Introduction
Sclerostin (Scl) is a negative regulator of osteoblast differentiation and bone formation. The current favored mechanism is via direct antagonism of the Wnt/β-catenin pathway. The expression pattern of this protein is thought to be highly restricted to osteocytes, localizing its effects to skeletal tissue. This high specificity and potent antagonism of bone formation has made sclerostin a recent target for treatment of skeletal conditions. It has been reported that a sclerostin antibody (Scl-Ab) acted as a bone anabolic agent and restored bone mass in the established osteopenic, ovariectomized (OVX) rat model. Further, Scl-Ab has been reported to enhance fracture healing in mouse and rat models. As most osteoporotic fractures are metaphyseal, we sought to examine the effect of Scl-Ab on bone repair in OVX rats using a tibial defect repair model.

Hypothesis
Scl-Ab treatment will enhance healing of metaphyseal defects in OVX rats via enhanced stimulation of bone formation.

Methods
OVX surgery was performed at 12 weeks of age in female Sprague Dawley rats. Four weeks later bilateral 3mm circular metaphyseal defects were created in the proximal tibia of all rats. Post defect surgery Scl-Ab or Saline was administered twice weekly at 25mg/kg s.c post defect surgery with both tibia and femora harvested for analysis at 1, 2 and 3 weeks post defect surgery. Radiographs were used to assess healing and systemic effects of the agent. Micro-CT (μCT) scans of the defect region were used to determine 3-dimensional (3D) Bone Volume/Total Volume ratio (BV/TV), Bone Surface (BS), Trabecular Number (TbN) and Trabecular Thickness (TbTh) within the defect, as well as 3D models.

Results
Radiographs revealed progressive healing of the defect over the time course of the study, with enhanced radiodensity in Scl-Ab-treated samples both within and surrounding the defect (Figure 1).

Discussion
By inhibiting the activity of sclerostin during healing in this bone repair model, the amount of bone formed at the repair site was increased in ovariectomized rats as determined by μCT analysis. BV/TV and BS were significantly increased by 3 weeks post surgery in Scl-Ab treated animals. These results were due to an increase in the number and not thickness of the trabeculae, suggesting that the sclerostin antibody increased the number of active bone formation surfaces. Histological analysis will be important to confirm that μCT analysis outcomes are a result of increased bone formation parameters.

Conclusion
Treatment with sclerostin-neutralizing antibodies may provide a new avenue to enhance bone repair, in particular in situations of compromised bone healing such as osteoporosis.

References

Acknowledgements
Funding and reagents for this study were derived from Amgen. Dr McDonald is supported by the Bone Growth Foundation fellowship.