Shortness of breath, difficulty in breathing especially after exercise, wheezing, persistent cough are the symptoms characteristic of the most common chronic respiratory diseases - asthma and chronic obstructive pulmonary disease (COPD). About one billion people worldwide suffer from it, which is 1/8 of the world's population, and it is estimated that another 100 million cases will occur by 2025. Both diseases significantly reduce patients' quality of life and create barriers in physical, mental and social spheres. Currently used therapeutic regimens suppress chronic inflammation, provide bronchodilation, but do not affect adverse structural transformations of the respiratory tract. The search for drugs that will affect all major pathological processes in asthma and COPD is an urgent need and challenge for modern science.

As a possible solution for a more effective treatment of asthma and COPD, we propose multi-target-directed ligands with simultaneous phosphodiesterase 4B (PDE4B) and phosphodiesterase 8A (PDE8A) inhibiting activity and TRPA1 ion channel antagonist properties, designed using a rational approach. Such a combination allows to achieve a synergistic bronchodilator, anti-inflammatory and anti-remodeling effects.

PDE4B, PDE8A and TRPA1 are highly co-expressed in airway smooth muscle and inflammation cells involved in the development of both diseases. They show a complementary effect of inhibiting the inflammatory process in the respiratory tract, as well as dilate the bronchi, suggesting a stronger therapeutic effect. In addition, inhibition of PDE8A prevents adverse airway transformation, which broadens the spectrum of activity of the designed multifunctional ligands.

The project includes comprehensive research carried out by computer-aided methods, as a result of which the selected compounds will be tested for their inhibitory activity. New multi-target-directed ligand chemotypes, with triple inhibitory activity at PDE4B, PDE8A and TRPA1, will be selected in virtual screening processes, based on two approaches: focused on the structures of biological targets and on the structures of their known ligands.

In the case of an approach based on the structure of biological targets, virtual screening will be carried out using appropriately generated pharmacophores - three-dimensional maps showing structural features that determine whether a molecule can bind to a potential target. Their development will require properly prepared and validated structural models of PDE8A, PDE4B and TRPA1 ion channel enzymes, which will illustrate the binding modes of their reference inhibitors. The desired models will be prepared using advanced computational methods. Virtual screening carried out in this part of the research will consist of three stages: matching the compounds to pharmacophore hypotheses, docking process and verification of their physicochemical properties and the predicted parameters describing bioavailability and metabolism (ADMET).

Research focusing on ligand structures will rely on developing empirical models based on machine learning and artificial intelligence. As a result of the virtual screening process, the selection of potentially effective inhibitors and the determination of inhibitory activity using the IC50 value will be performed.

Compounds that will be selected in these processes will be purchased and tested for their *in vitro* activity.

This project will result in discovery of potential PDE4B/PDE8A/TRPA1 multi-target-directed ligands, which may be a first step to improve the quality of life for millions of patients suffering from asthma and chronic obstructive pulmonary disease.