PBI-4050 Therapy Selectively Improves Pulmonary Hypertension, Lung Remodeling and Right Ventricular Function in Heart Failure With Reduced Ejection Fraction (HFrEF)

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Introduction. There is currently no approved treatment for the most prevalent form of PH that is associated with left heart disease (Group II PH). Heart failure with reduced ejection fraction (HFrEF) causes lung remodeling characterized by myofibroblasts proliferation and fibrosis leading to a restrictive lung syndrome contributing to PH and RV dysfunction.
Hypothesis. We evaluated PBI-4050, a novel first-in-class agent with anti-fibrotic and anti-proliferative actions, for the treatment of PH in a model of HFrEF.
Methods. HFrEF was induced by myocardial infarction (MI) after coronary artery ligation in rats. Two weeks after surgery, sham-operated and MI groups were treated with PBI-4050 (200 mg/kg/day by gavage) or with saline for 3 weeks. Animals were analyzed according to pathological infarct size into large MI (≥35% LV) and small to medium MI (< 35%). Hemodynamic evaluation was performed with microtip cathethers and lung function testing evaluated with a Flexivent respirator. Cardiac ultrasound was performed at 2 weeks and at 5 weeks. Scar size and lung fibrosis were quantified by histology.
Results. Pathological infarct size correlated with echocardiographic wall motion score index (r^2=0.73, p<0.001). Large MI (≥35% LV) resulted in PH and RVH with a restrictive lung syndrome. For a similar infarct size, PBI-4050 did not affect LV function but markedly reduced PH and RVH. The compensatory increase in RV contractility was normalized by PBI-4050. PBI-4050 reduced lung remodeling evidenced by a reduction in lung weight and improved respiratory compliance. Finally, lung fibrosis was reduced by PBI-4050 with histological evidence of reduced alveolar wall cellular proliferation.
Conclusion. PBI-4050 effectively reduces PH and RVH in HFrEF by reducing lung fibrosis and remodeling. This novel agent decreases the associated restrictive lung syndrome and recovers RV function without affecting LV function. PBI-4050 is a promising therapy for group II PH.

	Sham/Saline n=12	Sham/PBI n=11	S-M/Saline n=13	S-M/PBI n=9	Large/Saline n=21	Large/PBI n=22
Infarct size (%)	NA	NA	31 ± 2	30 ± 3	45 ± 6	44 ± 6
LVEDP (mmHg)	3.2 ± 2.3	3.4 ± 3.7	5.8 ± 3.2§	2.9 ± 2.5	26.1 ± 7.5‡	21.5 ± 8.1‡
LV dp/dt (mmHg/s)	6902 ± 1068	7017 ± 1155	6329 ± 937	5787 ± 1456§	5259 ± 857‡	5047 ± 987‡
RVSP (mmHg)	22.6 ± 3.2	21.8 ± 3.0	22.3 ± 3.2	24.5 ± 4.0	54.6 ± 13.5‡	36.1 ±12.5†#
RVH index	0.23 ± 0.04	0.24 ± 0.04	0.25 ± 0.04	0.23 ± 0.03	0.42 ± 0.11‡	0.32 ± 0.10§*
RV dp/dt (mmHg/s)	1420 ± 240	1537 ± 303	1389 ± 268	1298 ± 231§	2123 ± 288‡	1552 ± 452#
Lung lobe weight (g)	1.27 ± 0.28	1.22 ± 0.20	1.38 ± 0.33	1.22 ± 0.21	2.29 ± 0.66‡	1.75 ± 0.49†#
Lung compliance (mL/cm H_2O)	0.77 ± 0.15	0.84 ± 0.23	0.82 ± 0.26	0.71 ± 0.14	0.29 ± 0.17‡	0.46 ± 0.20†#
Lung fibrosis (%)	12.7 ± 5.8	9.9 ± 1.7	12.6 ± 4.9	12.6 ± 4.1	22.9 ± 7.6§	17.6 ± 3.8‡*

*p<0.05 and # p<0.001 vs respective saline; §p<0.05, †p<0.01 and ‡p<0.001 vs respective sham; S-M: Small to medium MI