**IRAP – A novel target in the treatment of Pulmonary Arterial Hypertension**

Supitchaya Watakul1, Peng-Cheng Wang1, Jana Goldenberg1, Robert E Widdop1, Barbara K Kemp-Harper1 and Tracey A Gaspari1. Dept of Pharmacol, Monash University1, Clayton, VIC, Australia.

Introduction. Pulmonary Arterial Hypertension (PAH) is a progressive and incurable disease with a high mortality rate. Current vasodilator therapies modestly lower pulmonary arterial pressure yet have limited ability to halt or reverse the cardiopulmonary remodelling associated with the disease. Insulin-regulated aminopeptidase (IRAP) inhibitors have demonstrated vasoprotective, anti-inflammatory and anti-fibrotic actions in multiple preclinical cardiovascular disease models and thus present as a potential novel treatment for PAH, a disease characterised by inflammation, vascular remodelling and right ventricular hypertrophy (RVH).

Aims. To investigate IRAP inhibitors as a novel treatment for PAH in a murine pre-clinical model.

Methods. PAH was induced in male and female C57BL/6J mice using the gold standard sugen-hypoxia (SuHx; 42 days, 10% O2) model. Lung IRAP expression was assessed during the development of PAH (14, 21, 35 and 42 days, n=6-9/timepoint) using immunofluorescent staining. Subsequently, SuHx mice were treated with the IRAP inhibitor, HFI-419 (0.72mg/kg/day; minipump) or the current standard-of-care, the phosphodiesterase 5 (PDE5) inhibitor, sildenafil (30mg/kg/day; oral) from day 21 to 42 (n=5-6/group). Endpoint measures included: right ventricular systolic pressure (RVSP), RVH and histological analysis of pulmonary vascular remodelling.

Results. Lung IRAP expression was ~6-fold higher in normoxic females compared to males. However, IRAP expression increased up to 10-fold throughout the time course of PAH development in male but not female mice, such that IRAP expression in males at day 42 was similar to that of females at day 42. The SuHx model was associated with increased RVSP, RVH, pulmonary vessel wall thickness and lung weight in both sexes. Treatments did not decrease RVH or lung weight/tibial length ratio in male and female SuHx mice. In male SuHx mice, both sildenafil and HFI-419 reduced RVSP (38.6±1.4 and 38.8±1.1 vs 45.2±1.7 mmHg respectively; P<0.05). By contrast, none of the treatments reduced RVSP in female SuHx mice. Interestingly, targeting IRAP inhibitors significantly reduced pulmonary vessel wall thickness (P<0.01) in SuHx male and female mice, an effect not observed with the PDE5 inhibitor sildenafil.

Discussion. IRAP inhibition shows promise as a novel target for vascular remodelling in PAH in both males and females. Future studies will explore the efficacy of IRAP inhibitors in combination with the current standard-of-care (sildenafil).