Autoimmune hepatitis (AIH) is a disease in the course of which it comes to a loss of immune tolerance to liver tissue, and in consequence it results in liver inflammation. This disorder, if not treated properly, results in cirrhosis and liver failure, when liver transplantation remains the only treatment option. Nevertheless, even if treatment is implemented, some patients do not achieve remission. The gold standard of treatment of AIH is an immunosuppressive drug azathioprine in combination with a corticosteroid - prednisolone. However, both of these drugs have serious adverse effects.

In recent years phosphodiesterase (PDE) inhibitors have been widely investigated compounds as a potential treatment of many inflammatory and autoimmune disorders. Especially, selective PDE4 inhibitors but also PDE3, PDE7, dual PDE4/7, and PDE3/4 inhibitors are developed and studied in this group of conditions. These enzymes are located in many immune cells and inhibitors of PDEs exhibit anti-inflammatory and immunomodulatory activity by decreasing the levels of pro-inflamatory cytokines that are present in high amounts in these diseases. Moreover, some PDE inhibitors may have an impact on the count of some immune cells, which are engaged in AIH development. Simultaneous inhibition of PDE3, PDE4, and PDE7 may improve the therapeutic effect obtained following selective inhibition of these PDEs, as well as that obtained using conventional therapy of AIH, and thus, provide a new potential strategy of treatment of this disease. The aim of this research project is to evaluate the anti-inflammatory and immunoregulatory activity, as well as the nature and the potency of possible interactions between selective PDE3, PDE4, and PDE7 inhibitors both, in vitro and in vivo. Based on the information obtained in these studies a new PDE inhibitor, with the most favourable PDE inhibitory profile, will be selected from the available library of newly designed compounds and assessed in a murine model of AIH.

This project is subdivided into several phases. In the first phase, pharmacological investigations will be carried out in vitro to assess the potency of selective PDE inhibitors as agents that modulate the innate immune response. Subsequently, interactions between selective PDE inhibitors will be assessed. Results from this part of the study will allow to determine the effective concentrations of each investigated compound and to choose the most beneficial combination of the tested PDE inhibitors. Then, a pharmacokinetic experiment will be carried out. All investigated compounds will be administered to mice. The collected biological material will be subjected to HPLC analysis in order to measure concentrations of the investigated compounds. These data will enable to choose appropriate doses and the most beneficial combination of the investigated compounds for in vivo pharmacodynamics studies. Then, investigated PDE inhibitors will be administered in combinations in a murine model of AIH to check whether simultaneous inhibition of PDEs may improve the therapeutic effect obtained after selective PDE inhibition. Finally, a non-selective PDE inhibitor, from an existing library of newly synthesized compounds, with the most promising PDE3/4/7 inhibitory profile will be selected and tested in AIH murine model. Advanced computational methods will be used in this project, such as isobolographic, combination index, and pharmacokinetic analyses and PK/PD modelling.

This project will provide the knowledge about effects of simultaneous inhibition of all three investigated PDEs. There is a lack of PK/PD models, which could be used in the development of new drugs for the treatment of AIH. The PK/PD models developed in this project can be used by other research groups not only to quantitatively assess the activity of new drugs for the treatment of AIH, but also to prepare simulations in order to design further experiments. The results of this project may contribute to the indication of new methods of treatment of AIH, as well as to set the new pathways for the search for drugs in other autoimmune diseases. The treatment and monitoring of AIH is very expensive due to the need for numerous hospitalizations and, in some cases, the need for liver transplantation. The development of new, more effective methods of treatment of AIH may increase the percentage of patients who will achieve complete remission of the disease. The conducted studies will allow to broaden knowledge on the immunomodulatory activity of PDE inhibitors used both in monotherapy and in combination. The extent and nature of pharmacodynamic interactions between inhibitors of PDEs assessed in this project can be used in design of new non-selective PDE inhibitors with the optimal profile of inhibition of PDEs for the treatment of AIH, as well as other autoimmune diseases. Based on the results obtained in this project, it will be possible to develop dosage regimens of the selective PDE inhibitors to be used in combination to achieve an optimal anti-inflammatory and immunomodulatory profile of action. Results of this project may also contribute to a better understanding of the immunological mechanisms leading to development and participating in the course of AIH.