Colon cancer is a common and deadly form of cancer. Despite its prevalence, identifying and validating novel therapeutic targets has been a major challenge. While targeted and immune-based therapies are revolutionizing the treatment of many other cancers, colon cancer has remained refractory to these approaches. To address this need, we have been conducting kinome-wide screens to identify kinases involved in healthy colonic epithelial proliferation and colon cancer. We found Glycogen Synthase Kinase 3 (GSK-3) is a protein kinase uniquely positioned to act as a signaling by-pass for cancer cells to evade targeted therapies. We have shown that GSK-3 suppression can affect the cellular sensitivities to a broad spectrum of chemotherapies and targeted oncology drugs (e.g., inhibitors of RTKs, mTOR, PLK1). Combined with a kinome-wide RNAi screen, we have shown GSK-3 is a central drug response modulator that affects potency of ~50% of current, clinically relevant kinase-targeted drugs. Our findings suggest that the re-activation of GSK-3 would have potent anti-tumor activity as single agents or in combination therapies.

Small molecule inhibition of kinase activity is well established as a fruitful therapeutic strategy in oncology. Yet, almost completely neglected is the development of small molecule kinase activators for rationally selected targets. GSK-3 is a strong candidate for small molecule activation due to its many allosteric pockets, its central role in tumorigenesis, and its inactivation in numerous cancers. We are working to discover first-in-class GSK-3 activators by screening compound libraries with a biochemical kinase assay followed by a complex organoid-based secondary screen. From this drug discovery project, we will characterize small molecules that selectively target and activate GSK-3, useful for testing its function in various physiological and pathophysiological settings.