An Injectable Nanofiber-Hydrogel Composite with Interfacial Bonding for Soft Tissue Filling and Regeneration

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INTRODUCTION: Restoration of acquired, congenital, or age-related soft tissue defects using autologous or implantable materials can cause donor site morbidity, infection, device failure, and fibrosis. Injectable fillers are limited by variable resorption and fat grafting causes necrosis in large volumes. An alternative approach using the body's regenerative capacity and an injectable synthetic scaffold would allow immediate restoration of form while permitting native tissue regeneration. We developed a novel nanofiber-hydrogel composite using FDA-approved materials with optimal biomechanical properties, porosity, crosslinking density, and interfacial bonding to maintain immediate 3D structure and promote soft tissue regeneration upon subcutaneous injection.

METHODS: Electrospun poly-e-caprolactone (PCL) fibers grafted with poly-acrylic acid (PAA) and surface-modified with maleimide groups were ground using a cryo-milling system to uniformly disperse fibers inside a hyaluronic acid (HA) hydrogel to create the nanofiber-hydrogel composite with interfacial bonding. Liquid composites were set for 8 minutes at room temperature and injected into the inguinal fat pad of male Lewis rats to assess biocompatibility *in vivo*. Composites were explanted *en bloc* in groups of 5 animals at 1-, 2-, 4-, and 12-week intervals. Samples were fixed and stained using H&E and Masson Trichrome.

RESULTS: Composite morphology mimicked extracellular matrix composed of collagen and elastin with high porosity which permitted ASC migration *in vitro* (Figure 1). We hypothesize nanofibers become guides similar to native cytoskeleton to permit cellular migration. Prior to explant, composites demonstrated no evidence of infection or fibrosis, maintained volume, and were incorporated into native fat *in vivo*. Histology after 4 weeks demonstrated minimal inflammatory response without cellular atypia or fibrosis, and tissues demonstrated cellular infiltration, capillary formation, and fat regeneration (Figure 2).

CONCLUSION: We developed an injectable nanofiber-hydrogel composite with high porosity, crosslinking density, and interfacial bonding that promotes cellular migration. Composites maintain 3D volume after injection while predictably degrading to facilitate native tissue ingrowth without a foreign body response or fibrosis. Use of this novel injectable composite allows immediate filling and regeneration of soft tissue defects without the negative sequelae associated with implant-based devices, autologous transfers, or fat grafting.

LEGENDS:

Figure 1: SEM of nanofiber-hydrogel composite. Composite mimics native ECM to maintain 3D volume and promote cellular infiltration.

Figure 2: H&E staining of injectable composite after explant at POD 30. Injectable composite incorporates into native fat reconstituting mature adipocytes.