Title: Explanation of antifibrotic Mcpip1 role in the liver

The main goal of the project is to **explain the antifibrotic role of MCPIP1** (Monocyte chemoattractant protein-induced protein 1) **in the liver.**

Hepatic fibrosis is a common feature of non-alcoholic steatohepatits, HCV infection, alcoholic liver disease, cholestatic disorders and autoimmune hepatitis. It is characterized by enhanced deposition of extracellular matrix (ECM), which results from the wound-healing response of the liver to the chronic, repeatable injury. ECM replace damaged cells, forming a scar tissue, which disturb liver architecture and can further result in organ dysfunction The end stage consequence of long-term untreated fibrosis is a liver cirrhosis, which can have poor outcome and high mortality. Cirrhosis affects the hundreds of millions people worldwide. The main clinical consequences of cirrhosis are liver failure and portal hypertension. It is estimated, that liver cirrhosis is responsible for over 1 million deaths per year globally. The only therapeutic approach for patients with decompensated cirrhosis is liver transplant. It is the leading cause of adult liver transplants in Europe – with around 60,000 of transplants performed between 1988 and 2013. Cirrhosis is also associated with increased risk of development of hepatocellular carcinoma, which is also one of the major cause of premature death. Currently, the most effective way of elimination of fibrosis is the removal of profibrotic factor, by treating the primary cause of liver disease. However, in many cases it cannot be eliminated, or the reversal may not be quick enough to prevent serious liver damage. Several clinical trials are aimed to study effects of various antifibrotic drugs, but the effectiveness of these compounds often depends on the disease etiology, so not every patient could be treated the same way. Importantly, despite an extensive studies, an effective antifibrotic therapy approved for human use has not been developed yet.

The MCPIP1 protein, encoded by the *ZC3H12A* gene, degrades transcripts coding for proteins involved in e.g. inflammatory processes. At present, results concerning involvement of MCPIP1 in the process of fibrogenesis are contradictory. It is known that upon SiO_2 treatment MCPIP1 induces signaling events which can account for development of pulmonary fibrosis, however our preliminary results show that lack of Mcpip1 in hepatocytes promotes liver fibrosis in mice. Therefore, assessment of the MCPIP1 role in the context of liver fibrosis would be valuable.

Based on our preliminary results and the literature data, we postulate that MCPIP1 might be an important inhibitor of liver fibrosis development.

Our project is going to expand the knowledge concerning the involvement of MCPIP1 in the process of hepatic fibrogenesis. Firstly, we will analyze the Mcpip1 level in cells which are involved in liver fibrosis (hepatic stellate cells, hepatocytes, Kupffer cells) isolated from mice treated with carbon tetrachloride, which induces development of hepatic fibrosis. Secondly, we will investigate the molecular mechanism responsible for fibrosis development in mice with hepatocyte-specific deletion of Mcpip1. Screening approaches e.g. Next Generation Sequencing and protein mass spectrometry analysis of whole liver of these mice will help to reveal key profibrogenic factors, which will be further investigated using molecular and *in vitro* studies. Moreover, we will examine if *Zc3h12a* overexpression in murine liver diminishes the development of fibrosis, upon treatment with carbon tetrachloride.

We believe, that investigations planned in this grant will help to understand the mechanisms responsible for involvement of MCPIP1 in the development of hepatic fibrosis. We hope, that such data may potentially help to establish new effective therapies.