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RKER-012, A NOVEL ACTIVIN RECEPTOR TYPE II LIGAND TRAP, PROTECTED RATS FROM PULMONARY ARTERIAL HYPERTENSION-ASSOCIATED BONE LOSS IN SUGEN/HYPOXIA MODEL

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KEROS THERAPEUTICS

INTRODUCTION

- Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by elevated pulmonary vascular resistance due to severe constriction and progressive obliteration of pulmonary vessels, resulting in diminished oxygenation, impaired cardiac output and right ventricle overload[1].
- Osteoporosis and osteopenia are frequent comorbidities in advanced PAH patients, leading to reduced bone mineral density and bone loss.
- Unbalanced TGF-β signaling has been observed in PAH patients[2].
- TGF-β superfamily ligands, including activin A and B, negatively regulate bone remodeling and suppress bone growth[3,4].
- KER-012 is a modified ActRII ligand trap designed to bind and inhibit activins and SMAD2/3 signaling.
- ActRII ligand traps have been demonstrated to increased bone mineral density[4].

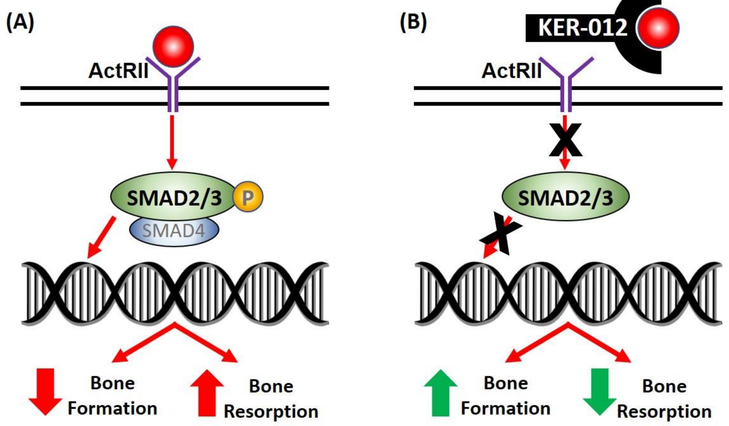

Figure 1. KER-012 is designed to inhibit SMAD2/3 signaling. **(A)** TGF-β ligands bind ActRII which phosphorylates SMAD2/3 causing it to complex with SMAD4 and regulate gene expression. The regulation of target genes in this manner leads to decreased bone formation and increased bone resorption. (B) KER-012 is designed to bind TGF-β superfamily ligands, including activins A and B, and to inhibit SMAD2/3 signaling. The inhibition of SMAD2/3 increases bone formation[5] and reduces bone resorption.

RESULTS

KER-012 prevented trabecular bone loss in proximal tibia

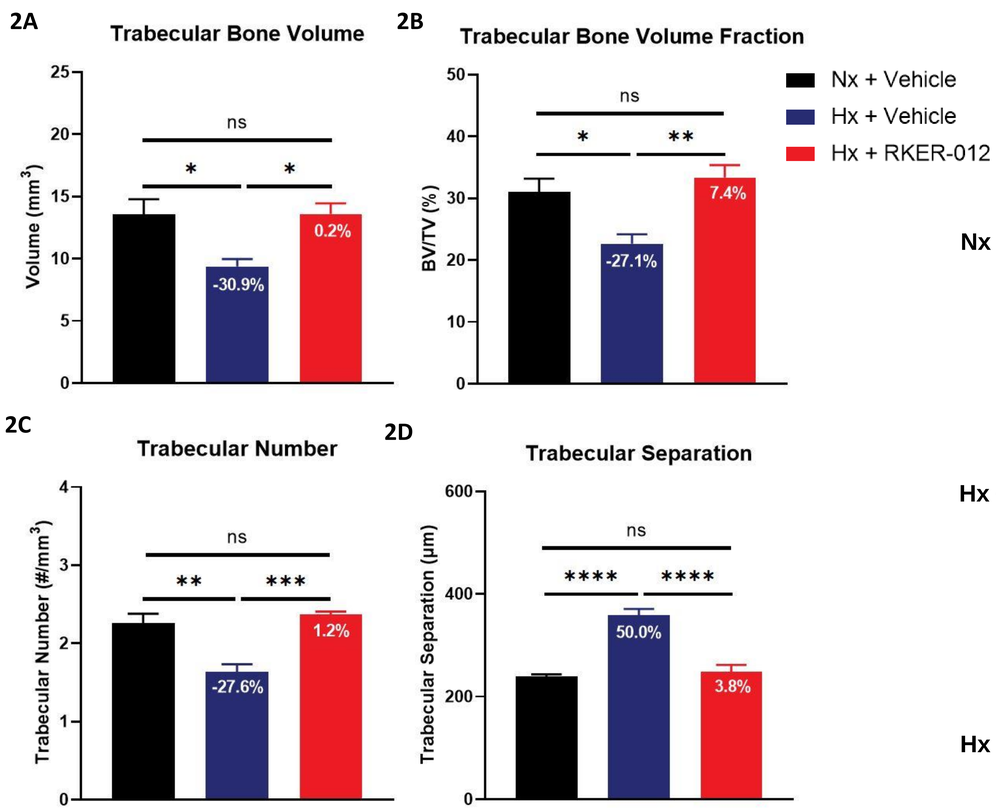

Figure 2. Relative to Nx + Vehicle rats, Hx + Vehicle had reduced bone volume (A), lower bone volume fraction (B), reduced trabecular number (C) and increased trabecular separation (D). Compared to Hx + Vehicle, Hx + RKER-012 rats had increased bone volume (A), higher bone volume fraction (B), increased trabecular number (C) and decreased trabecular separation (D). Hx + RKER-012 rats were equivalent to Nx controls, suggesting complete protection from PAH-induced bone loss. Percent change is relative to Nx + Vehicle. One-way ANOVA followed by Sidak post-hoc test. ns – not significant; *p ≤ 0.05; **p ≤ 0.01 ; ***p ≤ 0.001; ****p ≤ 0.0001

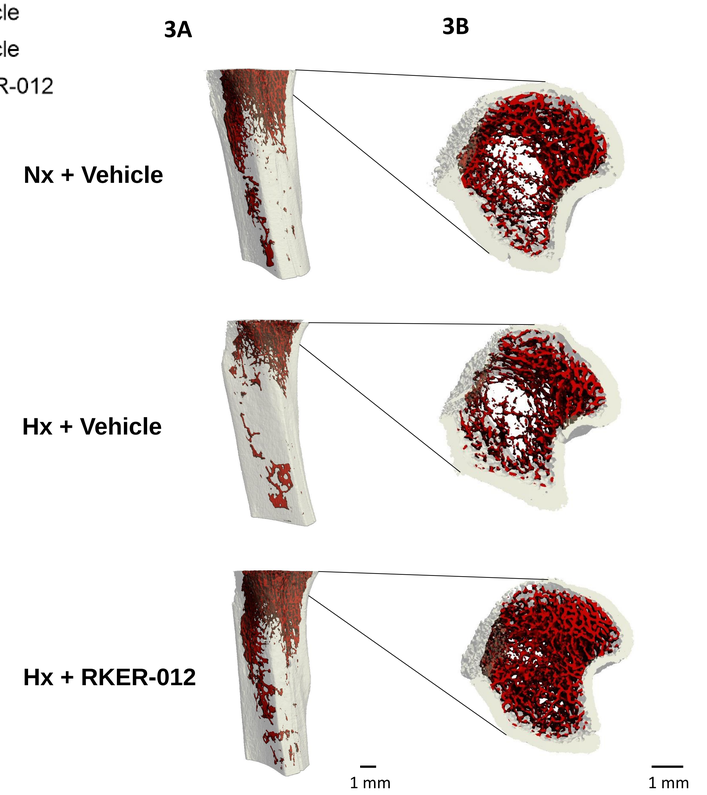

Figure 3. (A) Representative three-dimensional of the tibia from Figure 2 where trabecular architecture is reduced in Hx + Vehicle compared to Nx + Vehicle and Hx + RKER-012. (B) Transverse cross section of the proximal tibia depicting trabecular (red) and cortical (opaque) bone; Scale bar = 1 mm.

AIMS

The goal of this study was to determine the efficacy of a research form of KER-012 (RKER-012) on bone loss in a model of PAH, the Sugen/Hypoxia rat model.

METHODS

- 11-week-old male rats (Sprague Dawley; n=6/grp) were administered either vehicle or Sugen5416 (Sugen; 25 mg/kg) SQ once and placed in either normoxic (Nx; ~21% [O_2]) or hypoxic (Hx; ~10% [O_2]) conditions.
- Nx rats were treated with vehicle, while Hx rats were administered vehicle or RKER-012 (20 mg/kg) SQ twice weekly for 4 weeks.
- Tibiae were scanned using Quantum FX (10 mm FOV, 90 kV, 160 uA, 3 minutes; PerkinElmer).
- Trabecular bone at the proximal tibial metaphysis was evaluated using Bone Microarchitecture Analysis software (AnalyzeDirect).
- 3D representative images using Quantum GX2 (PerkinElmer) and images were acquired using Scanco Medical Software.

CONCLUSIONS

- The Sugen-Hx cohort treated with vehicle (Hx + Vehicle) exhibited decreased bone volume, bone volume fraction and trabecular number, and increased trabecular separation compared to normoxic controls.
- RKER-012 (Hx + RKER-012) prevented loss of bone volume, bone volume fraction and trabecular number, and reduced trabecular separation compared to the Hx + Vehicle rats. RKER-012-treated rats did not differ from the normoxic controls.
- These results suggest RKER-012 protected rats from PAH-induced bone loss.
- **KER-012 could potentially be an effective treatment for bone loss resulting from secondary osteoporosis such as PAH, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and cancer[6].**

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