Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide, the research shows that the incidence of HCC is almost 2-7 times higher in men compared to women, though this ratio varies between different countries. There are several possible alternatives to this disproportion: one of them is the dependence of HCC development on sex hormones. Research proves that female sex hormones - estrogens, show a protective effect against HCC development, while male sex hormones promote it. More specifically, estrogens inhibit production of several pro-inflammatory cytokines, that is, the proteins that stimulate the activity of the immune system. When this condition persists for long time, it leads to the development of inflammation and consequently HCC induction. Considering that the precise mechanism of HCC progression has not been known, the researchers have developed many mouse models for study this case. One of these methods is the administration of chemical carcinogen - diethylnitrosamine (DEN) to mice between 7 and 15 days of life, because the liver of infant mice is most susceptible to initiation of carcinogenesis. These studies show that long exposure to DEN leads to the development of HCC in almost 100% of males after 32-36 weeks, while in females the effectiveness of the induction ranges from 10-30%.

MCPIP1 protein is a negative regulator of inflammation, because due to ribonucleolytic activity regulates the level for several pro-inflammatory cytokines. Additionally, MCPIP1 protein plays an important protective role in cancer progression. The level of MCPIP1 decreases during the progression of breast cancer and clear cell renal cell carcinoma (ccRCC). MCPIP1 protein also inhibits several microRNA (miRNA) biogenesis by cleavage miRNAs precursors. miRNA is a small RNA molecule which, by regulating the expression of various genes, influences many cellular processes e.g tumor growth and metastases.

In our preliminary studies, we induce HCC development by DEN administration to control mice and mice without MCPIP1 protein in liver. The results show that the induction of HCC after DEN administration differs between male and female mice and is dependent on MCPIP1 expression. In males mice, the differences between groups were not statistically significant. In the control female mice, tumors did not develop, however, female mice lacking the MCPIP1 protein developed tumors in almost 100%. Additionally, the results indicate a different mechanism of HCC development in females and males mice.

The aim of the project is to study the molecular mechanism behind the differences in HCC development in females and males. Based on current knowledge we assume that MCPIP1 can modulate the estrogen signaling pathway in our model. Moreover, we suppose that HCC progression in female mice deficient in MCPIP1 protein is regulated by some miRNAs. The project is innovative and will contribute to expanding the current state of knowledge, because the participation of the MCPIP1 protein in HCC progression and the influence of the MCPIP1 protein on the signaling pathway for estrogens has not yet been studied.