Reduction in CD68 macrophage number causes a spontaneous, and
gender specific PAH phenotype in mice.

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Perivascular macrophages are well documented in patients and animal models of
pulmonary arterial hypertension (PAH). The exact role for macrophages, and whether
their presence or absence is required for the vascular remodelling seen in PAH is
unclear. Using a novel inducible macrophage (CD68) depletion model (MacLow) we
aimed to determine the requirement for macrophages in pulmonary arterial remodeling
associated with PAH. Following macrophage depletion (~50% of F4/80 postive cells)
for 6 weeks’ mice were phenotyped for PAH by echocardiography, closed chest
cardiac catheterization and immunohistochemistry (IHC). To investigate the origin of
the effector cells, male chimeric mice were generated, and to study gender-specificity
of the disease phenotype, mixed gender chimeric MacLow/wild type (wt) mice also
produced.

**Results:** Male but not female MacLow mice developed a PAH phenotype compared
to controls (RVSP 66 vs 24 mmHg, p< 0.0001, n=5-8), that was associated with right
ventricular Hypertrophy (RVH) and pulmonary vascular remodelling. IHC analysis of
demonstrated increased iNOS- |CD206+ |F4/80+ macrophages suggesting a M2-like
macrophage population drive the PAH phenotype in these mice. Studies on mixed
gender chimeric mice demonstrated that neither male or female MacLow BM
transferred into wild-type was sufficient to induce PAH, and female MacLow BM failed
to protect male *MacLow* mice suggesting that in a male gender specific manner, resident lung M2-like macrophages drive the development of disease in this model. Studies are currently underway to determine whether 17 beta-oestradiol treatment can prevent development of PAH in male *MacLow* mice.