Chronic obstructive pulmonary disease (COPD) presents the considerable socioeconomic burden. It affects 10-15% of the population over the age of 40 years and is associated with high mortality. It is estimated that COPD accounts for 3 million deaths worldwide annually (1). COPD is the 4th most common cause of death in the world, and it is predicted to rise to the 3rd position by the year 2020 (2). Meanwhile, the mechanisms responsible for the development of disease are not well understood. Thus, currently available therapies do not control, slow down disease progression. It is commonly accepted that neutrophils are the leading cell population in COPD patomechanism and the neutrophil-associated tissue damage is critical for COPD pathology. Yet, data regarding the switch in phenotypes of activated neutrophils (NEUs) under disease and non-disease conditions as well are insufficient.

Activated neutrophils are a major source of enzymes, mainly serine proteinases. In the normal setting, anti-proteinases, such as alpha-1 antitrypsin (AAT) provide an anti-proteinase screen to prevent deleterious effects of enzymes. It is believed that COPD characterized by an imbalance between enzymes and their inhibitors leading to excessive enzymatic activity that can cause lung tissue damage. Accordingly, inherited AAT deficiency is the only confirmed genetic risk factor of COPD even in never smokers. Data coming from our group as well as others show that AAT has broader neutrophil-regulating activities than previously anticipated. Therefore, it might play an important role in controlling neutrophil activation and functions in COPD.

We believe that NEUs phenotypic changes during inflammatory reaction in COPD, especially in terms of dynamic changes in neutrophil surface marker expression, are directly related to the levels of functionally active alpha-1 antitrypsin. Therefore, our research might offer new, pioneer insight into the mechanisms and signalling pathways regulating NEU functional activity (in healthy and COPD subjects). In long term, our findings are expected to provide opening for further research towards new therapies in neutrophil-driven disorders.

Objectives

1. To determine modulatory mechanisms of AAT on neutrophil functions under basal conditions and during pro-inflammatory activation, in vitro.
2. To determine the effect of AAT on peripheral blood and broncho-alveolar lavage (BAL) neutrophil surface receptor expression in COPD patients with a normal (PiMM) and deficient (PiZZ) variant of A1AT
3. To characterize blood and BAL neutrophil phenotype in COPD patients with PiMM and PiZZ variant of A1AT, specifically with regards of the expression of receptors for adhesion, chemotaxis and degranulation
4. To investigate effects of AAT therapy on blood and BAL neutrophil surface receptor expression in COPD patients with AATD.
5. To establish the relationships between changes in neutrophil receptor expression during therapy with AAT and soluble serum markers of inflammation linked to COPD.

To achieve our aims we intend to analyse neutrophils and serum from peripheral blood as well as cells and supernatant from bronchoalveolar lavage (BAL). Biological material will be donated by: clinically matched COPD patients characterized by frequent and rare disease exacerbations (n=10ea), patients with different variants of AAT deficiency (MM and ZZ variant) (n=10ea), AATD patients without/on augmentation therapy (n=10ea) as well as healthy volunteers (n=20).