Targeting UDP-glucose and P2Y$_{14}$ receptor interaction for therapeutic modulation of inflammatory lung diseases

Lung diseases are some of the most common medical conditions in the world. Entities such as asthma or idiopatic pulmonary fibrosis are the result of ongoing inflammatory processes. Asthma is a chronic disease of the bronchial tubes, where the airways overreact to external factors like smoke, air pollution, and allergens. The bronchial tubes become narrower due to the ensuing inflammation in the tissue lining the airways. This results in the symptom of dyspnea, where the patient complains on trouble breathing and has difficulty moving air in and out of the lungs. Pulmonary fibrosis is another chronic lung disease that is related to scarring or thickening of the lungs, which affects oxygen exchange. Often, the cause for this disorder is unknown. Pulmonary fibrosis can produce a dry cough as well as fatigue, unexplained weight loss, and musculoskeletal pain. More recently, the viral infections were brought into the interest of general society, due to COVID-19 pandemy caused by a novel coronavirus first detected in late 2019. This disease, like other viral infections, can cause a dangerous lung complications such as pneumonia and, in the most severe cases, acute respiratory distress syndrome.

Therapies for lung disease can be effective in symptomatic treatment but not curative. They initially consists of corticosteroids, which are associated with multiple side effects, including candidiasis, cataracts, and osteoporosis. **Given that more than 35 million people in the United States live with some chronic lung disease, and the total cost of treatment is estimated at around $154 billion annually, there is a strong need for innovative and effective therapies that can slow the progress of inflammatory lung diseases**.

The Project attempts to provide the proof of concept for potential **application of purinergic P2Y$_{14}$ receptor (P2Y$_{14}$R) antagonists in therapies of selected lung diseases**, associated with the increased release of endogenous pro-inflammatory mediator and P2Y$_{14}$R agonist – uridine diphosphate glucose (UDP-G). This relatively poorly known biological target is characterized by predominant expression on immune cells, which suggests that the P2Y$_{14}$R and its ligands UDP-sugars play a pivotal role in immune or inflammatory responses. The ultimate goal is to propose **novel therapeutic interventions for pulmonary disorders** that would act on their own or would help to reduce the dosing of already approved medications, including glucocorticosteroids and biologics. The Project consists of three main complementary areas (**Figure 1**). It starts with detailed studies on the mechanism of UDP-G/P2Y$_{14}$R interaction on the cellular level, followed by research focused on new applications of existing P2Y$_{14}$R antagonists in lung diseases: asthma with coexisting obesity, viral infections and idiopathic pulmonary fibrosis. Finally, the Project aims at creating novel P2Y$_{14}$R ligands with improved drug-like properties and their application in animal models of lung diseases.

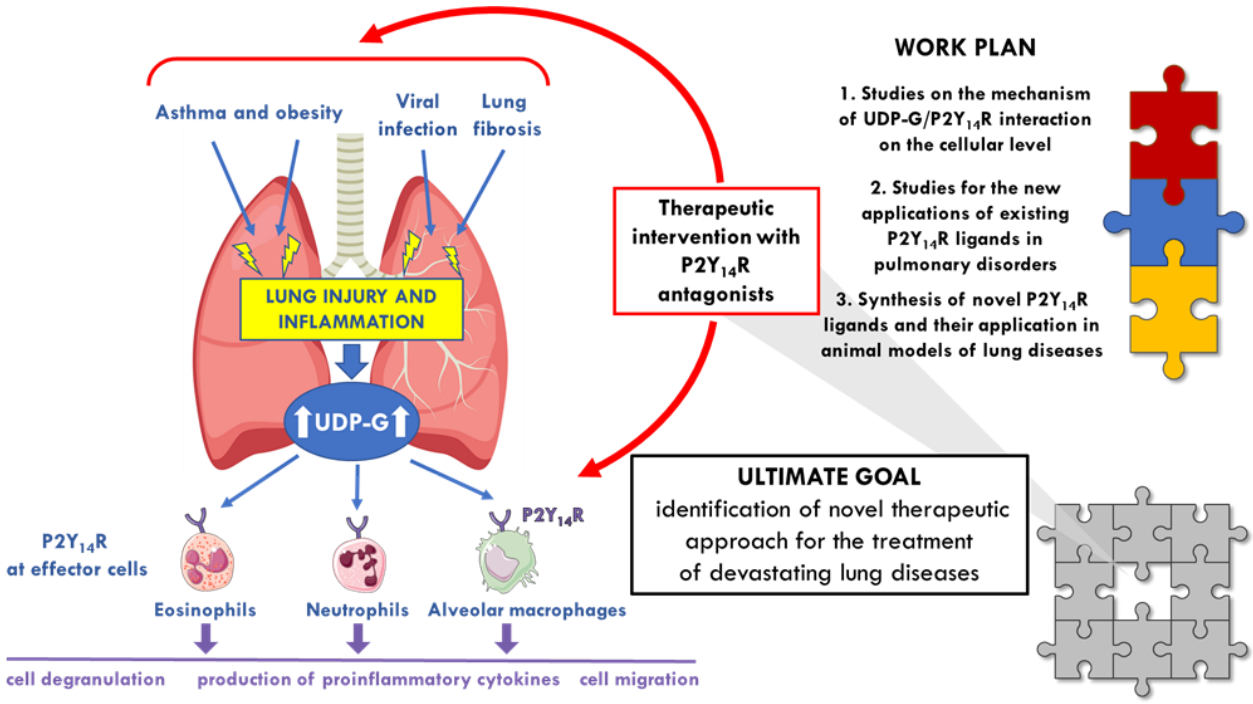

Figure 1. The main assumptions of proposed Project, work plan and the ultimate goal of planned research.

As an outcome of the proposed research we are expecting to verify the potential of P2Y$_{14}$R as a therapeutic target in several pulmonary conditions and to provide novel, improved pharmacological tools that could be used for selective blockade of this receptor in the lung. Successful implementation of studies planned within the Project **may result in the identification of completely novel approach for the treatment of devastating lung diseases, associated with severe pulmonary inflammation**.