Targeted therapy strategies for gastrointestinal cancers

Our laboratory focuses on targeted therapies directed against specific mutations commonly found in human gastrointestinal cancers, with a focus on BRAF and KRAS mutant cancers. Our work explores the hypothesis that the optimal therapy for individual tumors may vary widely based on the genetic alterations present, and that prior knowledge of these genetic changes and an understanding of the signaling pathways involved will allow us to select an optimal targeted agent or combination of agents capable of inhibiting the critical survival signals within a given tumor. Knowing that cancer cells often become resistant to these targeted therapies by activating alternative signaling pathways, we focus on identifying these key resistance signals in cancer cells. We utilize this information to devise effective combinations of targeted therapies that anticipate and ultimately overcome these mechanisms of drug resistance. Overall, our goal is to develop promising therapeutic strategies that can be evaluated in clinical trials for patients whose cancers are driven by specific mutations.

BRAF mutant colorectal cancer

BRAF mutations occur in 10-15% of colorectal cancers and confer poor prognosis. Interestingly, while BRAF inhibitors have shown dramatic anti-tumor activity in the ~50% of melanomas that harbor BRAF mutations, these agents have been largely ineffective in BRAF mutant colorectal cancers. Therefore, our laboratory has focused on determinants of resistance to BRAF inhibitors in BRAF mutant colorectal cancers. We have identified BRAF amplification as a potential cause of acquired and de novo resistance in BRAF mutant colorectal cancers (Science Signaling, 2010), and have shown that combined BRAF and MEK inhibition can overcome resistance. Additionally, we have found that EGFR-mediated reactivation of MAPK signaling contributes to the relative insensitivity of BRAF mutant colorectal cancers to BRAF inhibition, compared to BRAF mutant melanomas, and that combined BRAF and EGFR inhibition can overcome resistance, leading to tumor regressions in BRAF mutant colorectal cancer models in mice (Cancer Discovery, 2012). We are also focused on identifying additional causes of de novo resistance in BRAF mutant cancers using a combination of preclinical models and
patient tumor specimens. Simultaneously, we are developing biomarkers to predict response to therapy (Cancer Discovery, 2011), including real-time pharmacodynamic assessment of signaling changes in on-treatment patient tumor biopsies (Science Translational Medicine, 2013), and combination therapy strategies to overcome resistance.

**KRAS mutant cancers**

KRAS is the most commonly mutated oncogene in human cancer and is mutated in ~20% of all cancers, with particularly high frequency in pancreatic (~90%) and colorectal cancers (~40%). However, currently no effective therapies exist for KRAS mutant cancers, likely because KRAS itself has proven difficult to target directly with small molecules. Our current work focuses on identifying novel target pathways in KRAS mutant cancers though hypothesis-based and large-scale pooled RNA interference screening approaches to identify other potentially effective targets and therapeutic strategies in KRAS mutant cancers.

**Translational Oncology**

The overall goal of our research is to develop improved treatments for patients with gastrointestinal cancers and to identify molecular markers that may help us identify those patients most likely to respond to a given therapy. As such, our laboratory takes a highly translational approach with a central focus bringing new therapeutic strategies into the clinic for evaluation in novel clinical trials. Based on our observation that combined BRAF and MEK inhibition can overcome certain resistance mechanisms in leads BRAF mutant colorectal cancer models, we developed and completed a clinical trial assessing combined BRAF and MEK inhibition in patients with BRAF mutant colorectal cancer, which showed promising activity in a subset of patients. (ASCO abstract, J Clin Oncol, 2013). Based on our observations that EGFR may contribute to resistance in many BRAF mutant colorectal cancers, we are currently enrolling patients to clinical trials evaluating the combination of BRAF and EGFR inhibitors. Finally, we are developing a clinical trial combining the BCL-XL/BCL-2 inhibitor navitoclax with the MEK inhibitor trametinib in KRAS mutant cancers.

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**Selected Publications:**


* denotes equal contribution