CYP2E1 is one of the main members of cytochromes P450 superfamily, which is primarily found in the liver and to a lesser extent, in extrahepatic tissues, including intestines. CYP2E1 is responsible for the metabolism of many compounds with toxicological importance, such as ethanol. The enzyme generates toxic intermediates and may produce excessive amounts of reactive oxygen species (ROS). Therefore, the activity of CYP2E1 has been implicated in various pathophysiological conditions. Current literature shows that overactivity of intestinal CYP2E1 leads to the loss of intestinal wall integrity and contributes to the development of the leaky-gut syndrome (LGS). It was demonstrated that the presence of CYP2E1 is necessary for the development of epithelial hyperpermeability in cellular and animal models of alcohol-induced LGS. Moreover, similar results were observed after treatment with fructose, which is one of the main dietary factors increasing intestinal permeability. It was showed that high doses of fructose increased the levels of intestinal CYP2E1 protein in rodents and caused LGS. Genetically modified mice without CYP2E1 gene were fully resistant to this effect.

LGS is observed in numerous gastrointestinal (GI) disorders, including inflammatory bowel diseases (IBD). The main diseases belonging to the group of IBD, ulcerative colitis (UC) and Crohn's disease (CD) are characterized by chronic and relapsing inflammation affecting the GI tract. It is well-established that the activity of CYP2E1 may contribute to the severity of inflammation due to the production of ROS. Current literature suggests that ROS play key roles in the pathomechanism of IBD.

In preliminary studies, we observed that diallyl sulfide (DAS), a selective inhibitor of CYP2E1 maintained intestinal epithelial barrier integrity and alleviated inflammatory response in vitro. We hypothesize that other selective CYP2E1 inhibitors may share similar beneficial properties. Our findings highlight that future studies on the role of intestinal CYP2E1 in pathological states are needed.

The main aim of the project is to evaluate the effect of CYP2E1 inhibitors as potential drugs maintaining intestinal permeability and alleviating intestinal inflammation *in vitro* and *in vivo*. So far, the effect of CYP2E1 inhibition on the pathophysiology of GI tract was evaluated by the use of non-selective inhibitors. Hence, in this project we plan to evaluate the action of selective ones. The additional purpose is to analyze the changes of intestinal CYP2E1 expression. Although intestinal CYP2E1 is found in rodents and humans, still little is known about its expression in inflamed intestinal tissues. In this project we plan to examine the changes of CYP2E1 level in the gut during inflammation in mice and IBD patients.

In *in vitro* phase, we intend to verify the hypotheses that treatment with selective CYP2E1 inhibitors protects against increased permeability and ameliorates inflammatory response of cells mimicking human intestinal epithelium. In second phase, we plan to evaluate the influence of CYP2E1 inhibition on epithelial barrier integrity and inflammation *in vivo*. We will use mouse models reflecting LGS and intestinal inflammation. We plan to analyze CYP2E1 expression as well as verify whether the treatment with CYP2E1 inhibitor prevents development of GI disorders. In clinical part, we will perform analysis of the CYP2E1 expression in inflamed colon samples from humans. Moreover, we will investigate into potential associations between CYP2E1 level and selected disease parameters of IBD.

Realization of this project will increase the knowledge about the role of CYP2E1 in the pathological states of the gut. Evaluation of the effects of CYP2E1 selective inhibitors may bring additional opportunities to develop novel therapeutics for IBD and LGS. The incidence and prevalence of IBD are high and still increasing. In Europe, approximately 2.2 million people suffer from CD or UC. As a result, healthcare systems experience high direct costs associated with consultations, diagnostic procedures and drug therapies. Additionally, IBD sufferers incur indirect costs related to workplace productivity losses. Unfortunately, current therapies for IBD are not optimal and pose risk of serious adverse effects or lack of expected efficiency. Moreover, effective drugs for LGS are also desirable since current treatment is based on dietary recommendations alone.