Three-Dimensionally Printed b-Tri-Calcium Phosphate/Hydroxyapatite Scaffolds for Long Bone Regeneration

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Statement of Purpose: The use of a three-dimensional (3-D) printing technique referred to as direct-write fabrication (DW), with its ability to produce scaffolds that direct the repair of natural bone, may represent an optimal solution for the fabrication of bone repair in the craniofacial, and orthopaedic arenas. The beta-Tri-Calcium Phosphate (b-TCP) / Hydroxyapatite(HA) shell and strut components will provide mechanical strength, conduct bone throughout the scaffold directionally and remodel over time. B-TCP scaffold material was one of the first to be utilized in vivo due to its similar composition to mineral phase native bone. B-TCP scaffolds are strongly osteoinductive, osteoconductive and exert their effects via interaction with a2b1 integrins on osteogenic cells and subsequent downstream activation of MAPK/ERK signaling pathways in these cells. Nonetheless, b-TCP scaffolds have a compressive and tensile strength similar to native cancellous bone and may thus be used without the risk of compressive dissolution of the scaffold. We hypothesize that these scaffolds may successfully regenerate bone over critical sized bone defects in an *in vivo* model.

Methods: The b-TCP/HA scaffolds were designed using ROBOCAD- computer aided design software and fabricated using a 3-D Printing Robocast machine. Scaffolds were sintered at 1100°C for 4 hours. Scaffolds measured at 10 mm long, 4.5 mm outer diameter, 2.25 mm inner diameter and were implanted in New Zealand White Rabbits within a 10 mm full critical size radial defect for 2, 4, 8, 12 and 24 weeks, Figure 1. Micro-CT, nanoindentation and histological analysis were conducted in order to determine the degree of new bone formation and remodeling.

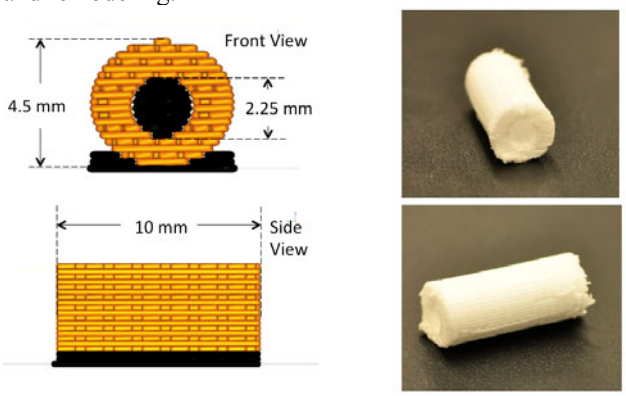

Figure 1. Computer design and fabricated scaffold

MicroCT image reconstruction was conducted using Amira image analysis software. Histological analysis was used to access the immunogenic response, the amount of bone formation and osteoconduction. Nanoindentation was used to quantitatively determine the degree of new bone formation and remodeling.

Results: Grossly, scaffolds were well integrated with no signs of an immunogenic response. MicroCT images show new bone formation and bridging across the scaffold as time progressed from the 2 week (Figure 2) to the 24 week time points (Figure 3). The reconstructed microCT images show more bone formation, remodeling and integration at 24 weeks. Histological analysis showed increased bone formation over time and bone remodeling cells throughout the scaffold. Nanoindentation, quantitatively confirmed bone remodeling as a function of time as well.

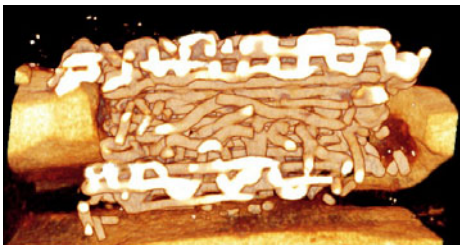

Figure 2. 2 week time point

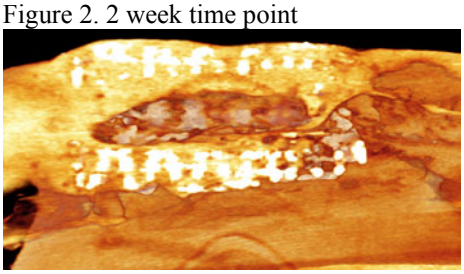

Figure 3. 24 week time point

Conclusions: B-TCP/HA scaffolds are highly biocompatible and can rapidly and successfully regenerate and remodel bone in critically sized long bone defects in a rabbit model. Custom designs (micro and macro-porosity) and fabrications of b-TCP/HA scaffolds may be used in the potential repair of critical sized defects in the long bone. Different ceramic inks can be used to fabricate different regions of the scaffold, depending on anticipated mechanical and remodeling requirements. Also, scaffolds may be filled with different component materials that can be released at different times. For instance, a certain portion of the long bone replacement segment might be filled with a more concentrated bone stimulating growth factor, designed to be release at a later time. Altering the outer cap, strut size and interconnectivity of the scaffold may also offer several potential advantages: continuous supply of nutrients, greater cellular and tissue ingrowth, and enhanced revascularization. Thus, making these scaffolds efficient and customizable for the specific need of the patient. Ideally, eventual translation of this research to humans would eliminate the need for allograft and/or autograft in large bony defects and allow for a customizable 3D scaffold material relative to patient needs.