RECIPRO-CRC: Reciprocal relationships in metastatic colorectal cancer and its niche – from adaptation to host organs to induced parenchymal progenitors

This proposal introduces RECIPRO-CRC, a study focused on the reciprocal interactions between metastatic colorectal cancer (CRC) and the specific microenvironments of the liver and lungs, where the cancer develops during metastasis. The project aims to understand how cancer cells adapt to the unique conditions of these organs and affect surrounding healthy tissues (parenchyma). The initiative will be carried out through the collaboration with Swiss team from ETH Zürich, combining our complementary expertise and resources.

Colorectal cancer is the third most commonly diagnosed cancer worldwide, posing a serious public health challenge. Metastases to the liver and lungs are the leading cause of deaths related to CRC. Although genetic differences between primary tumors and metastases may be minor, significant changes in gene expression often occur due to local environmental factors specific to the affected tissues. Investigating these changes, especially in CRC lung metastases, which are less frequently resected and, therefore, less well-studied, is crucial for advancing our understanding of metastatic CRC and developing new therapeutic strategies.

Not only does cancer adapt to its surrounding environment, but also actively transforms nearby healthy tissues to promote metastasis. An important mechanism in this context is reflected stemness, where normal cells in the surrounding tissue are transformed into progenitor-like cells that actively support tumor growth. While the proliferation of progenitor cells near liver metastases has been observed for years, the potential role of reflected stemness in metastasis has only recently gained attention. These transformed cells are now considered key players in regulating tumor growth, modulating immune responses, and reshaping the structure of the tissue surrounding the tumor.

RECIPRO-CRC adopts a holistic approach to CRC, treating it as a disease of the entire tissue rather than solely the cancer cells. A central component of the project is a comprehensive collection of archival metastatic tissue samples and associated clinical data, curated by the Polish team. Using advanced molecular techniques, including whole-exome sequencing, spatial transcriptomics, and single-nucleus RNA sequencing, the team will create a detailed molecular database of this unique clinical material and identify factors driving organ-specific metastasis. The Swiss team will complement these efforts by investigating mechanisms of progenitor cell transformation through technologies such as CRISPR screens, advanced mouse models, and in vitro systems. Validation of selected factors and their impact on cancer progression and the surrounding tissue environment will be conducted using advanced spatial biology tools.

RECIPRO-CRC aims to fill critical knowledge gaps regarding the mutual adaptations between metastatic CRC and its microenvironments in the liver and lungs. Alongside advancing fundamental understanding of cancer biology, the project has the potential to identify new biomarkers and therapeutic targets, enabling more effective strategies to combat CRC metastasis.