Surface Treatments for Orthopaedic Implants which Prevent Bacteria Growth and Support Cell Proliferation

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Statement of Purpose: Through improvements in surgical techniques, infection rates of orthopaedic implants have come down to around 2%. However, re-infection rates can be as high as 30% with debilitating complications. This situation is amplified with combat injuries, where improvised explosive devices (IEDs), high-energy projectiles and shrapnel create contaminated extremity wounds with infection rates as high as 40-50%. The goals of orthopedic trauma injury management are to prevent infection, promote fracture healing, and restore function. Titanium and stainless steel implants have been the standard for fracture fixation. These materials offer good biocompatibility, but do not actively resist infection. There is resistance among the medical device community to incorporate long-last antibiotics into implants, for fear of encouraging the development of drug resistant strains. On top of this, antimicrobial agents are known to generally inhibit cell proliferation at therapeutic doses. Because of this, it is standard to forgo ISO cytotoxicity testing of antimicrobial materials. The next generation of orthopaedic implants will use economical surface treatments which can demonstrate the ability to prevent bacteria growth, while supporting the proliferation of healthy human cells. Here we answer the question, whether thin films of hybridized mixed metal oxides can be used to create such a surface treatment.

Methods: A BioIntraface™ Patent Pending wet chemistry approach was used to synthesize siloxane containing thin films of hybridized titanium and noble metal oxides, directly on the bottom of cell culture microplates. The dip coating method was optimized to provide uniformed coverage of trauma fracture fixation devices. These were rapidly screened for the bioresponses of soft tissue and hard tissue cell bioresponses (fibroblasts and osteoblasts) and bacterial growth (1) Cell culture polystyrene (PS) was used as a positive control and silver oxide as a negative control. *Human cell growth*: Cell proliferation on surface treatments was measured using standard colorimetric WST-1 (Roche) and fluorescent calcein AM assays. *Cell attachment and adhesion*: Cell seeding efficiency (attachment) and adhesion after centrifugation were measured using calcein AM as a label, as previously described (1). *Bacterial adhesion and growth:* To determine the antimicrobial properties, coated microplates where inoculated with bacteria (*Staph. aureus, E. coli*), incubated and washed with PBS to remove non-adherent cells. The wells were refilled with medium and the growth monitored by the change in optical density (OD). Third-party ISO 10993 cytotoxicity and ASTM E2180 antimicrobial testing performed at NAMSA, Inc., allows for comparison of these lab results to Industry standards.

Results: Noble metal doping influenced cell proliferation to hybrids in a bi-phasic manner. Once a threshold was met, cell proliferation dropped off steeply with increased doping for both cell types (Fig 1 top, middle). Bacteria were more sensitive to doping concentrations than the normal human cell types tested (Fig 1 bottom). This is contrary to results obtained with similarly doped sol-gel derived titanium oxide coatings, where doping arrested human cell proliferation at lower concentration that those required to stop bacteria growth (2). Initial additions of metal oxides to siloxane caused a rapid increase in human cell adhesion, which leveled off rapidly.

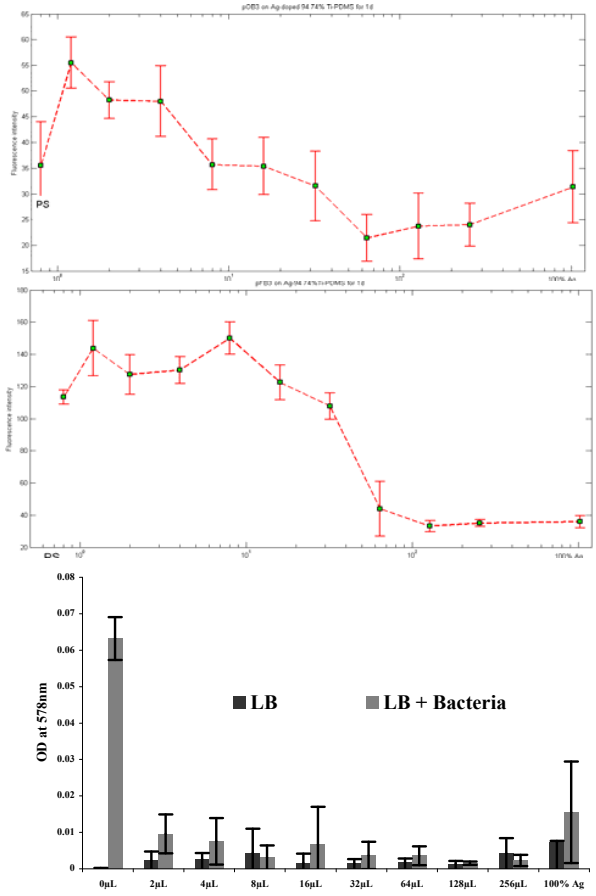

Fig 1. Growth of osteoblasts (top), fibroblasts (middle) and Gram negative bacterial (bottom) on hybrid coatings as a function of noble metal oxide doping.

Conclusions: Several thin film surface treatment compositions were identified which prevented bacterial growth, while supporting normal human cell proliferation. Comparing these results with ISO 10993 cytotoxicity testing and ASTM E2810 bacterial testing allows for the selection of surface treatments suitable for the creation of the next generation of commercial orthopaedic devices.

References: (1) Jarrell JD. J Biomed Mater Res A, 2010;92A:1094-1104. (2) Jarrell JD. ProQuest Dissertations and Theses, Brown Un, 2008 140-174.