baseline and monthly electrophysiology measurements are performed with a Sierra Wave electrodiagnostic system. At 12 months, the nerves are tested by electrophysiology, harvested and analyzed by histomorphometry while the thenar eminence hand muscles are harvested, fresh frozen and analyzed for neuromuscular junction (NMJ) density and morphology.

Results: At 6 weeks, the mouse HHK group showed thicker nerve diameters and increased vascularization compared to saline-filled conduit and autograft controls. Electrophysiology results showed that the nerve conduction latency was significantly lower in the HHK group than the saline conduit group ($p<.05$). The compound motor action potential (CMAP) was significantly higher in the HHK group ($p<.05$) over the saline conduit group. At 3 months, the rabbit HHK group showed significantly shorter nerve conduction latency ($p<.01$) than the saline conduit and autograft groups and significantly higher compound motor action potential (CMAP) ($p<.05$) than saline conduits. Preliminary results for the NHP study show an average return of hand function at 32 weeks and an average recovery of the uninjured contralateral nerve conduction velocity of 75.6% at 12 months for the HHK group.

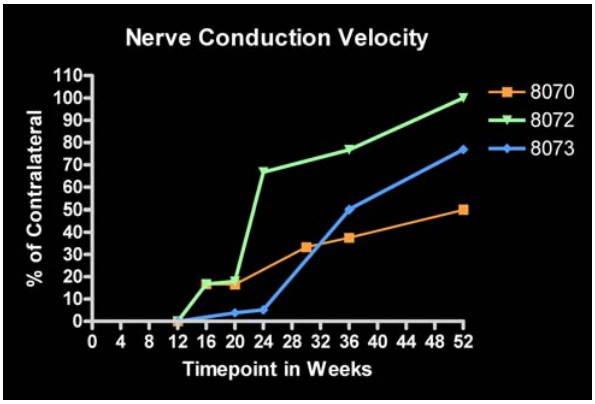

Figure 1. Transdermal and terminal direct stimulation of the median nerve shows return of the fastest motor nerve conduction velocity to the abductor pollicis brevis muscle for the HHK NHP group over 12 months.

Conclusions: Based on these preclinical studies, the first-ever randomized, prospective, blinded human clinical trial of a keratin biomaterial has been approved for peripheral nerve regeneration. The clinical trial will compare the use of saline-filled conduits to those filled with HHK hydrogel in patients with nerve injuries to the lower arm and hand.