Adhesive Antimicrobial Wraps to Treat Infection and Improve Bone Regeneration

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Statement of Purpose: Every year, millions of patients require bone grafting procedures to treat large defects. Current grafting treatments include structural allografts or synthetic grafts when autografts are not available. However, these treatments are limited by post-operative infections which often result in revision surgeries. In this work, we are developing an adhesive, antimicrobial wrap that will serve as an adjunct treatment for bone grafts to prevent bacterial infections and enhance regeneration. We have previously developed a multifactor release system using bimodal crosslinking of electrospun gelatin for delivery of VEGF and SDF-1 with independent release kinetics. In this study, poly(lactide-co-glycolide) (PLGA) is added through co-spinning to deliver gallium maltolate (GaM), a broad spectrum antimicrobial agent, and to provide mechanical reinforcement for the wrap. The bactericidal activity of GaM and release kinetics were determined. Finally, adhesion of the wrap to the bone graft is expected to enhance local dispersion of the factors and prevent displacement during regeneration. To this end, the co-spun mesh was modified with dopamine to promote adhesion to the graft surface.

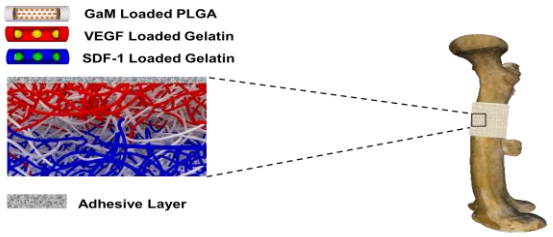

Figure 1: Schematic of adhesive, antimicrobial wrap.

Materials and Methods: Fabrication of the adhesive layer was achieved by in-line blending gelatin with a hexamethylene diisocyanate (HDI) crosslinker and dopamine during electrospinning. This reactive crosslinking mechanism facilitated both crosslinking of the gelatin and conjugation of the dopamine. The dopamine was oxidized to yield reactive functional groups that would enable adhesion to the graft. The dual release systems were fabricated by co-electrospinning acid-terminated PLGA (50:50) blended with GaM, reactive crosslinked gelatin blended with VEGF, and photo-crosslinked gelatin methacrylate blended with SDF-1 directly atop the adhesive layer to yield a single multifunctional wrap. The minimal inhibitory concentrations (MICs) of GaM for the planktonic and biofilm forms of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (*S. aureus*) were investigated via macrodilution method where the inoculum suspensions were tested with various GaM concentrations for 24 hours. Absorption values were read at an optical density of 625 nm to determine the MIC required to inhibit 90% of the isolates. Additionally, release kinetics were evaluated and expected to result in the determined GaM MIC being released between 24 to 48 hours. Furthermore, adhesion strength was investigated using ASTM F2255-05 lap shear analysis for tissue adhesives.

Results: The MIC of GaM for planktonic MRSA and *S. aureus* was determined to be 1 mg/mL and 2 mg/mL, respectively (Figure 2A). As expected, the release of GaM from electrospun fiber meshes demonstrated an initial burst release of 13 ± 6% within 3 hours followed by sustained release of 91 ± 2% over a 10 day period. The sustained GaM release over this period was attributed to the rapid degradation of the acid-terminated PLGA due to autocatalysis. After 48 hours, a total release of 1 mg of GaM was achieved which corroborates the potential to release the GaM MIC for MRSA (Figure 2B).

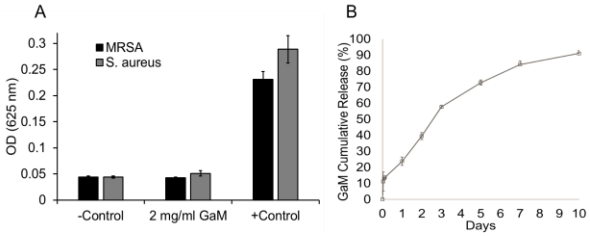

Figure 2. A) MIC for GaM B) GaM cumulative release from electrospun PLGA.

Initial lap shear analysis indicated marked tissue adhesion after dopamine coating with tissue adhesive strength that increasing with dopamine concentration from 4.2 ± 0.9 kPa to 12.8 ± 0.1 kPa, respectively.

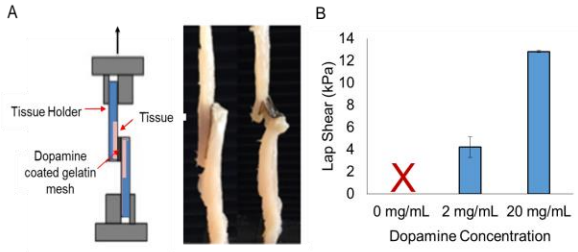

Figure 3. A) schematic of lap shear analysis **B**) effect of dopamine concentration on adhesion strength.

Conclusion: Overall, this system demonstrates strong promise as an adhesive antimicrobial mesh. Future studies will evaluate the combination of bactericidal activity with co-delivery of growth factors using standard cell assays. In addition, we will investigate the efficacy of this wrap in an in vivo infected wound model. This research highlights a potential platform to provide infection prevention and improve regeneration in a variety of open-fracture grafting treatments.