Cancer cells of solid tumors, including colorectal cancer, are prone to oxygen deprivation (hypoxia) as a result of excessive tumor growth coupled with increased distance between cells and blood vessels. Unfortunately, cancer cells can adapt to this undesirable microenvironment by triggering specific transcriptional program mainly dependent on gene activation by transcription factor, hypoxia inducible factor. Importantly, transcriptional activity is substantially modulated by the chromatin context, which has great influence on the binding ability of a transcription factor to its genomic target sites. During hypoxia, various chromatin alterations are observed, but the exact role of epigenetic modifications in hypoxia adaptive response was largely not investigated so far. All experiments implying the role of epigenetic changes in hypoxic response were performed so far only for selected chromatin factors implying that many factors are still undiscovered. Consequently, our objective is to identify crucial chromatin factors in hypoxia response in a highly innovative and unbiased approach. We aim to investigate more than 1100 chromatin-associated genes using advanced multiplexed RNAi screening technologies and functionally characterize the most promising ones using various advanced methods.

The identification of novel epigenetic modifiers in hypoxia will have a significant impact on the field of cancer research. Low tumor oxygenation negatively affects patient prognosis and HIF-driven responses severely decrease the efficacy of both ionizing radiation therapy and chemotherapy. Even cancer resection results in the lower outcome as occurrence of hypoxic regions promotes invasion and metastasis. Consequently, this project will also identify crucial chromatin factors as biomarkers of specific hypoxia-activated programs within colorectal cancer cells and as potential targets of novel therapies to improve patient outcome.