Bone Healing Is Unaffected by PNDJ at the Implant Inferface

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Statement of Purpose: Biofilms are resistant to many antimicrobials, with MIC 100 to 1000-fold greater concentrations than those required to kill the same organism in a planktonic state.

Treatment of PJI requires thorough removal of diseased tissues (debridement) and is augmented by local administration of antimicrobials.

Hydrogels based on the temperature-responsive polymer PNDJ (poly(*N*-isopropylacrylamide-*co*-dimethyl-γ-butyrolactone acrylate-*co*-Jeffamine® M-1000) hydrogels are in situ gelling, allowing for complete implant coverage. They provide tunable, partition-controlled release of hydrophilic antimicrobials and re-dissolve completely via hydrolysis with minimal generation of acid groups. This study is intended to evaluate if the presence of these gels will inhibit the healing response at the bone/implant interface.

Methods: Two different batches of PNDJ copolymer (PNDJ15- 1.5 % Jeffamine, PNDJ22 -2.2 % Jeffamine) were synthesized by free radical polymerization. Hydrogel was mixed at 30 wt% in PBS with either 50 mg/mL (H) or 5 mg/mL (L) gentamicin sulfate. Bone healing was studied in a trans-cortical press-fit bone healing model in Female New Zealand White Rabbits[1]. A drill bit was used to make a 3.5 mm wide, 8 mm deep defect on the lateral side of the femur and tibia bilaterally in the hind legs. Hydrogels were delivered using a 1 cc syringe fitted with an 18G needle. Hydrogels were injected, pressed into the defect using the thumb, defects were filled again prior to implant insertion to further drive the gel into interstices in the nearby bone. Prior to insertion of the Ti-6Al-4V implant, the implant was also dip-coated in gel to ensure complete surface coverage of the implant. A total volume of about 300 µL was used in each gel site. The coated implant was driven into the defect with a dowel attached to a hand chuck until the top (4.7 mm diameter face) of the implant was flush with the bone surface. Animals were allowed to survive for 8 weeks, at which point they were sacrificed. The tibia and femur were collected, fixed with 10% formalin, and sent for hard tissue histology processing.

Results: PNDJ22 hydrogel has an *in vitro* degradation time of 28 days and PNDJ15 has an *in vitro* degradation time of 56 days at 37°C in PBS[2].

Bone healing was visible primarily between the teeth of the implants. The quality of bone healing at the implant interface for all formulations is generally indistinguishable from that of PBS controls at 8 weeks post-surgery (Figure 1). Cortical bone was observed to heal around the implants in the femur, whereas primarily cancellous bone was observed around the implants in the tibia.

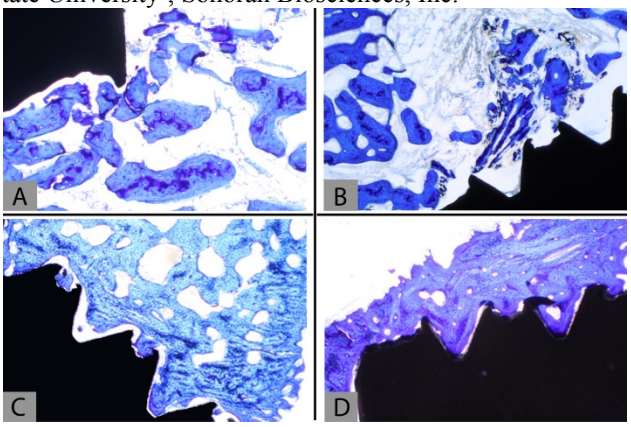

Figure 1: Results of Bone Healing Study. A and B show sections stained with toluidine blue collected from specimen immediately after insertion. C shows a section from an implant coated with PBS. D shows an implant coated with PNDJ15H at 8 weeks.

Conclusions: The results of this study indicate that neither PNDJ degradation time nor gentamicin dose affected bone ingrowth and healing rate for the materials tested. There was concern that the high viscosity of the material or acidity/toxicity produced by high concentrations of gentamicin sulfate might prevent normal bone healing to Ti-6Al-4V surfaces under compression

We observed *in vitro* degradation times of 4 and 8 weeks for the PNDJ hydrogel formulations used *in vitro*. These times are likely shorter in vivo because of the effects of proteins on polymer LCST, termed “salting out”. These degradation rates appear to be adequately rapid to not inhibit bone ingrowth in this model. Ingrowth in an animal model will tend to over-estimate ingrowth in a human subject, and the implants tested in this experiment, while creating compressive force to spur bone healing, are minimally load bearing, and not placed to prevent instability. Despite these limitations, the results are encouraging that an in situ gelling, viscous, anti-infective gel will be able to be successfully resorbed without inhibiting the normal healing of the surrounding bone.

References:

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