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Poster presentation



# Manipulating the natriuretic peptide system for the treatment of pulmonary hypertension

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## Background

We have recently reported that the combination of a neutral endopeptidase inhibitor (NEPI; prevents the breakdown of natriuretic peptides) and a phosphodiesterase 5 inhibitor (PDE5-I; prevents the hydrolysis of cyclic GMP), synergistically prevents pathogenesis in a hypoxia-induced model of pulmonary hypertension (PH; [1]). Herein, we have assessed the efficacy of this novel combination therapy to reverse disease severity in (a) established PH and (b) bleomycin-induced pulmonary fibrosis.

## Methods and results

### *(a) Reversal of existing PH*

In this study, the combination therapy (NEPI: ecadotril 60 mg/kg/day; PDE5I: sildenafil 30 mg/kg/day) was initiated after rats had been exposed to 3 weeks of chronic hypoxia (10% $O_2$) to induce PH. This intervention resulted in a less pronounced elevation in right ventricular pressure (Control: 21.57 ± 3.432 mmHg, Hypoxia: 34.32 ± 3.882 mmHg, Hypoxia + combination therapy: 29.17 ± 1.965 mmHg) and reduced right ventricular hypertrophy (RV/LV+S ratio; Control: 0.2839 ± 0.01874, Hypoxia: 0.3411 ± 0.03317, Hypoxia + combination therapy: 0.3063 ± 0.01412) compared to untreated animals.

### *(b) Bleomycin-induced pulmonary fibrosis*

Pulmonary hypertension often complicates interstitial lung disease, where it is associated with higher mortality. Bleomycin, a peptide antibiotic, causes oxidant-mediated DNA scission leading to fibrogenic cytokine release and is a commonly used mouse model of pulmonary fibrosis. Our data suggest that the NEPI/PDE5-I combination is effective in ameliorating the rise in right ventricular systolic pressure (RSVP) in response to bleomycin (1 U/kg; Control: 21.14 ± 4.028 mmHg, bleomycin: 33.84 ± 2.397 mmHg, bleomycin + combination therapy: 25.18 ± 1.902 mmHg; Figure 1).

## Conclusion

These data demonstrate that the NEPI/PDE5I combination is effective in ameliorating disease severity in two models of PH with disparate aetiologies. First, the combination is valuable in reversing established (hypoxia-induced) PH and, second, the dual therapy is capable of reversing the pulmonary haemodynamic dysfunction in bleomycin-induced pulmonary fibrosis. Thus, this work substantiates the therapeutic potential of this novel combination therapy in PH.

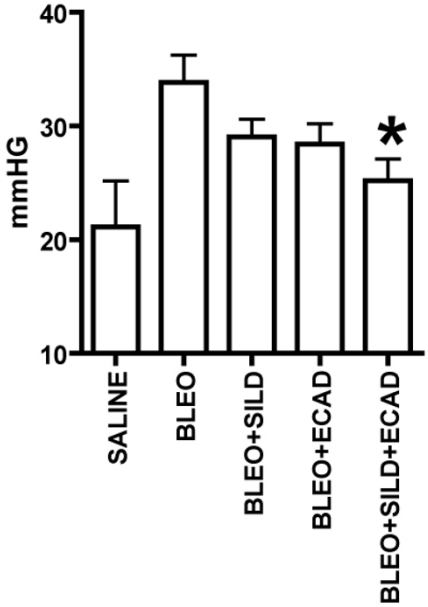


**Figure 1**
**RSVP in control animals (n = 6) and bleomycin-treated animals (n = 6) in the absence and presence of sildenafil (SILD, n = 7), ecadotril (NEPI, n = 8) and combination treatment (SILD+NEPI, n = 9)**. *P < 0.05.

## References

1. Baliga RS, Zhao L, Madhani M, Lopez-Torondel B, Visintin C, Selwood D, Wilkins MR, MacAllister RJ, Hobbs AJ: **Synergy between natriuretic peptides and phosphodiesterase 5 inhibitors ameliorates pulmonary arterial hypertension.** *Am J Respir Crit Care Med* 2008, **178**:861-869.