**IDR-1018: An Immunodulatory Host Defense Peptide that Decreases Bacterial Burden and Preserves Osseointegration in a Murine Model of Orthopaedic Implant Infection**


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**Introduction:** Orthopaedic implant infection is becoming more difficult to treat in both the military and civilian settings due to the increased prevalence of multiple drug resistant bacteria. IDR-1018 is a 12 amino acid, synthetic host defense peptide that reduces soft tissue infections [1]. IDR-1018 is less likely to induce resistance than antibiotics because, rather than directly killing bacteria, it primarily acts as an immunomodulator that regulates chemokine production and thereby recruits and activates host immune cells [2]. The purpose of the current study was to characterize the immunomodulatory effect of IDR-1018 on macrophages (MØs) and to determine whether IDR-1018 decreases orthopaedic implant infection in a previously described murine model [3].

**Methods:** Effects on MØs: The effect of IDR-1018 (7-700 ug/ml) on secretion of the chemokine MCP-1 and pro-inflammatory cytokines TNF-α and IL-6 by RAW264.7 MØs in the absence or presence of ultrapure LPS (100 pg/ml-10 ug/ml) was measured by ELISA. Effects on murine model of implant infection: Bioluminescent Staphylococcus aureus (Xen36 strain, Caliper Life Sciences) were adhered to titanium alloy implants (1 mm diameter, 3.2 mm length) before insertion into pilot holes in the mid-diaphysis of the femur of 6-8 week old mice [2]. IDR-1018 (200ug/injection) was administrated i.p. 4 hours before and 24 and 48 hours after implant insertion. Bacterial burden was measured longitudinally by bioluminescence imaging. Mice were euthanized at 14 days post operation and the effect of IDR-1018 on osseointegration was quantified by biomechanical pullout-testing.

**Results:** Effects on MØs: IDR-1018, in the absence of other stimuli, induces production of the chemokine MCP-1 and pro-inflammatory cytokines TNF-α and IL-6 by RAW264.7 MØs in the absence or presence of ultrapure LPS (100 pg/ml-10 ug/ml) was measured by ELISA. Effects on murine model of implant infection: Bioluminescent Staphylococcus aureus (Xen36 strain, Caliper Life Sciences) were adhered to titanium alloy implants (1 mm diameter, 3.2 mm length) before insertion into pilot holes in the mid-diaphysis of the femur of 6-8 week old mice [2]. IDR-1018 (200ug/injection) was administrated i.p. 4 hours before and 24 and 48 hours after implant insertion. Bacterial burden was measured longitudinally by bioluminescence imaging. Mice were euthanized at 14 days post operation and the effect of IDR-1018 on osseointegration was quantified by biomechanical pullout-testing.

**Discussion:** We demonstrated that IDR-1018 is a novel anti-bacterial treatment that can improve osseointegration of infected orthopaedic implants by recruiting macrophages and blunting excessive
production of pro-inflammatory cytokines and chemokines. Future studies are needed to assess the translational relevance of IDR-1018. For example, IDR-1018 may be more effective in combination with antibiotics, the most likely clinical application.

Significance: This study demonstrated the potential of IDR-1018 to decrease implant infection in a different manner from conventional antibiotic and thereby prevent impaired osseointegration.

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