

## **An In Vivo Model of Continuous Infusion of Ultra High Molecular Weight Polyethylene Particles**

+\*Ma, T; McCally, R E; Ortiz, GS; Huang, Z; Ren, P; Smith, R L; Goodman, S B

+\*Stanford University, Stanford, CA

Ultra high molecular weight polyethylene (UHMWPE) wear particles from orthopaedic implants affect both initial osseointegration and subsequent bone remodeling around total joint replacement (TJR) implants. Continuous wear and exposure to particles adversely affects bone formation and resorption, resulting in periprosthetic osteolysis. Current animal models of particle-induced periprosthetic osteolysis either are not well representative of the clinical scenario or involve more advanced species. The aim of this study was to develop and validate a murine model which would better mimic the clinical scenario in humans through continuous particle infusion in an intramedullary environment. UHMWPE particles were isolated from serum collected from *in vitro* hip joint simulation tests (Hospital for Special Surgery, New York) and determined to be endotoxin free. A total of approximately  $5 \times 10^{10}$  particles were suspended in a carrier of normal mouse serum and loaded into a pump (0.25 $\mu$ l/hour delivery rate, Durect, Cupertino, CA) for infusion. Animals were randomly assigned to one of two groups. One group of animals (N=13) received surgical implantation of a rod and infusion of carrier solution in the right femur, while the left femur was not operated upon. The other group of animals (N=10) received bilateral femoral implants. In this group, particles in serum were continuously infused into the right femur, while the left femur did not receive infusion. Surgically, the medullary cavity was accessed using a 23-gauge needle used to manually drill through the intercondylar notch. A 23-gauge, 6-mm long rod was press fit into the distal femur, and, when indicated, the rod was connected to an Alzet pump via polyvinyl tubing. Subsequently, the pump was implanted subcutaneously between the scapulae, the quadriceps-patellar complex was repositioned, and the medial quadriceps arthrotomy and dorsal incision for the pump were repaired with 5.0 Vicryl sutures. Animals were euthanized in a CO<sub>2</sub> chamber 4 weeks after surgery and femurs were harvested. Once femurs were collected, microCT imaging was performed on the distal 2/5 of the femur at 10 micron sections. Cross-sectional images were contoured to assess total volume (TV) and a threshold was applied to determine the bone volume (BV). Bone density was calculated (BV/TV) and used for statistical analysis. Paraffin embedded sections of the femurs were stained for Alkaline Phosphatase (ALP) using a monoclonal antibody. Image Pro software was used to determine total tissue section area and total positive staining area. The percent of positive staining area was used for statistical analysis. A paired t-test was performed to compare the left femur with the right femur within each animal group. For the group of animals that received surgery and carrier infusion in one femur and had no surgery on the contralateral femur, the bone density of the distal 2/5 of the femur did not differ. In contrast, UHMWPE particle infusion showed significantly reduced bone density compared to contralateral femurs with implantation alone. Alkaline Phosphatase comparisons showed decreased ALP in non-surgery femurs compared to femurs that received serum infusion ( $p = 0.04$ ). UHMWPE particle infusion showed the same level of ALP expression as the contralateral femur in which only the rod was implanted.