

Session/Poster#

Presenter

B04

Huma Ahmed

Internal Medicine Fellow

Advisor(s): Dr. Patrick Geraghty, Pulmonary

Chemical Activation of Protein Phosphatase 2A Slows Progression of Alpha-1 Antitrypsin Deficiency associated Loss of Lung Function

Introduction/rationale to the study: We previously reported that the activity of protein phosphatase 2A (PP2A), a serine threonine phosphatase, is reduced in cells from alpha-1 antitrypsin (AAT) deficient patients. Our group recently demonstrated that chemical activation of PP2A reduces loss of lung function in smoke-exposed mice. Here we hypothesize that treatment with a PP2A activator would reduce loss of lung function decline in aged AAT deficient mice. Methods used: Male and female age-matched Serpina1a-e knockout mice daily received 5 mg/kg of an improved small molecule activator of PP2A, ATUX-792, by oral administration for 4 months. Forced oscillation and expiratory measurements were recorded in each animal using the Scireq Flexivent System. Airspace enlargements were quantified by mean linear intercept measurements. The PP2A activator utilized here, ATUX-792, is a tricyclic-sulfonamide compound with improved metabolic stability and oral bioavailability compared to the prototype PP2A activator used in our previous study.

Results of the study: Long-term ATUX-792 administration resulted in no notable toxicity in mice, with external appearance, behavior, and body weight similar to vehicle groups. As expected, aged AAT deficient animals receiving a placebo had changes in pressure volume loops, airway inflammation, lung compliance, inspiratory capacity and FEV0.05/FVC compared to wild type age matched controls. Importantly, treatment with ATUX-792 reduced progression of these disease parameters in AAT deficient mice. ATUX-792 treated animals had enhanced PP2A activity within their lungs and reduced phosphorylation of MAP kinases.

Conclusions of the study: Our study indicates that the decrease in PP2A activity that occurs in AAT deficiency could be restored by PP2A activators, such as ATUX-792, to slow the rate of lung function decline.