The main goal of this research proposal, is to determine how RNase Mcpip1 regulates and controls cholangiocyte pathobiology.

Cholangiocytes account for 3-5% of hepatic cell population and line intrahepatic biliary ductal system. These cells are important in many physiological liver processes, mainly in the regulation of bile flow and composition. The biliary tree can be affected by a diseases called cholangiopathies. Most of them are complex diseases of unknown etiology and pathogenesis, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Most often cholangiopathies are caused by dysfunction of cholangiocytes that progresses chronically, leading to end-stage liver diseases. Cholangiopathies are rare, but they account for up to 20% of liver transplantations in the adult population and up to 80% in the pediatric population. Although these diseases are classified as an autoimmune disease, factors leading to their development are not fully understood. That is why, the investigation of causes of these diseases which can further lead to development of an effective treatment strategies is very important.

The MCPIP1 protein, encoded by the *ZC3H12A* gene, degrades transcripts coding for proteins involved in e.g. inflammatory processes. Our preliminary studies have shown that livers of mice with deletion of Mcpip1 in liver epithelial cells, namely hepatocytes and cholangiocytes, are characterized by hyperplasia of bile ducts, infiltration of immune cells and fibrosis which resemble PBC. Additionally, the level of IgG and IgM in plasma of 6 weeks old and 6 months old knockout mice is significantly increased when compared to control animals. That is why, assessment of the MCPIP1 role in the context of biliary pathobiology would be valuable. Also, our preliminary data indicate that MCPIP1 is highly expressed in human cholangiocytes among other liver cell types. Therefore, we postulate the potential important role of MCPIP1 in cholangiocyte pathobiology.

Our project is going to expand current knowledge about the involvement of MCPIP1 in development of biliary pathology. Firstly, we will identify key molecules regulated by Mcpip1, that are responsible for proper function of cholangiocytes. Then, we will overexpress Mcpip1 in livers of mice subjected for damaging compounds to evaluate its protective effect during liver injury. Moreover, we will analyze if deletion of Mcpip1 only in cholangiocytes will also effect in development of PBC symptoms. Finally, we are going to examine PBC influence on MCPIP1 protein level liver biopsies collected from patients.

We believe, that investigations planned in this grant will help to understand the molecular mechanisms responsible for protective role of MCPIP1 in the liver homeostasis. We hope, that such data may potentially help to establish new effective therapies.