RANKL INHIBITION DECREASES FEMORAL HEAD DEFORMITY FOLLOWING ISCHEMIC OSTEONECROSIS OF THE CAPITAL FEMORAL EPIPHYSIS

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INTRODUCTION
Legg-Calvé-Perthes disease (LCPD), a juvenile form of femoral head osteonecrosis, remains one of the most common pediatric hip disorders that can result in permanent deformity and premature osteoarthritis. Ischemic necrosis is the key pathogenic process involved in LCPD. In these patients, predominant bone resorption in the early stage of repair produces a fragmented appearance and a collapse of the femoral head. It is hypothesized that the inhibition of osteoclastic bone resorption during the early stage of repair will prevent the development of femoral head deformity. Receptor activator of NF-κκ (RANKL) has been elucidated as a soluble decoy receptor for RANKL that inhibits osteoclastogenesis and subsequent bone resorption. The therapeutic potential of RANKL inhibitors to inhibit bone resorption and prevent femoral head deformity following ischemic osteonecrosis has not been investigated. We hypothesize that inhibiting RANKL will prevent pathologic bone resorption and preserve the structural integrity of the femoral head following ischemic necrosis. The purpose of this study was to investigate the effectiveness of RANKL inhibition in the prevention of femoral head deformity in a large animal model of LCPD.

METHODS
The animal protocol was approved by the local IACUC. A piglet model of ischemic necrosis was used. Ischemic osteonecrosis was surgically induced in the right femoral head of 10 animals. Two weeks following the induction of ischemia (early repair stage), OPG-Fc or saline were administered subcutaneously (5 animals per group) twice per week for 6 weeks using an incremental dosing regimen. The left femoral head of animals that received saline served as normal controls. The animals were euthanized 8 weeks after the induction of ischemia. Histomorphometric assessment revealed significantly greater preservation of epiphyseal bone volume in the animals treated with OPG. The mean BV/TV in the OPG group was 16.5 ± 2.1 compared to 1.3 ± 2.6 in the saline group (**p<0.0001). The mean BV/TV of normal femoral heads was 19.2 ± 2.4 (Fig. 3). No significant difference was observed between the OPG and normal control groups. In the animals that received saline, the trabecular bone was almost entirely replaced by fibrovascular tissue. The mean area occupied by the fibrovascular tissue where all trabecular bone had been resorbed was significantly greater in the saline group compared to the OPG group (**p<0.001). Furthermore, a significantly greater number of osteoclasts were observed in the animals that received saline. In the saline group, the mean osteoclast number/mm² was 35.6 ± 6.7 compared to 1.8 ± 2.2 in the OPG group (**p<0.0001). The mean osteoclast number/mm² in the normal femoral heads was 13.0 ± 3.3 (Fig. 4).

RESULTS
In all OPG treated animals, a radiodense band was present below the growth plate, indicating suppression of bone resorption due to RANKL inhibition. In addition, serial serum NTx levels were markedly reduced following the initiation of OPG treatment at all time points (Fig. 1: *p<0.01 at 1 and 6wks). Western blot analysis of bone from the distal femoral condyle showed an increase in OPG and a decrease in RANKL in the OPG group compared to saline group (data not shown). Radiographic assessment showed significantly greater preservation of ischemic femoral heads in the OPG group compared to the saline group. The mean epiphyseal quotient of the OPG group was 0.39 ± 0.05 compared to 0.24 ± 0.06 in the saline group (**p=0.005). The mean epiphyseal quotient of the normal femoral heads was 0.46 ± 0.03. No significant difference was observed between the OPG and normal control groups (Fig 2).

DISCUSSION
To our knowledge, this is the first study to examine the therapeutic role of RANKL inhibition for the prevention of femoral head deformity following ischemic osteonecrosis. This study is the first to show that RANKL inhibition favorably alters the early stage of repair following ischemic necrosis. Our findings demonstrate that RANKL inhibition in the piglet model decreases pathologic bone resorption and preserves femoral head structure. RANKL inhibitors may therefore represent a novel and promising therapeutic approach to prevent bone resorption and thereby preserve the structural integrity of the infarcted femoral head.

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