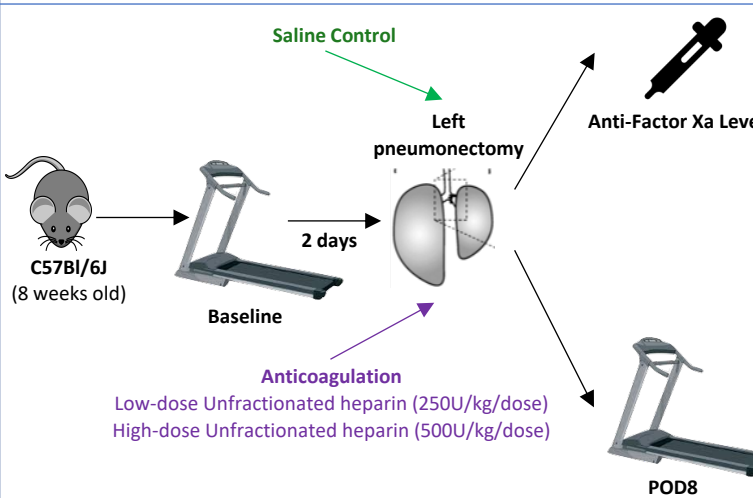
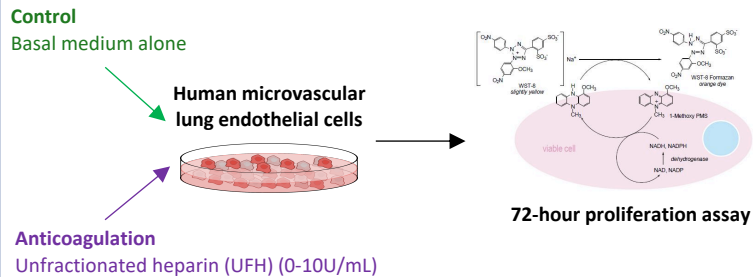


## Purpose

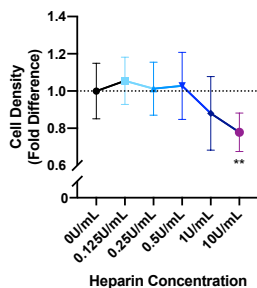
Neonates with congenital diaphragmatic hernia suffer from pulmonary hypoplasia. The most critical patients may require extracorporeal membrane oxygenation with systemic anticoagulation. Many more will require central venous access and lower doses of anticoagulation to maintain line patency. Previously, we demonstrated that high-dose heparin inhibited murine compensatory lung growth (CLG). We investigate the functional effects of low and high dose heparin in this model.

## Methods

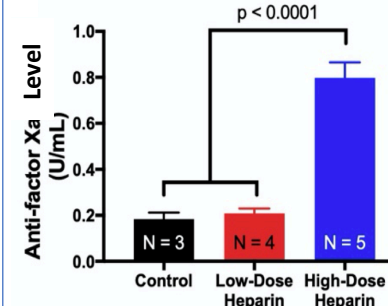


## Results

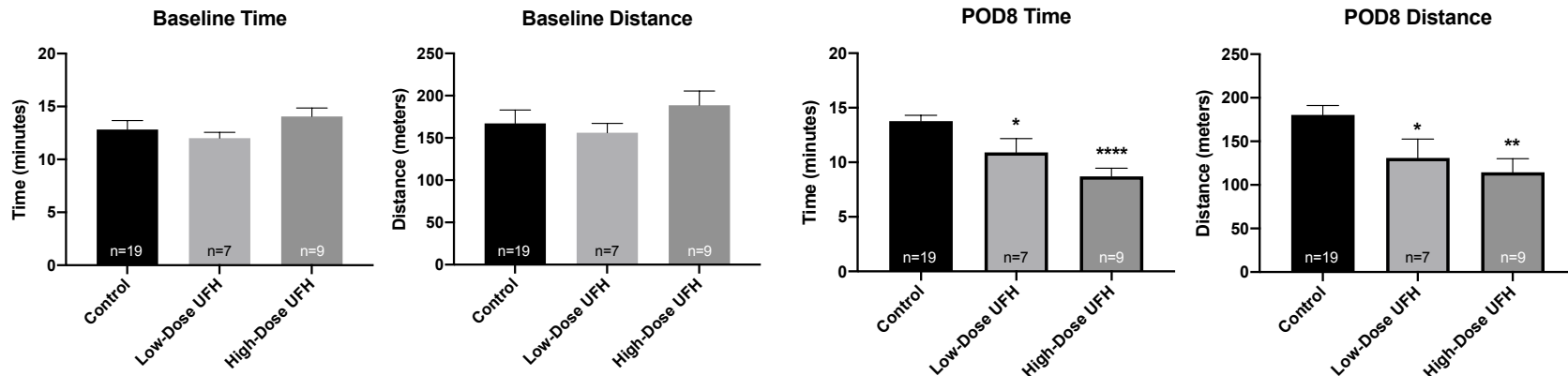
**Human Lung Endothelial Cell Proliferation**



**Figure 1. Heparin inhibits lung endothelial cell proliferation.** HMVEC-L treated with increasing doses of UFH exhibit a dose-dependent decrease in cell proliferation. Experiment was performed in a 96-well plate, with 12-wells per treatment group included in analysis. Treatment effect was assessed by one-way ANOVA compared to no treatment. Significance represented by \* ( $p < 0.05$ ), \*\* ( $p < 0.01$ ).



**Figure 2. High-dose heparin elevates anti-factor Xa level while low-dose heparin does not.** Compared to controls, high-dose heparin significantly increases anti-factor Xa level, while low-dose heparin does not.



**Figure 3. Heparin impairs treadmill exercise tolerance in a murine model of compensatory lung growth.** At baseline, the mice randomized to later receive control versus low- or high-dose heparin were not significantly different in treadmill exercise tolerance, as measured by time spent running and distance run. However, eight days after left pneumonectomy, mice administered heparin ran for significantly less time and shorter distance than those administered saline control. Heparin impaired treadmill exercise tolerance in a dose-dependent manner. Significance represented by \* ( $p < 0.05$ ), \*\* ( $p < 0.01$ ), \*\*\* ( $p < 0.001$ ), \*\*\*\* ( $p < 0.0001$ ).

## Acknowledgements

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## Conclusions

Heparin inhibits lung endothelial cell proliferation in a dose-dependent manner and decreases post-pneumonectomy exercise tolerance at therapeutic and subtherapeutic doses. These data suggest that therapeutic and subtherapeutic heparin may worsen outcomes for neonates with CDH and other pulmonary hypoplastic diseases through inhibiting pulmonary endothelial proliferation and impairing pulmonary function. Accordingly, the choice of drug, dose, and duration of therapy for neonates with hypoplastic lung disease requiring anticoagulation should be reconsidered.