**Abstract:**
Increase in the number of copies of tumor promoting (onco-) genes is a hallmark of many cancers, and cancers with copy number amplifications are often associated with poor outcomes. Despite their importance, the mechanisms causing these amplifications are incompletely understood. In this talk, we describe our recent results suggesting that a large fraction of amplification is due to formation of extrachromosomal DNA (ecDNA). EcDNA play a critical role in tumor heterogeneity, accelerated cancer evolution, and drug resistance through their unique mechanism of non-chromosomal inheritance. While predominant, ecDNA are not the only mechanism to cause amplification. We also describe recent algorithmic methods required to distinguish ecDNA from other mechanisms including Breakage Fusion Bridge formation, Chromothripsis, and simpler events such as tandem duplications and translocations. The talk is a mix of published and unpublished work, largely in collaboration with Paul Mischel's lab at UCSD. EcDNA was recently recognized as one of the grand challenges of cancer research by Cancer Research UK and the National Cancer Institute.

**Suggested Readings:**
- AmpliconReconstructor integrates NGS and optical mapping to resolve the complex structures of focal amplifications
- Extrachromosomal Oncogene Amplification in Tumor Pathogenesis and Evolution