Chronic obstructive pulmonary disease (COPD), characterized by the chronic and progressive obstruction of airflow in the lungs is the fourth leading cause of mortality and morbidity worldwide. COPD is a highly heterogeneous disorder resulting from gene-environment interactions. Even in patients with similar limitations in airflow, the clinical presentation can vary significantly from patient to patient.

A fraction of patients with COPD has inherited alpha1-antitrypsin deficiency (AATD). The most prevalent AATD variant is Z, which differs from the normal M variant in the substitution of Glu342 with Lys. Severe homozygous ZZ AATD is related to the significant risk for developing early onset emphysema, especially for cigarette smokers. AAT is one of the most abundant acute phase proteins in human blood and the major inhibitor of neutrophil elastase, and it is considered that the most important role for AAT is to protect lungs from proteolytic damage. According to the current knowledge PiZZ carriers experience a lack of functional AAT in the systemic circulation and the peripheral organs, and therefore are predisposed to the development of lung emphysema. Puzzling is that despite the same PiZZ mutation individuals with AATD show large variability in onset of lung disease, severity of symptoms and the response to the therapy. Some AATD carriers remain clinically asymptomatic lifetime. This variability makes hard to diagnose and to provide medical care for PiZZ carriers. Hence, the identification of bio-markers or "signatures" that can distinguish between AATD-PiZZ phenotypes could improve our understanding of the disease-driving mechanisms and medical care for those who developed disease or are at high risk for developing lung diseases.

In this project we raise the hypothesis that the differences in susceptibility for lung disease among PiZZ AATD carriers may depend on the molecular forms of AAT protein and their divergent abilities to modulate neutrophil biology. We specifically propose that Z AAT polymers (which are present in all PiZ carriers without exceptions) in complex with short hydrophobic fragments of AAT (generated during the cleavage of AAT or *de novo* synthesized) can become a source of pro-inflammatory stimuli for blood neutrophils and neutrophil-induced lung damage. In long term this may lead to the lung disease development. In other words, generation of AAT fragments may be among important factors promoting Z polymer toxicity, neutrophil activation and dysfunction, and development of AATD-related lung disease.

To test this hypothesis we will use i) blood neutrophils from patients and controls, ii) isolated Z and M AAT proteins, iii) C-terminal peptide of AAT (C-36) and iv) specific antibodies against molecular forms of AAT. For experiments we will employ modern technologies for gene expression and protein analysis. Further on we intend to verify our in vitro observations on biological activity of Z-AT, C-terminal peptide and their complexes in the *in vivo* mice model of respiratory inflammation. Likewise, we plan to assess the plasma concentration of Z-AT and C-36 in well-matched unique patient groups: healthy PiZZ, PiZZ with COPD; PiMM with CPD, healthy PiMM, in total 200 subjects. The long-term expertise of our team in AAT research and our recent exciting findings position us well to pursue this promising project. We strongly believe that generated results will improve our knowledge regarding the differences in lung diseases susceptibility among PiZZ carriers.