Lung adenocarcinoma (LUAD) is the most common subtype of non-small cell lung cancer (NSCLC), which is observed with activating mutations in epidermal growth factor receptor (EGFR) occur in approximately 27% of patients. As such, multiple tyrosine kinase inhibitors (TKIs) have been developed to target these EGFR mutations. However, despite the initial efficacy of TKIs, acquired resistance to these drugs is a major limitation that hinders treatment. The oncogene amplification, especially in form of extrachromosomal DNA (ecDNA), has been reported to be a common mechanism for acquired therapy-resistance in cancer. My studies have demonstrated that TKI-resistant LUAD cells exhibit oncogene amplification and their hyperactive transcription.

 It is well-known that a small population of cells, termed drug-tolerant persisters (DTPs), survives initial TKI treatment. A preliminary screening of ~100 nuclear factors identify an epigenetic regulator, METTL7A, that is critical for the adaption and clonal selection from DTP to acquired resistance, as well as the long-term maintenance of the resistance cells. My studies suggest METTL7A is essential for the acquisition of TKI-resistance by promoting hyperactive transcription and chromatin remodeling of oncogene amplicons. My studies indicate that the nuclear hubs of oncogene ecDNA play critical roles in supporting hyperactive transcription of the oncogenes. And I hypothesize that METTL7A plays critical role in chromatin remodeling, which facilitate the transcription of ecDNA.

To investigate roles of oncogene amplification and ecDNA in acquired TKIs in LUAD and screen the roles of the epigenetic factors in clonal selection from DTP to acquired TKIs resistance, I developed live-cell DNA imaging systems to characterize the dynamics of oncogene ecDNA and their transcription. Further, I investigate the potential factors that regulate ecDNA organization and its hyperactive transcription via using chemical or genetic inhibition approaches. Additionally, I detect the chromatin deposition of METTL7A and chromatin looping via genetics and genomic approaches to fully characterize the functions of METTL7A in chromatin remodeling and transcription. Further, I detect METTL7A interactome via biochemistry approaches to fully characterize the mechanism of METTL7A by investigating the function of the interacting proteins. This study contributes to our understanding of the mechanism for resistance in anti-EGFR therapy.