A Strongly Adherent, Biocompatible, Efficacious Bisbiguanide Containing Coating for Orthopedic Implants

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Statement of Purpose:

Implant-associated infections remain the single largest complication in orthopedic medicine. [1] For certain high risk procedures, infection rates can exceed fifty percent creating a large health and economic burden. Additionally, current clinical practices for treating orthopedic implant infections have limited utility and often require removing the infected implant.

While medical devices coatings have garnered praise for reducing clinical infection rates, a coating that features all of the qualities needed for clinical success for orthopedic implants remains elusive. [2] Herein we present preclinical results for a novel bisbiguanide-containing coating for orthopedic implants including the *in vivo* activity of the coating in a rat polymicrobial infection model.

Methods:

The bisbiguanide-containing coating is applied to various orthopedic implants using a proprietary process developed by Bacterin International Inc. (Belgrade, MT).

Multiple *in vitro* assays were performed to assess the performance of the bisbiguanide-containing coating. The adhesive strength of the coating was demonstrated by drilling coated K-wires through porcine tibias and fibulas using standard operating room techniques. Elution of the bisbiguanide agent from the coating was measured for ten weeks in PBS at 37 °C using UV-Vis spectrophotometry. Coated pins were tested for *in vitro* efficacy using an established pin track infection model for 21 days against *S. aureus*, *S. epidermidis*, *E. faecalis*, *E. coli*, *P. aeruginosa*, *K. pneumonia*, and *A. baumannii*. [3] Repeat zones of inhibition (ZOI) were monitored by transferring coated implants from plate to plate for 21 days against *S. aureus*. Finally, a full suite of biocompatibility testing was performed on the coating according to ISO 10993.

The *in vivo* activity of the coating was demonstrated through a polymicrobial infection model. Briefly, coated and control devices were implanted into the dorsal midline region distal to the skull of adult Sprague-Dawley rats. The implants were inoculated with a polymicrobial suspension of *S. aureus*, *E. coli*, and *P. aeruginosa* and surgically closed. Following incubation, the implants and a biopsy of soft tissue surrounding the implants were processed for quantification of adherent colony forming units (CFUs).

Results:

The bisbiguanide-containing coating was shown to be remarkably adhesive with only minimal quantities (less than 5%) becoming dislodged upon drilling coated K-wires through two cortical layers of porcine bones. Additionally, the coating proved to have exceptional sustained release of the bisbiguanide agent. Quantities above pathogenic minimal inhibitory concentrations were seen out to at least 10 weeks (**Figure 1**).

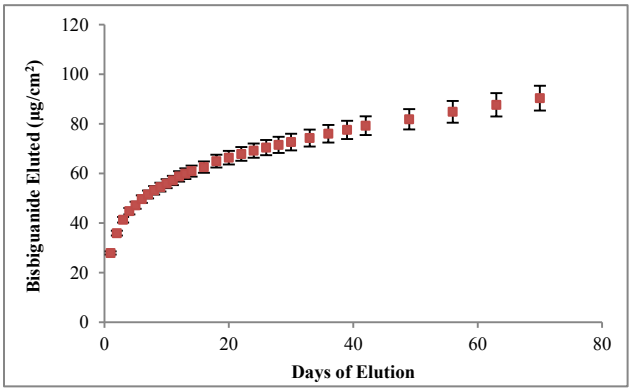

Figure 1: Elution of the bisbiguanide agent.

Coated devices possessed very promising *in vitro* activity by reducing adherent CFUs in the pin track infection model of all pathogens examined by at least 4 logs compared to untreated controls. Additionally, the coating continued to produce sizeable zones in the repeat ZOI experiment for at least 21 days.

The coating produced non-toxic results in the full suite of biocompatibility testing as outlined in ISO 10993 including a 13-week implantation, full systemic toxicity study in rabbits.

Finally, the *in vivo* activity of the coating was demonstrated in a polymicrobial infection model of *S. aureus*, *E. coli*, and *P. aeruginosa*. The coating successfully reduced adherent CFUs on the implanted devices by 2.5 logs compared to untreated controls.

Conclusions:

As device-related infections continue to present serious complications in orthopedic medicine, we sought to develop a coating that could maintain all of the qualities needed to potentially be clinically successful. This novel coating proved to be strongly adherent, biocompatible, and efficacious in reducing adherent CFUs in several different *in vitro* assays and an *in vivo* model of device contamination. While the *in vitro* and *in vivo* efficacy of this novel coating is clearly demonstrated herein, the clinical efficacy of this treatment strategy has not been established and future work is needed to relate these studies to human clinical data.

References:

[1] Trampuz A. *Curr Opin Infect Dis*. **2006**, 19, 349-356.

[2] Darouiche RO. *Int J Artif Organs*. **2007**, 30, 820-827.

[3] Gaonkar TA. *J Antimicrob Chemother*. **2003**, 52, 389-396.