

## **Modifying Antibiotics to Provide Biofilm Penetration in the Treatment and Prevention of Endoprosthetic Biofilms**

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**Introduction:** Antibiotics used in orthopaedic bone cement, poly-methyl-methacrylate (PMMA) are often ineffective against biofilm formation and propagation because they rely upon bacterial growth to exert their mechanism of action. Bacterial biofilm is made up of less active, “persister” bacterial cells that have the ability to avoid penetration by antibiotics in their senescent state. Recently, our team modified tobramycin with a short transporter sequence optimized for bacterial membranes. Consequently this conjugate is able to cross membranes of persister bacteria with down-regulated intake mechanisms, dramatically increasing the drug’s potency against slow-growing, antibiotic-tolerant bacteria (i.e. biofilm).

**Question/Purpose:** Evaluate the efficacy of tobramycin modified to target bacterial biofilms (Pentobra) as compared to commercially available tobramycin when delivered by PMMA using an established mouse model of implant infection.

**Methods:** Survival surgery was performed in which circular orthopedic-grade titanium disks were implant subcutaneously on the backs of 25 lysEGFP mice. These disks were coated in poly-methyl-methacrylate (PMMA) cement mixed with either Pentobra, tobramycin, or no antibiotic (control). The disks were inoculated with  $1 \times 10^7$  colony-forming units (CFU) of bioluminescent *S. aureus*. Bacterial burden and neutrophil inflammation was followed via bioluminescent and fluorescent imaging, respectively on post-operative days (POD) 0, 1, 3, and 5. Implants and surrounding tissue were subsequently removed and cultured. Statistics were performed via ANOVA analysis.

**Results:** Implants containing Pentobra and tobramycin showed significantly lower bacterial bioluminescent signal when compared to the control group throughout the 5 day experiment ( $p < 0.05$ ). Moreover, Pentobra had significantly lower bioluminescence than tobramycin throughout the same period ( $p < 0.05$ ). Pentobra neutrophil fluorescence was significantly lower than tobramycin and the control on all days ( $p < 0.05$ ). Both Pentobra and tobramycin demonstrated significantly lower implant and tissue CFU counts compared to the control ( $p < 0.05$ ).

**Conclusions:** Pentobra demonstrates superior efficacy over tobramycin *in vivo* in decreasing bacterial burden after implant infection. The use of Pentobra in orthopaedic procedures should be further investigated.

