Development of an Antioxidant Inflammation Modulator as a Targeted Therapeutic for Pulmonary Hypertension
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Purpose
Pulmonary Hypertension (PH) is an incurable and often fatal medical condition characterized by remodeling of the pulmonary arteries, leading to high blood pressure in the lungs and right heart failure. Current treatment options for patients with PH, like vasodilators or endothelin receptor antagonists, are only moderately effective in a subset of patient populations and have toxic side effects. Previous studies have uncovered the influence of oxidative stress and inflammation on the vascular remodeling process, creating a target for therapeutic intervention for PH. Novel therapies using antioxidant inflammation modulators (AIMs) have been shown to have a protective effect against inflammation and oxidative stress and are being developed for use in other diseases like obesity and metabolic syndrome. However, AIMs usually lack the site specific distribution that is necessary for it to be an effective lung therapy and thus needs to be developed as targeted therapeutics. The overall hypothesis of this project is that targeted delivery of AIMs specifically to the lungs can be developed for the treatment of PH. For this study, we have identified a possible AIM, Compound B, that we propose can be further developed as a targeted therapeutic for the lung vasculature.

Methods
Antioxidant activity of Compound B was first assessed using OxiSelect total antioxidant capacity assay. We then conducted a pilot study in C57BL/6J mice. 4-week old male mice were kept in hypobaric hypoxic conditions (at a simulated altitude of 18,000ft and 10% oxygen) for 21 days to induce PH. These mice were then given tail vein injections of Compound B up to 3x weekly throughout the duration of the hypoxic treatment. Controls included normoxic mice, and mice that were injected with vitamin C and a SOD mimic as positive controls, and mice injected with PBS as negative controls. The development of PH was evaluated by measuring right ventricular systolic pressure (RVSP). Right ventricular hypertrophy was evaluated by measuring right ventricle and left ventricle + septum weights (RV/LV+S). Pulmonary artery muscularization was evaluated by immunohistological analysis of α-smooth muscle actin in inflation-fixed lung sections.

Results
In the total antioxidant capacity assay, a dose-response assessment of Compound B (17.8 uM to 71.4 uM) ranged from 18 uM to 140 uM copper reducing equivalents. In the mouse pilot study, Compound B, as well as vitamin C and an SOD mimetic, were found to significantly attenuate RVSP (25 mmHg - 33 mmHg) in hypoxic mice when compared to hypoxic mice treated with PBS alone (40 mmHg). In addition, mice treated with Compound B were protected from right ventricular hypertrophy (36.6% RV/LV+S)) compared to PBS treatment (47.5% (RV/LV+S). Lung histology analysis show that in hypoxic mice, Compound B increased neovascularization and decreased pulmonary artery medial wall thickening compared to mice treated with PBS alone.

Conclusion
These findings illustrate the protective effect of Compound B alongside effects of well-known modulators of oxidative stress and inflammation. Given the results of this study, we have determined that systemic delivery of Compound B via tail vein injections were able to successfully reduce the underlying causes of pulmonary hypertension in a hypoxic mouse model. This leads us to believe that it could be used as a treatment for PH by mitigating pulmonary vascular remodeling, right heart abnormalities and increased blood pressure in the lungs. However, localization of Compound B in the lungs is necessary to increase the protective effect against pulmonary hypertension. We plan to conduct future studies in order to optimize the delivery, localization and functionality of Compound B, namely the conjugation of Compound B with a peptide that specifically targets pulmonary artery endothelium and airway epithelia. To improve our preclinical drug development studies, we also aim to develop a device for inhaled delivery of our compound that can increase the ease, consistency and viability of inhaled dosing in rodent models of lung diseases. The name of the AIM compound cannot be shared as of yet, and we have named it Compound B.