Primary biliary cirrhosis (PBC) is an incurable, long-term liver disease, characterized by the blockage of bile flow. As a consequence bile builds up in the liver and irreversibly damage the liver cells leading to the scarring called cirrhosis and in the end liver failure. The obstruction of bile flow is accompanied by the ongoing inflammation what is manifested by the presence of autoantibodies in sera of PBC patients. PBC affects primarily middle-aged women and often is associated with complications severely affecting the physical and psychological condition of patients such as: fatigue, pruritus, maldigestion and liver cancer. **The exact etiology of disease is unknown, although it is widely thought to be the result of impaired immune response. To provide more information about immune-madiated pathogenesis of PBC we decided to decipher the epigenetic regulation of immune system, focusing on microRNAs (miRNAs)**.

`miRNAs represent an important class of small regulatory RNAs that are vital in the post-transcriptional gene control. Circulating miRNAs, which are extremely stable and protected from RNAse-mediated degradation have emerged as candidate biomarkers for many diseases. In autoimmune diseases miRNAs might, on the one hand, modulate inflammatory response underpinning immune homeostasis. On the other hand this molecules might be used as a hallmark of disease progression. **Taking into account the information mentioned above we aim to identify the microRNAs which modulate the immune response in PBC. The studies will allow us to gain knowledge about disease etiology and in future, might contribute to the improvement of . PBC treatment.**

The preliminary results from the liver miRNAs expression profile in PBC patients confirmed the altered expression of several high immunogenic miRNAs. We have chosen four which are known to regulate the maturation and differentiation of lymphocytes, the production of pro-inflammatory cytokines as well as the secretion of chemokines. Therefore, they might be a valuable indicators of distinctive changes specific for immune response in PBC.

Owing to the collaboration with Hepatology and Internal Medicine Unit, Warsaw Medical University, the studies will be carried out on a cohort of more than 300 patients with PBC. In the beginning, we plan to perform a detailed analysis of the chosen miRNAs in sera, peripheral blood mononuclear cells (PBMCs) and liver tissue samples. The analysis will be expanded to include additional information on cytokines and TGFβ level in sera of PBC patients. Cytokines and TGFβ are signature of immune system activity, centrally involved in the pathogenesis of autoimmune diseases. Therefore, to highlight the complex interplay between miRNAs and inflammation in PBC, we will evaluate the correlation between cytokines, TGFβ and microRNAs. Moreover, to have knowledge about disease progression, we will took into consideration the information concerning clinical features of PBC patients.

In the next step of our studies, we will check the influence of analyzed miRNAs on a tight regulation of cellular proteins expression in liver tissues and in PBMCs of PBC patients. The evaluated proteins are known to fulfill immunomodulatory function and to be postranscriptionally regulated by the studied microRNAs.

Finally, to better understand the causative factor of PBC progression we aim to examine the possible mechanisms which may induce miRNA expression. Inflammation in PBC is accompanied by nitrosative stress, generated by the release of nitrogen monoxide (NO) by inducible NO synthase (iNOS). NO known as a inflammatory mediator is able to trigger miRNAs expression. Therefore, we will investigate the impact of nitrosative stress, on miRNA expression in cultured hepatocytes and cholangiocytes.

The PBC etiology is an ongoing challenge to all those investigating this disease. Lack of knowledge is the reason why, up to now, the treatment of PBC does not allow to cure patients but only slow disease progression. In our project we aim to better understand the PBC pathology focusing on epigenetic modulation of immune system by microRNAs during disorder developement. A large cohort study will produced many important links between miRNAs expression and immune response in PBC patients. **The expected results will enable to acquire new knowledge which might be used in future clinical researches.**