RKER-012, a Novel Activin Receptor Type IIB (ActRIIB) Ligand Trap, Reduced Cardiopulmonary Pathology in a Rodent Model of Pulmonary Arterial Hypertension

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Introduction

- Pulmonary arterial hypertension (PAH) is a debilitating disorder characterized by elevated pulmonary vascular resistance, resulting in diminished oxygenation, impaired cardiac output, and right ventricle (RV) overload (1).
- PAH is associated with imbalanced TGFß superfamily signaling, including insufficient activation of SMAD1/5/8 (Illustration 1; 1,2).
- Previous studies demonstrated that rebalancing SMAD signaling by inhibiting ligands that bind ActRIIA provides benefit but may be dose-limited due to erythropoietic effects, including increasing red blood cells (RBCs; 3).
- KER-012 is a modified ActRIIB ligand trap designed to target ligands that bind and signal through ActRIIB in a manner expected to be permissive for SMAD1/5/8, potentially rebalancing the defective signaling in PAH.

Our goal was to test the effect of a research form of KER-012 (RKER-012) on pulmonary and RV dysfunction in an established model of PAH.

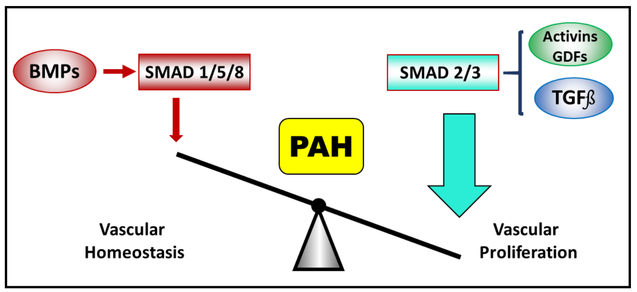

Illustration 1. Imbalanced TGFß signaling may lead to PAH. Specifically, insufficient activation of SMAD1/5/8 favors SMAD2/3 signaling, leading to enhanced myogenic and fibrogenic differentiation.

Methods

***In Vitro* Studies**
- KD values for TGFß superfamily ligands were obtained by kinetic evaluation utilizing surface plasmon resonance (Biacore).
- KER-012's ability to inhibit TGFß ligands was measured using luciferase reporter cell assays.

***In Vivo* Non-human Primate Study**
- 3 female cynomolgus monkeys were dosed with 3 mg/kg KER-012. RBCs were assessed 14 days later.

***In Vivo* Rat Study**
- Male Sprague Dawley rats (n=6/group).
- 2 groups of rats received a single subcutaneous (SQ) dose of 25mg/kg SUGEN5416 and were placed in a hypoxic environment (11% O_2; SH).
- 1 group received SQ vehicle and remained in a normoxic environment.
- For 4 weeks, SH rats received either vehicle or 10mg/kg RKER-012 twice weekly SQ. Normoxic rats received vehicle SQ twice weekly.
- Rats were assessed terminally for RBCs and markers of PAH.

Results

KER-012 is designed to bind SMAD 2/3 signaling ligands and to inhibit their activity without inhibiting BMP-9

A

Activin A	Activin B	GDF-11	BMP-9
64 pM	105 pM	172 pM	31 nM

B

Activin A	Activin B	GDF-11	BMP-9
250 ng/mL	140 ng/mL	110 ng/mL	>100 ug/mL

Figure 1. (A) Dissociation constant (K_D) concentrations, Activin A, Activin B, GDF-11, and BMP-9. (B) IC_{50} values of KER-012's inhibition of TGFß superfamily ligands activin A, activin B, and GDF-11, which normally signal through SMAD2/3. KER-012 did not inhibit BMP-9 which signals through SMAD1/5/8.

KER-012 and its research form, RKER-012, did not increase RBCs in two model species, indicating a lack of dose-limiting RBC effect

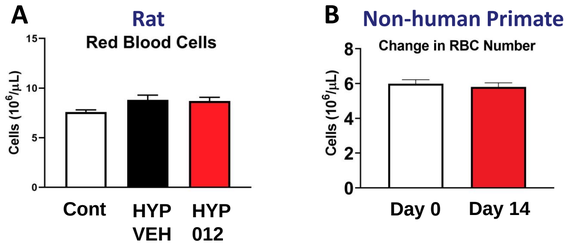

Figure 2. (A) RKER-012 did not increase RBC number in hypoxic rats, relative to either vehicle-treated hypoxic rats or normoxic controls. (B) KER-012 did not increase RBC number in healthy naïve non-human primates, a model highly translatable to humans. **Cont=controls, HYP=hypoxic, VEH-vehicle, 012=RKER-012.**

RKER-012 reduced remodeling of lung and heart in the rat Sugen/hypoxia model

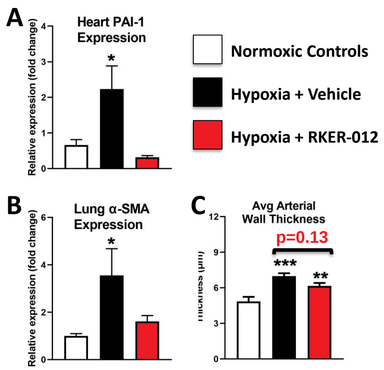

Figure 3. Relative to normoxic controls, vehicle-treated SH rats had significantly greater (A) RV plasminogen activator inhibitor-1 (PAI-1) expression (+236.7%; p<0.05), (B) α-smooth muscle actin (α-SMA) expression (+255.4%; p<0.05), and (C) increased arterial wall thickness (+43.8%, p<0.001), consistent with enhanced pulmonary vascular remodeling and cardiac fibrosis. Treatment with RKER-012 reduced heart PAI-1 expression and lung α-SMA to levels equivalent to normoxic controls and reduced wall thickness, supporting potential prevention of disease development.

RKER-012 reduced PAH-associated inflammation

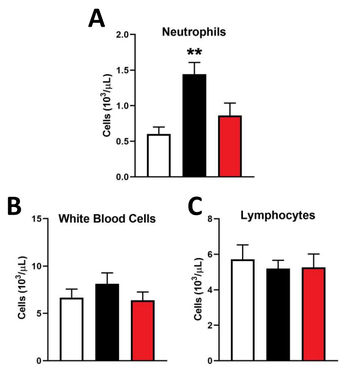

Figure 4. Relative to normoxic controls, vehicle-treated SH rats had significantly greater (A) neutrophil number (+139.2%; p<0.01) with no effect on (B) white blood cells or (C) lymphocytes. Treatment with RKER-012 reduced neutrophils to levels of normoxic controls, indicating reduced PAH-associated inflammation.

RKER-012 reduced cardiac compensation to PAH

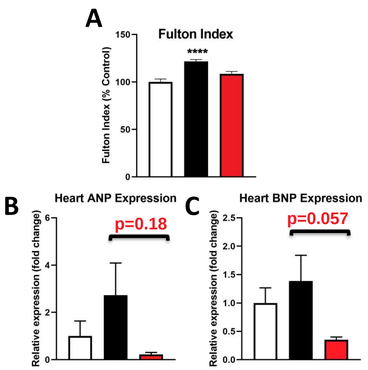

Figure 5. Relative to normoxic controls, vehicle-treated SH rats had significantly greater (A) Fulton index (+21.7; p<0.0001), and trends for increased (B) atrial natriuretic peptide (ANP; +172.8%; p=ns) and (C) B-type natriuretic peptide (BNP; +38.7%; p=ns. Treatment with RKER-012 reduced Fulton Index to control levels, and reduced ANP and BNP expression to levels below controls, supporting reduced PAH-induced cardiac compensation.

Conclusions

- **KER-012 is a modified ActRIIB ligand trap that is designed to inhibit SMAD 2/3 signaling without inhibiting the SMAD 1/5/8 ligand BMP9.**
- **KER-012 did not alter RBC number in either rats or the translatable non-human primate species.**
- **KER-012 prevented inflammation, fibrosis, and vascular remodeling in a rat Sugen/hypoxia PAH model.**
- **Together, these results provide early evidence that KER-012 has the potential to treat human PAH.**

References

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2. Orriols M et al. (2017). Cell Mol Life Sci. PMID:28447104.
3. Cappellini MD et al. (2019). Haematologica. PMID:30337358.

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