

TMEM100 Preserves Lung Growth and Prevents Pulmonary Hypertension in Bronchopulmonary Dysplasia

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Background

- BPD is the chronic lung disease of prematurity that is characterized by sustained abnormalities of lung structure due to disruption of distal lung alveolar and vascular growth after preterm birth. (1)
- In addition to extreme prematurity, exposure to antenatal stresses, such as chorioamnionitis, increase risk for BPD, and is associated with late respiratory disease and pulmonary hypertension (PH). (2)
- Mechanisms through which antenatal inflammation increased susceptibility for BPD are poorly understood, but past studies shown that decreased angiogenesis impairs alveolar and vascular growth in the developing lung, leading to late PH. (3)
- Transmembrane protein 100 (TMEM100) is a key regulator of angiogenesis, especially during lung development (4), but whether lung TMEM100 expression is decreased in BPD and whether therapy that increases TMEM100 preserves lung structure and decreases BPD-PH are unknown.
- Recent studies have led to the development of lung nanoparticles that can deliver specific genes to lung endothelium, but its effects in experimental models of BPD are uncertain. (5)

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- Jakkula, M., et al., Inhibition of angiogenesis decreases alveolarization in the developing rat lung. Am J Physiol Lung Cell Mol Physiol, 2000. 279(3):L600-7.
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Hypothesis

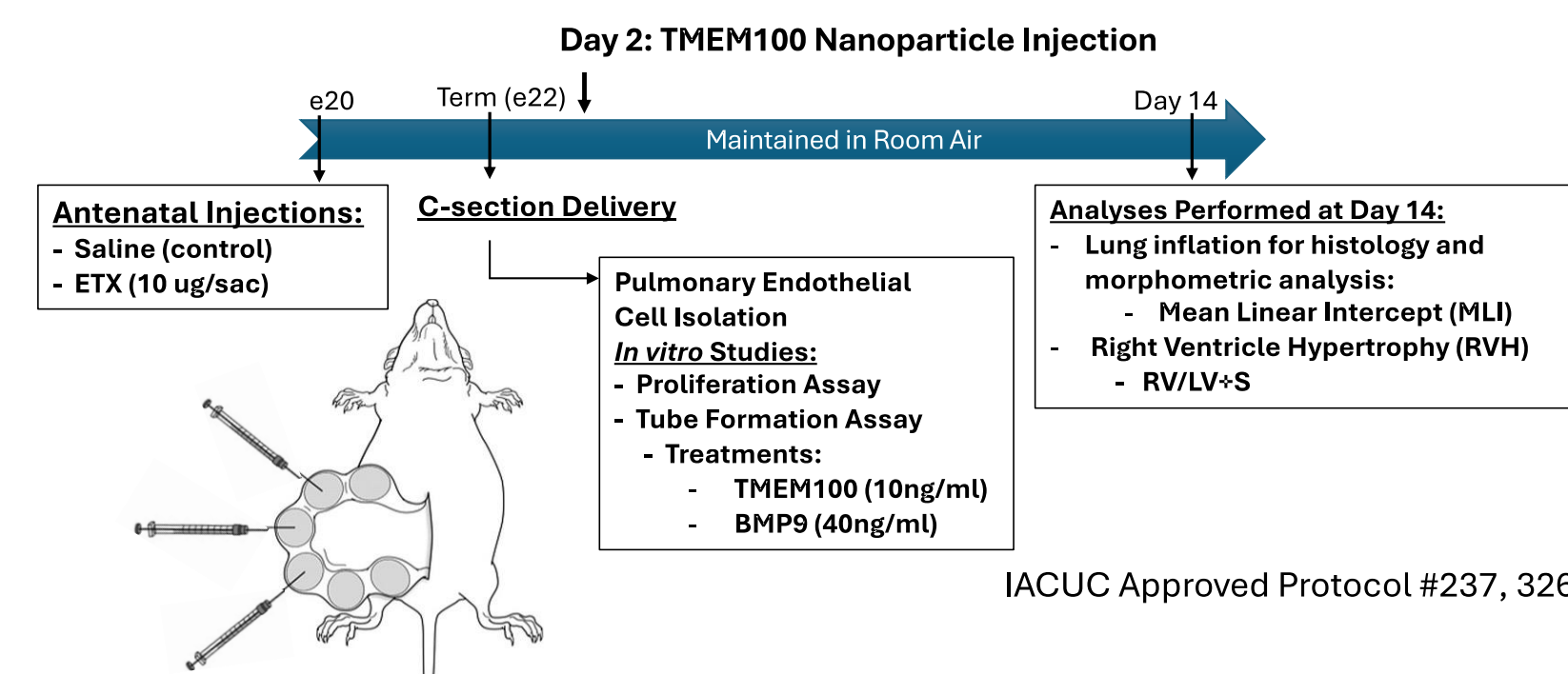
Treatment with TMEM100, a potent pro-angiogenic factor, will improve lung vascular and alveolar growth and prevent pulmonary hypertension (PH) in an experimental model of BPD due to antenatal inflammation

Study Questions

- Is neonatal lung TMEM100 expression decreased after prenatal exposure to intra-amniotic injections of endotoxin (ETX)?
- Will lung endothelial-specific delivery of TMEM100 preserve lung growth and prevent PH in neonatal rats after exposure to antenatal ETX?
- Will treatment with exogenous TMEM100 or BMP9, a known TMEM100 agonist, increase endothelial cell growth and tube formation *in vitro*?

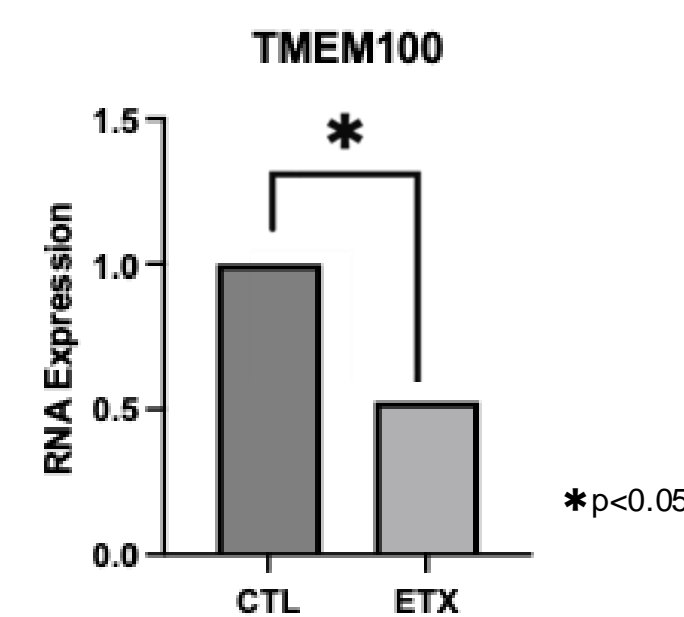
Methods

Study Design: Antenatal Endotoxin to induce BPD



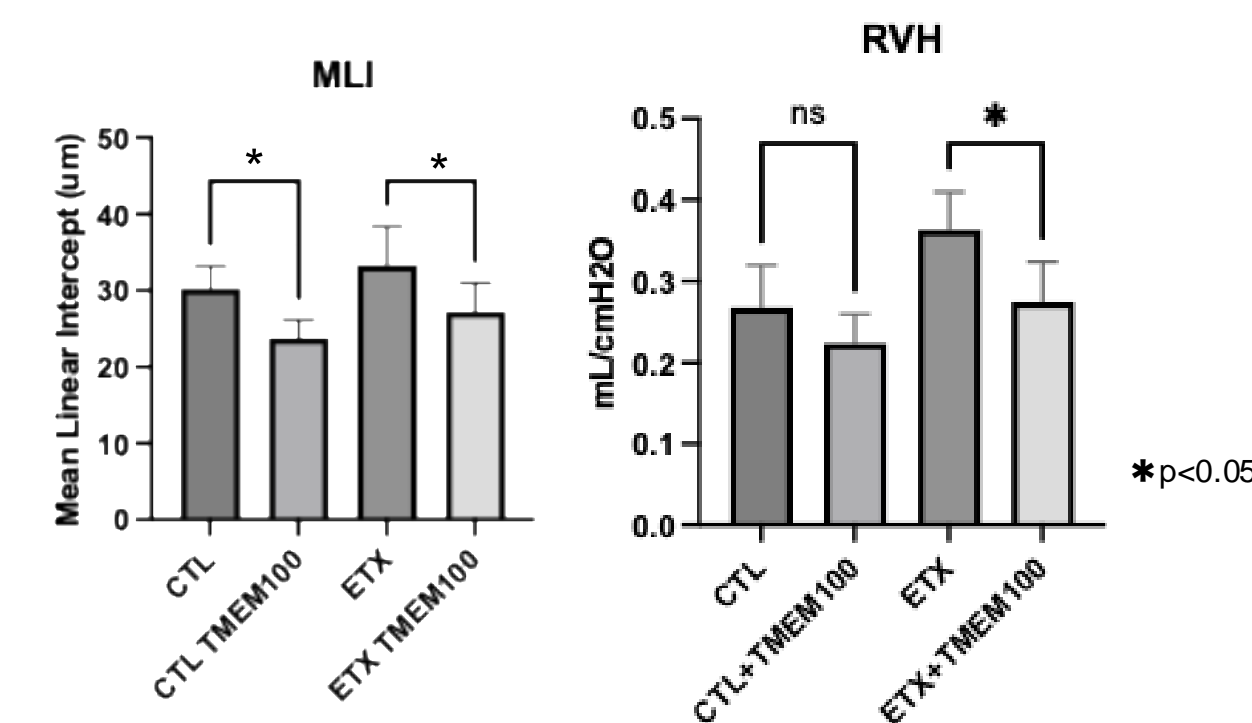
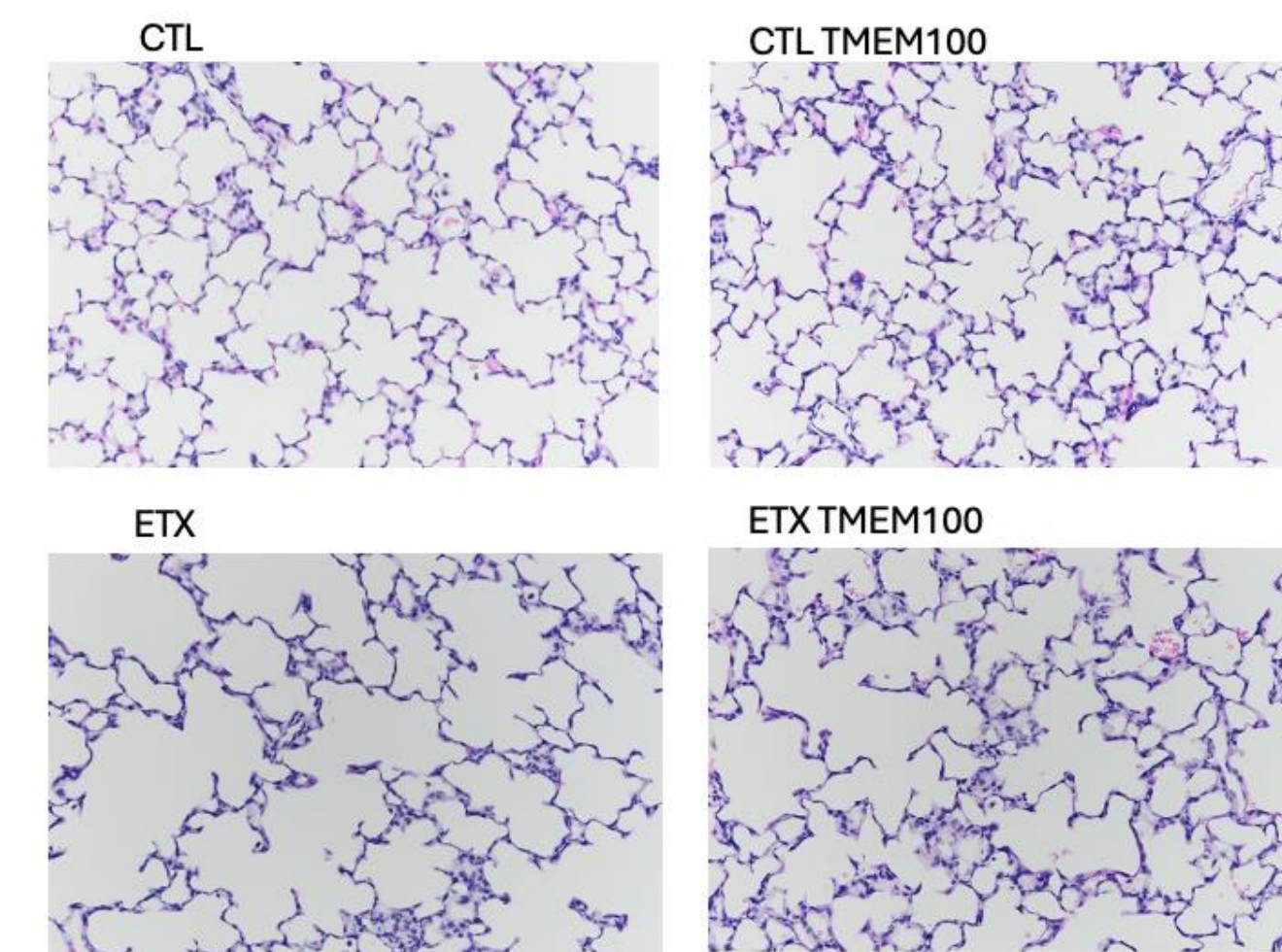
Results

Neonatal Lung TMEM100 RNA Expression is Decreased After Antenatal ETX Exposure

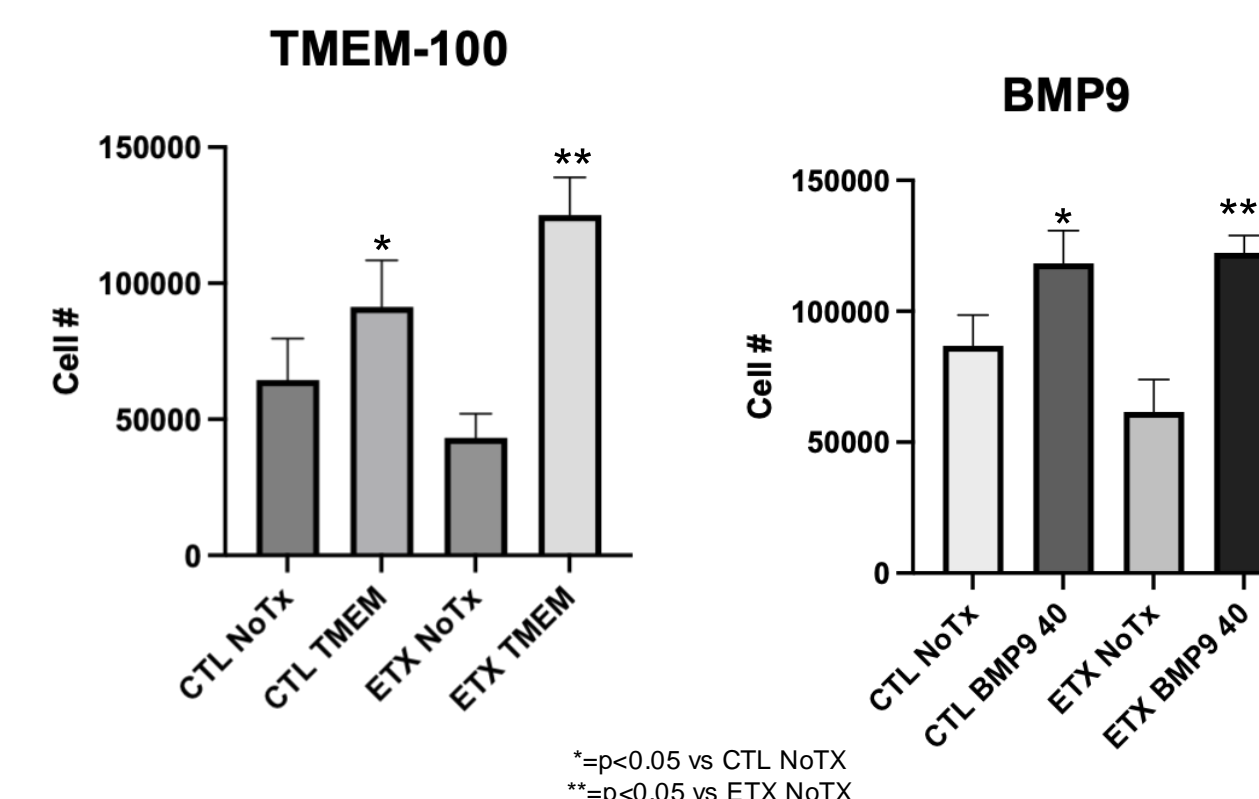


Results

TMEM100 Treatment Increased Alveolarization and Decreased Right Ventricular Hypertrophy In ETX Exposed Rats

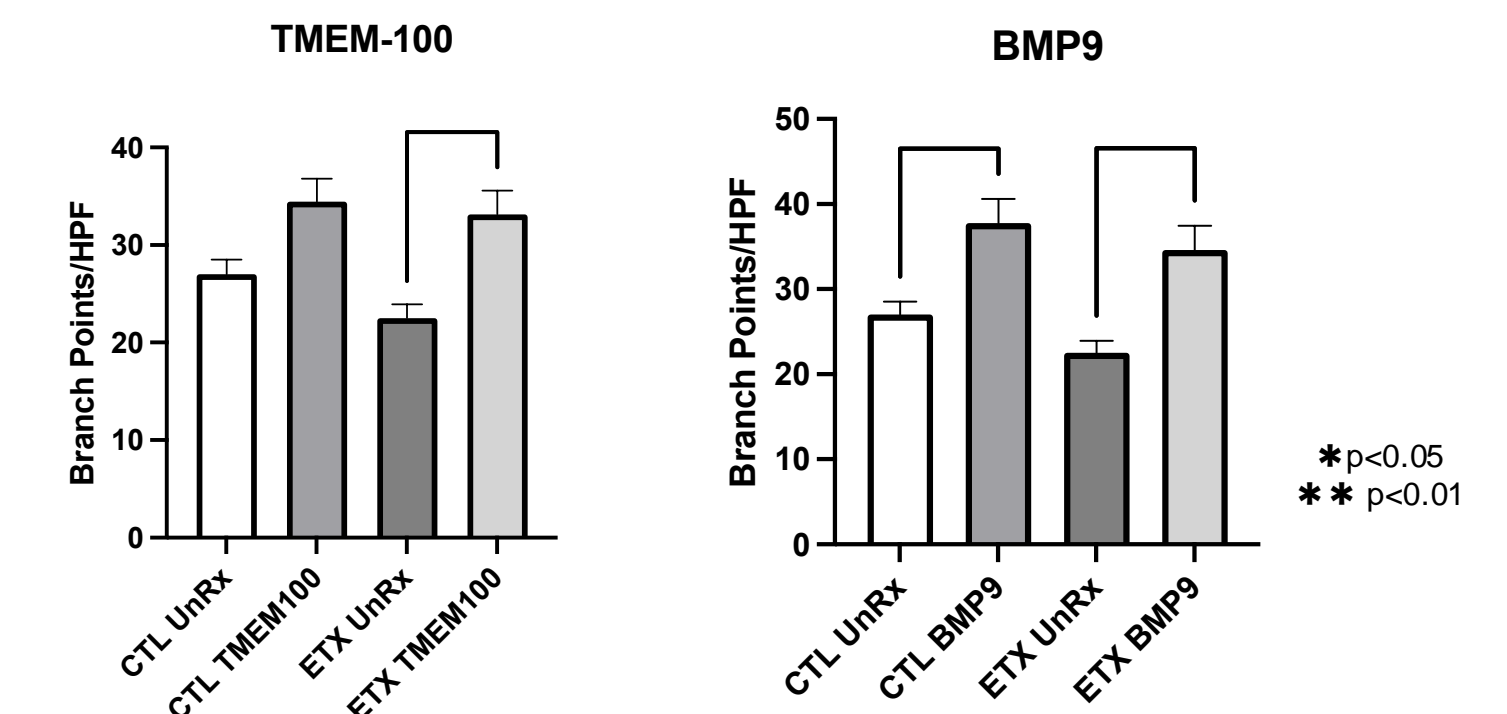


TMEM100 and BMP9 Increased Proliferation in CTL and ETX PECs in vitro



Results

TMEM100 and BMP9 Increased Tube Formation in CTL and ETX PEC *in vitro*



Summary

- Antenatal ETX exposure decreases lung TMEM100 RNA expression in neonatal rats;
- Postnatal TMEM100 treatment preserved alveolar growth and prevented RVH after antenatal ETX exposure;
- TMEM100 treatment increased endothelial cell proliferation, and tube formation *in vitro*
- BMP-9, a TMEM100 agonist, enhanced PEC growth and tube formation *in vitro*.

Conclusion

Lung endothelial-specific nanoparticle delivery of TMEM100 improved alveolarization and reduced RVH in antenatal ETX-induced BPD and enhanced PEC growth and tube formation *in vitro*.

Speculation

Enhancement of the TMEM100 signaling pathway may preserve angiogenesis and alveolarization, which may prevent BPD and BPD-PH