Description for the general public project entitled: "7,8-disubstituted theophylline derivatives that are potent inhibitors of selected PDE isoenzymes as a new compounds with the potential limiting bronchial tree remodeling in asthma - in vitro and in-vivo studies"

Bronchial asthma is a chronic inflammatory disease of the lower respiratory tract. In recent years there has been a high prevalence of this disease particularly in highly industrialized and developing countries. Bronchial asthma affects people of all ages, but among children is the most common chronic disease. Asthma accompanies the patient throughout life, causing bothersome symptoms and in extreme cases, uncontrolled or poorly treated, it can lead to patient death. The main symptoms of asthma include a troublesome cough, chest pain, wheezing, and shortness of breath. Chronic inflammation ongoing in the airways is primarily responsible for the development of this disease. In the course of the disease immune cells infiltrate the bronchi of patient and release various cytokines and growth factors. These compounds have an adverse effect on the whole structure of bronchial tree. Prolonged exposure to these compounds lead to irreversible changes in the structure of the whole bronchi, known as airway remodeling. The effect of remodeling is primarily a narrowing of the airway lumen, which leads to reducing the amount of air flowing through them. While the contemporary pharmacotherapy of bronchial asthma copes with chronic inflammation, remodeling is still a major problem in the treatment of this disease.

One of the drugs that poses anti-inflammatory and spasmolytic properties is theophylline. The usage of this drug in bronchial asthma, due to side effects is of marginal importance. It is worth noting that theophylline is an inhibitor of phosphodiesterases, enzymes of particular significance in escalation of inflammatory reactions. Recently, a group of this inhibitors is sought for new, potential anti-asthmatic drugs. In our team the group of new 7,8-disubstituted theophylline derivatives has been synthesized. These compounds are special as they possess anti-inflammatory activity but above all can simultaneously inhibit the activity of several phosphodiesterases isoenzymes. The preliminary results of our research on their anti-fibrotic activity are extremely promising and lead to further evaluation of their properties.

Airway remodeling is a multistep process. It is well known that significant role in this process play: increased proliferation of smooth muscle cells and fibroblasts, fibroblasts to myofibroblasts transition, increased secretion of extracellular matrix proteins, as well as irreversible changes in the epithelium. Therefore, during the project experiments using *in vitro* models of epithelial cells, smooth muscle cells, and fibroblasts will be used. The impact of a 7,8-disubstituted theophylline derivatives on the processes underlying gene expression, determining the level of intracellular marker proteins of fibrosis, and cellular secretion of various components of the extracellular matrix of the connective tissue will be examined. The studies will be performed at a number of cell lines treated with cytokines and growth factors present in the bronchial tree person suffering from bronchial asthma. In order to better understand the anti-asthmatic properties of 7,8-disubstituted theophylline derivatives for the two most active compounds, experiments in the mouse bronchial asthma model will be performed. This will allow the actual determination of the antifibrotic potential of the tested compounds in mice in which the bronchial asthma will be experimentally induced.

The obtained results will answer the question of whether a group of newly synthesized 7,8-disubstituted theophylline derivatives are compounds favoring inhibition of the bronchial tree reconstruction, as well as what is the mechanism of their activity in various cells involved in the remodeling process. Undoubtedly, the results of this project will expand the current knowledge about remodeling processes of bronchial tree in asthma. They will open a new horizon in the searching for multidimensional acting drug, efficient in curing this touching more and more people around the world disease.