Spatial gene-regulomics to study T-lymphocyte tumor niches

Gene regulation fine-tunes gene expression to drive cellular functions, enabling cells to interact and contribute to tissue functionality, including the immune system's response to cancer. In multiple tumor types, as cancer progresses, T-lymphocytes become increasingly dysfunctional. While therapies targeting their restoration have shown promise, the gene regulation mechanisms underlying their dysfunction within the tumor microenvironment remain poorly understood. *In situ* sequencing has recently emerged as a powerful tool to measure and localize thousands of RNAs in tissue samples, adding a spatial dimension to transcriptomics. However, a significant challenge persists in understanding the spatial regulation of genes, beyond their expression. This proposal aims to bridge gene regulation studies with *in situ* sequencing through the development of a novel *in situ* "gene-regulomics" platform to understand how genes drive tissue function. We seek to advance our understanding of "tissue niches" by examining the spatial co-regulation of resident cells' genes. Through this approach, we expect to uncover new mechanisms leading to the progressive disruption of T-lymphocytes' tumor-killing potential. Specifically, the first goal of this proposal is to newly define T-lymphocyte niches in colorectal cancer (CRC), the second deadliest tumor globally. We will then reveal how key genes are spatially (dys)regulated within each niche. Finally, we will extend our insights to multiple clinically-relevant human CRC samples. Our study will bridge innovative imaging-based molecular data with clinical significance, elucidating the links between gene regulation and the architecture of T-lymphocyte niches in cancer. These newly defined functional units are poised to become effective targets for enhanced cancer therapies.