\# 109 Bakr Jundi Advisor(s): Dr. Patrick Geraghty Ph.D.

Targeting S100A9 signaling protects lung function in alpha-1 antitrypsin deficiency

We previously reported S100 calcium-binding protein A9 (S100A9), a damage associated molecular pattern protein, is increased in plasma and bronchoalveolar lavage fluid of COPD patients, and inhibition of S100A9 signaling preserves lung function in animal models of COPD. We also observe higher plasma levels of S100A9 in alpha-1 antitrypsin (AAT) deficient patients and both proteins bind to each other. Here, we hypothesize that targeting S100A9 signaling could counter loss of lung function in AAT deficiency. Primary human bronchial epithelial (HBE) cells were treated with AAT protein prior to S100A9 stimulation. Twenty-four hours later, mRNA was isolated from each study cohort (N=3/group) and RNA-sequencing was conducted to evaluate changes in gene expression between the study groups. Male and female age-matched Serpina1a–e knockout mice were orally administered the S100A9 inhibitor, paquinimod, daily for 4 months and pulmonary function testing was performed using the Scireq Flexivent System. Airspace enlargements were quantified by mean linear intercept measurements. Transcriptome analysis was performed on HBE cells treated with S100A9 with and without AAT. Unsurprisingly, comparison of the control and S100A9 cohorts identified 20 differentially expressed (DEX) genes, primarily involved in cytokine and chemokine signaling. Comparing the S100A9 groups with and without AAT, we identified 7 DEX genes, demonstrating AAT as a negative regulator of S100A9-mediated apoptosis. Paquinimod treatment reduced airway inflammation, airspace enlargements, and loss of lung function in the Serpina1a–e knockout mice. In conclusion, loss of AAT results in elevated circulating levels of S100A9 that impacts HBE inflammation and cell survival. Targeting S100A9 signaling countered loss of lung function in Serpina1a–e knockout mice. Therefore, S100A9 signaling plays a major role in the lung disease associated with AAT deficiency.