**THE ROLE OF ACTIVIN SIGNALING IN THE PATHOGENESIS OF RENAL OSTEODYSTROPHY OF CKD-MBD**

Hartmut Malluche¹, Marie-Claude Monier-Faugere¹, Yifu Fang², Olga Agapova², William Smith³, Victoria Sung³ and Keith Hruska²

¹University of Kentucky, Nephrology, Lexington, KY, ²Washington University, Nephrology, St Louis, MO, ³Celgene Corporation, Inflammation & Immunology, Warren, NJ

**Introduction and Aims:** Chronic kidney disease-mineral/bone disorder (CKD-MBD) includes vascular calcification and osteodystrophy. We previously demonstrated that CKD increases circulating activin (a ligand of the TGFβ superfamily) and activin signaling. Inhibition of activin signaling with RAP-011, an activin type IIA receptor-IgG1 fusion protein, inhibits vascular calcification and prevents cardiac hypertrophy. We report the role of activin signaling in the pathogenesis of renal osteodystrophy.

**Methods:** Sham operated ldlr⁻/⁻ high-fat fed mice (SHAM; n=12) manifest diabetes and hypercholesterolemia. CKD with hyperphosphatemia, elevated FGF-23, and 60% reduction in glomerular filtration rate (CKD-3) was induced by 5/6 nephrectomy at 14 weeks of age in the ldlr⁻/⁻ high-fat fed mice, and is a model of atherosclerotic vascular calcification. CKD-3 mice were treated with RAP-011 10 mg/kg (RAP-011; n=15) or vehicle (VEH; n=13), injected intraperitoneally weekly beginning at 22 weeks of age and studied at 28 weeks by skeletal histomorphometry and micro-computed tomography. Results of CKD-3 were compared with wild type (WT; n=5) mice and SHAM.

**Results:** Relative to WT (cancellous bone volume/tissue volume [BV/TV]: 12.90%), SHAM mice demonstrated reduced BV/TV (10.92%) associated with adynamic bone disease. Induction of CKD-3 caused high turnover bone disease in VEH mice, and lower BV/TV (11.22%); this was reversed by 6 weeks of RAP-011 treatment (BV/TV: 13.28%). Similar trends were noted in trabecular thickness. CKD-3 VEH-treated mice demonstrated higher erosion surface/bone surface and higher osteoclast number/100 mm bone length (1.83% and 62.32/100 mm, respectively) compared with SHAM (1.05% and 33.40/100 mm), which were mitigated by RAP-011 (1.23% and 38.37/100 mm). CKD-3 VEH-treated mice also demonstrated higher osteoblast surface/bone surface and higher osteoblast number/100 mm bone length (1.58% and 110.63/100 mm respectively; P<0.05) when compared with WT or SHAM. RAP-011 significantly reduced both osteoblast surface/bone surface and osteoblast number/100 mm bone length (0.68% and 43.18/100 mm; P<0.05) compared with VEH. Despite the significant reduction in the osteoblast number relative to VEH, the mineral apposition rate with RAP-011 treatment was maintained (0.42 and 0.40 µm/day, respectively), with a significantly higher bone formation rate/osteoblast (0.17 vs. 0.48 µm³/100 cells/year, respectively; P<0.05 vs. VEH), which was similar to WT (0.42 µm³/100 cells/year). RAP-011 did not affect hyperphosphatemia and FGF-23 levels.

**Conclusions:** Increased circulating activin contributes to the high turnover osteodystrophy associated with CKD-3. Activin inhibition with RAP-011, an ActRIIA ligand trap, increased bone volume in CKD-3 by inhibiting bone resorption and normalizing the mineral apposition rate and bone formation rate/osteoblast, counteracting the negative effects of CKD.