An *In Situ* Forming, Injectable PLGA Composite for Orthopedic Applications

Paul D. Fisher,[1] Todd A. Milbrandt,[2] J. Zach Hilt,[3] David A. Puleo.[1]
[1]Department of Biomedical Engineering, University of Kentucky, Lexington, KY, USA
[2]Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA
[3]Department of Chemical and Materials Engineering, University of Kentucky, Lexington, KY, USA

Statement of Purpose: *In situ* forming poly(lactic-co-glycolic acid) (PLGA) implants have been thoroughly investigated as drug delivery systems, but their potential as scaffolds is limited due to poor mechanical properties and low porosity.[1,2] Previously, we reported that drug delivery from these systems could be greatly enhanced through the addition of poly(β-amino ester) (PBAE) and hydroxyapatite (HA) microparticles.[3] Here, the effect of hydroxyapatite concentration and size (micro- or nanoparticulate) on the mechanical properties of such a system was investigated. Scaffolds with suitable injectability and similar mechanical properties to trabecular bone were developed. *Ex vivo* injections into intact porcine femoral heads were used to investigate the space-filling and mechanical reinforcement potential of these injectable composites in a trabecular bone network.

Methods: PLGA solutions (30% w/v) were prepared using N-methyl-2-pyrrolidone as the solvent. Various concentrations of PBAE microparticles and HA microparticles (MHA) or nanoparticles (NHA) were mixed into the solution. The mixtures were injected into cylindrical molds and immersed in buffer for 3 days to completely solidify. The effects of increasing HA content, different MHA:NHA ratios, and different PBAE content were quantified by compression. Injectability was quantified by measuring the volumetric flow rate for different of injection forces. An optimal mixture composition was chosen for injection into unfixed femoral heads from young pigs. Fluoroscopy was used to demonstrate the ability to monitor the injections in real-time, and 3-d reconstructions of the femoral heads pre- and post-injection were generated using microCT. Cylindrical samples of bone with and without injections were harvested from the femoral heads, and their compressive properties were compared.

Results: HA significantly increased the compressive modulus and strength of the material at concentrations above 10%, and NHA provided significantly more benefit than MHA ($p<0.05$). The material properties reached a plateau at 30% NHA, beyond which additional HA decreased strength and modulus. Increasing PBAE microparticle concentration did not change compressive properties until 15%, when a significant decrease in modulus occurred ($p<0.05$). SEM imaging of 30% NHA implants revealed NHA embedded throughout a porous PLGA matrix. The addition of HA caused a significant increase in accessible pore volume compared to controls without HA, and increasing HA content resulted in significant increases in material density ($p<0.001$). While increasing either MHA or NHA caused the mean pore size to decrease, NHA caused a larger reduction at equivalent concentrations. *Ex vivo* injections resulted in good space-filling, and the injected material was constrained by the articular cartilage and growth plate. Injected femoral heads possessed significantly higher modulus (180 vs 81 MPa) and strength (5.9 vs 3.5 MPa) ($p<0.01$).

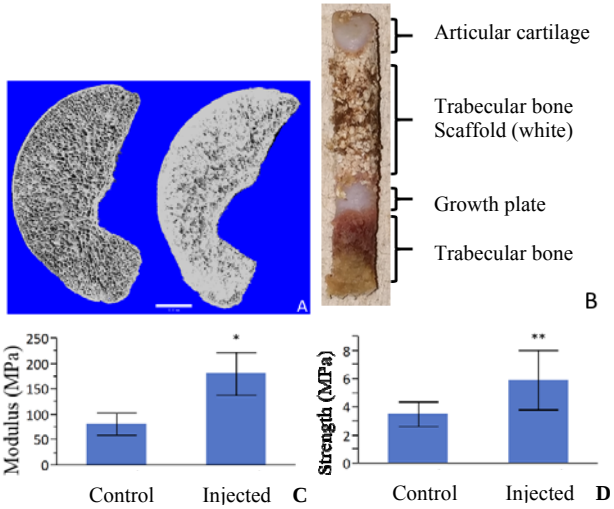

Figure 1. *Ex vivo* injections. A) Femoral head prior to injection (left) and post-injection (right) (1 mm scale bar). B) Scaffold is constrained within the targeted bone tissue. Injections increased both modulus (C) and strength (D).

Conclusions: The addition of HA enables *in situ* forming PLGA implants to be used in a variety of orthopedic applications because the mechanical properties can be adjusted simply by varying the HA concentration and particle size. These composite scaffolds have a more homogeneous pore structure, and the high accessibility of these pores allows a greater surface area for potential cell access and tissue contact. The addition of HA also allows these materials to be visualized during injection via fluoroscopy to ensure the target site is receiving the treatment, and the material rapidly solidifies and is effectively retained within the target tissue. Once solidified, the implanted material improves the mechanical properties of bone to prevent collapse of damaged or diseased tissue, and the material degrades over the course of 6 weeks, which is an appropriate period to allow drug release and bone repair.

References:

1. Parent M. J Contr Rel. 2013;172:292-304
2. Schloegl W. E J Pharm and Biopharm. 2012;82:554-562
3. Fisher, P. J Biomater Sci Polym Ed. 2014;25:1174-93