# Exploring mechanisms of therapy-facilitated metastasis and the role of CAAX proteins-processing enzymes in liver cancer

Therapy resistance and development of metastasis is the major cause of cancer-related mortality. It is widely accepted that changes in cell-cell contacts, cell shape, and invasiveness are central for acquiring a metastatic competence and that tumor environmental factors profoundly affect these processes. Therefore, a better understanding of mechanisms governing metastasis development is not only important from a basic biology perspective, but can also lead to new therapies and diagnostic modalities.

Hepatocellular Carcinoma and intrahepatic Cholangiocellular Carcinoma are primary liver cancers with limited effective treatment options and very poor prognosis. The majority of liver cancer patients die within five years from diagnosis, primarily due to local relapse or development of metastatic disease. However, the exact mechanisms responsible for the relapse and metastasis are not fully elucidated. For example, it is not clear whether all liver cancer cells are metastasis-competent or whether there are some specific cell subsets which are able to disseminate. Similarly, the impact of the local tumor microenvironment on acquisition of metastatic traits and how to influence these traits for the benefit of patients is still in infancy.

We developed a new mouse model of liver cancer, wherein expression of a strong oncogene is selectively induced in a liver and results in the development of metastatic liver cancer. We found that a liver cancer cell capable of seeding distant metastases bears highly fibroblast-like, sarcomatoid features, suggesting that it was generated through a process of epithelial-to-mesenchymal transition. In this process, epithelial cancer cells acquire mesenchymal appearance and behavior facilitating metastasis. Moreover, we found that treating these mice with a selective inhibitor of the initiating oncogene increased the metastasis incidence. In an attempt to explain the increased metastasis, we used RNA sequencing and identified a purported drug-induced, metastasis-promoting factor.

The goal of this project is to define which cells in the liver are responsible for metastasis formation and exploration of how the expression of the identified pro-metastatic factor is regulated by oncogene-targeting drug. In addition, we will determine the role of post-prenylation enzymes in the development and metastasis of liver cancer using knockout mice.