Nintedanib, an Anti-Fibrotic Drug, Preserves Lung Alveolar and Vascular Growth and Prevents Pulmonary Hypertension in an Experimental Model of Hyperoxia-Induced Lung Injury

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BACKGROUND

- Bronchopulmonary dysplasia (BPD), the chronic lung disease associated with prematurity, is characterized by decreased alveolar and vascular growth, interstitial fibrosis, and associated comorbidities, including pulmonary hypertension (PH).
- The pathophysiology of BPD is partly due to hyperoxia- induced postnatal injury, and in addition to impaired distal lung growth, lung fibrosis can contribute to abnormal lung function.
- Therapies directed for the prevention of BPD and BPD-associated PH remain lacking.
- Recent work has shown that anti-fibrotic agents, including Nintedanib, can preserve lung function in adults with idiopathic pulmonary fibrosis. Whether early Nintedanib treatment can prevent BPD by preserving lung alveolar and vascular growth, improving lung function, and reducing the development of PH is unknown.
- However, Nintedanib, which is a tyrosine kinase receptor inhibitor, decreases growth factor signaling, which potentially can have adverse effects on growth of the developing lung.

HYPOTHESIS

To determine if Nintedanib treatment will preserve lung alveolar and vascular growth, improve lung function and prevent PH in a postnatal hyperoxia model of BPD in rats.

STUDY QUESTIONS

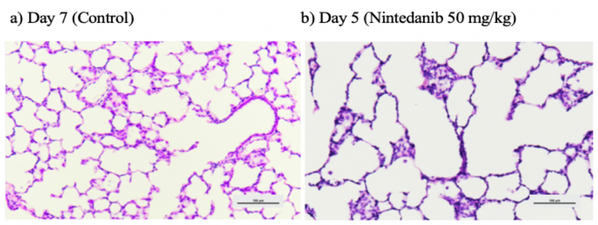
- Does postnatal Nintedanib exposure, especially at high or adult levels of dosing, adversely affect normal lung development?
- Will low dose Nintedanib improve lung structure and function and reduce RVH in experimental BPD due to postnatal hyperoxia?

METHODS

- <u>Dose-ranging Studies:</u>
- Hyperoxia Studies: On day of life 1, Sprague Dawley rats were exposed to room air (RA) or Hyperoxia (90% O2) conditions for 14 days
  - Daily SQ injection of saline or Nintedanib 1mg/kg
- Study Endpoints:
  - Lung function, total lung resistance & compliance by Scireq flexiVent
  - Lungs inflated with 4% PFA and paraffin embedded for histologic measurements
  - Radial Alveolar Counts (RAC)
  - Mean Linear Intercepts (MLI)
  - Pulmonary vessel density (PVD) and Pulmonary Vessel Wall Thickness (PVWT) were determined on vWF immunostained vessels
  - Right ventricular hypertrophy (RVH) was quantified by cardiac weights RV/(LV+S)

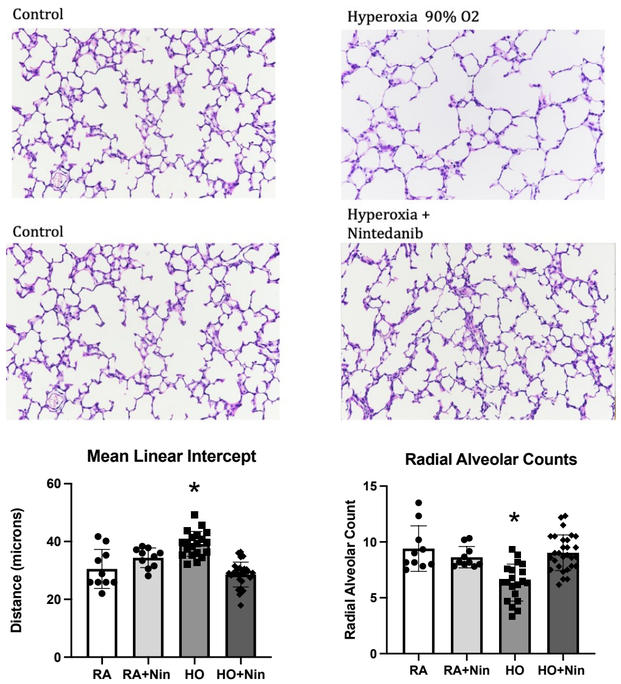
RESULTS

Daily Nintedanib 50mg/kg (Adult Dose) Impairs Lung Growth and Increases Mortality



RESULTS

Nintedanib Improves Distal Lung Growth in Experimental BPD



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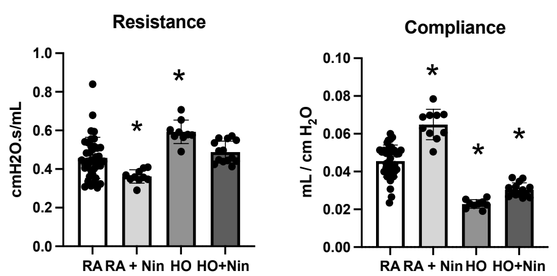
Nintedanib Improves Total Lung Resistance and Compliance Following Postnatal Hyperoxia



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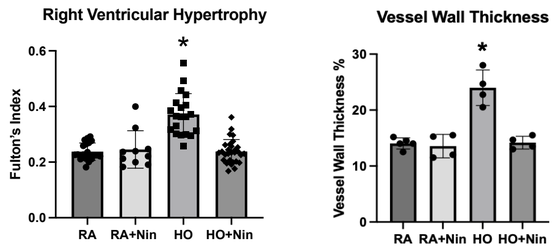
RESULTS

Nintedanib Improves Vessel Wall Thickness and Prevents RVH



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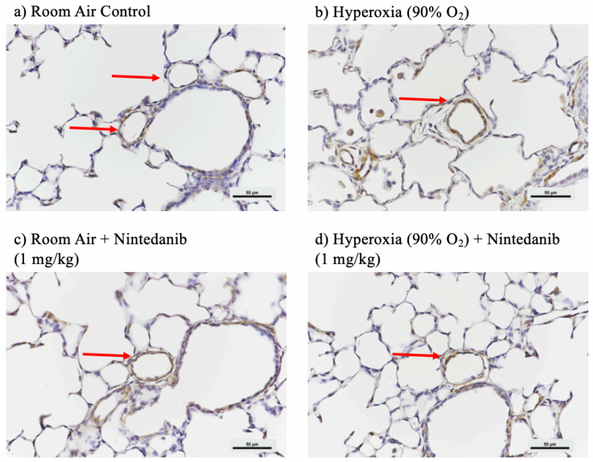

CONCLUSION

- Adult dose Nintedanib impairs lung growth and increases mortality in neonatal rats;
- Nintedanib treatment of hyperoxia exposed rat pups:
  - Improves lung growth and function
  - Improves pulmonary vessel density
  - Prevents right ventricular hypertrophy

SPECULATION

We speculate that low-dose antifibrotic agents, such as Nintedanib, may provide a novel strategy for the prevention and treatment of BPD.