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Targeted Osteomyelitis Management Using Metallic Nanoparticles

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Extended Abstract

Osteomyelitis is a serious bone infection which can be caused by the bacteria *Staphylococcus aureus*. The bacteria can survive inside osteoblast cells and overcome the effect of the immune system as well as various antibiotics. Silver-Copper-Boron (AgCuB) nanoparticles were found to be effective against *S. aureus* in both *in vitro* and *in vivo* studies. For accurate therapy, targeting the site of infection is essential. In this study, for targeted bone therapy, AgCuB nanoparticles are coated with bone targeting antibodies (Anti-OB-Cadherin antibody that are specific to osteoblast cells) or bone targeting molecules or anti-*S. aureus* antibodies to increase the action of the antimicrobial nanoparticles specifically in the bone tissue and is evaluated by *in vitro* studies and using *in vivo* mice model.

Staphylococcus aureus is one of the primary causes of bone infection and its persistence in osteoblast cells leads to relapse and acute osteomyelitis [1]. *S. aureus* survives inside mammalian cells and remains protected from the immune system. Due to the sheltered environment, such acute or chronic infection is difficult to manage [2]. Moreover, this intracellular bacterial reservoir remains protected from a wide range of antibiotics including vancomycin [3]. Earlier we have shown the antimicrobial activity of Silver-Copper-Boron (AgCuB) nanoparticles and also that an AgCuB dose of 1 mg/kg body weight is safe in mice [4]. Also, we have shown that AgCuB nanoparticles reduced more than 99% reduction of infection when an AgCuB dose of 1 mg/kg body weight was introduced intravenously in *in vivo* mice model [5]. In this study, we aimed to evaluate the targeted antimicrobial activity at the intracellular level in both *in vitro* and *in vivo* models. Here, bone targeting or antibody coated AgCuB antimicrobial nanoparticles were evaluated for their activity in intracellular infection, employing an *in vitro* osteoblast infection model as well as an *in vivo* osteomyelitis mice model. Our *in vitro* osteoblast infection model showed that 1 µg/ml concentration of nascent AgCuB nanoparticles reduced more than 90% infection within 24 hours of treatment.

AgCuB nanoparticles were synthesized by green chemistry and were characterized by scanning electron microscopy. Furthermore, AgCuB nanoparticles were conjugated with Anti-OB-Cadherin antibodies or anti-*S. aureus* antibodies labeled with an AF-594 fluorophore for osteoblast cell targeting or *S. aureus* targeting respectively. Osteoblast cells targeted with AgCuB-Anti-OB-Cadherin (NP-AntiCad) were evaluated for membrane binding by optical fluorescent microscopy. To measure the antimicrobial activity of NP-AntiCad, *S. aureus* cultures were grown in osteoblast cell culture media with varying concentrations of NP-AntiCad and were incubated for different time periods. Optical density was measured to check the inhibition of *S. aureus*. To measure the antimicrobial activity of NP-AntiCad against internalized *S. aureus* infection, Osteoblast cells were co-cultured with *S. aureus* and then Gentamicin was used to clean the extracellular infection. Co-cultured cells were added with NP-AntiCad and incubated for 24 hours or 48 hours. After incubation cells were washed and harvested by trypsinization and lysed with Triton-X100. The lysate was serially diluted and plated on TS agar plate, incubated overnight and the following day CFU's were enumerated. The *in vitro* studies showed that targeted AgCuB nanoparticles could be an effective treatment strategy for osteomyelitis and lead to targeted *in vivo* studies.

AgCuB nanoparticles can be used as an alternative for treating osteomyelitis. Targeting the site of infection by using AgCuB nanoparticles that are linked to bone targeting agents or specific antibodies could help to lower the dose of nanoparticles used and also to accurately target the site of infection. This unique bactericidal nanoparticle may bring new hope to clinical therapies. More studies have to be conducted to accurately target the site of bone infection.

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