Identifying acquired vulnerabilities driven by lineage plasticity and drug resistance in CRC

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Abstract**:** For many decades, tumor evolution and progression were believed to be due in large part to the sequential acquisition of cancer driving genomic mutations that induced oncogenic pathways to promote growth and metastasis. Colorectal cancer (CRC) was an archetypal example, whereby the Vogelgram depicted the series of genetic events leading to malignancy. Recent work from our labs and others have revealed the emergence of nongenetic, fetal and regenerative transcriptional programs that are linked with drug resistance and metastasis. The similarity of regenerative signatures across different contexts suggests it may be a common path in tumor progression, but no study has investigated how such programs are intertwined in tumor evolution.

In this proposal, we aim to define how the development of lineage plasticity and regenerative programs is influenced by different cell stressors, whether these changes drive metastasis and/or cross-resistance to treatments with distinct mechanisms of action, and whether emergent dependencies could be exploited therapeutically. To do this, we will exploit an extensive collection of patient-derived CRC organoids, including matched primary and metastatic organoids, as well as genetically defined pre-clinical models. We will use single cell technologies to map lineage transitions under therapy and systematically uncover define regulatory nodes through focused CRISPR screens in 3D culture. Understanding and targeting these dynamic changes associated with CRC progression is key to improving activity of existing treatments and developing new and effective therapeutic strategies.