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The design of a new truncated and engineered Alpha-1 antitrypsin based on theoretical studies: An antiprotease therapeutic for pulmonary diseases

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Alpha1-antitrypsin (α1AT) inhibits a broad range of proteases and protects the lung from neutrophil elastase during inflammation or infection. This inhibitor is an acute phase protein, the plasma concentration of which increases manyfold upon inflammation. The absence or inefficient function of α1AT in the lungs leads to uncontrolled function of elastase and elastin breakdown, resulting in respiratory problems such as Chronic Obstructive Pulmonary Disease (COPD) and emphysema. Association between α1AT and a number of diseases including asthma, rheumatoid arthritis, anterior uveitis and systemic lupus erythematosus suggests that α1AT is not only an anti-inflammatory protein but also an immune system regulator. Besides, researchers have shown that the protease-antiprotease imbalance is an important factor in the pathogenesis of COPD and other pulmonary diseases, such as bronchitis. COPD is one of the most important causes of irreversible lung damage and thus the fourth most common cause of death in the U.S. In this process, exogenous proteolytic enzymes lead to lung damage. Besides different physiological roles of α1AT including the control of insulin secretion, antiprotease activity, protecting β-cells against cytokine-induced apoptosis, acting as an anti-inflammation compound, it is also regarded as an antiapoptotic factor in lung epithelial cells. Therefore, only with appropriate and adequate concentrations of α1AT the lungs' correct function can be maintained. One of the treatment strategies for optimum activity of α1AT during inflammation is replacement therapy using intravenous infusion (Prolastin, Zemaira, Aralast and Glassia). In the infusion form, only 10%-15% of α1AT reaches the target organ. Another possible treatment strategy is through airway delivery. In this form of treatment not only the aerosolized α1AT directly reaches the target organ, but also prevents the accumulation of excess drug in the blood, therefore, a much lower level of drug is required.

The pulmonary drug delivery strategies for protein and peptide-based medicines are based on using particles with a lipid origin (liposomes) and polymeric particles (PLGA, Chitosan).

α1AT involves being internalized by endothelial cells mostly by the process of clathrin-mediated endocytosis. In the case of particle uptake, clathrin-coated pits expand and enclose particles of around 200 nm. In addition, particles with an aerodynamic diameter of less than 0.1μm are able to reach the deepest regions of the lung, the alveoli. Therefore my research focused on PLGA nanoparticles for engineered α1AT for targeted delivery to the lung. Engineered α1AT was newly constructed through fermentation in yeast and purified using a novel technique. Subsequently, PLGA nanoparticles incorporating α1AT were synthesized and characterized for targeted delivery to the lung. Different nanoparticles were prepared and nebulized for the rabbit lung perfusion experiment.

Key words: protein purification, structure-based-drug design, bionanotechnology, biotechnology, yeast, fermentation, drug delivery, lung disease, protein engineering