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Corcoran Laboratory

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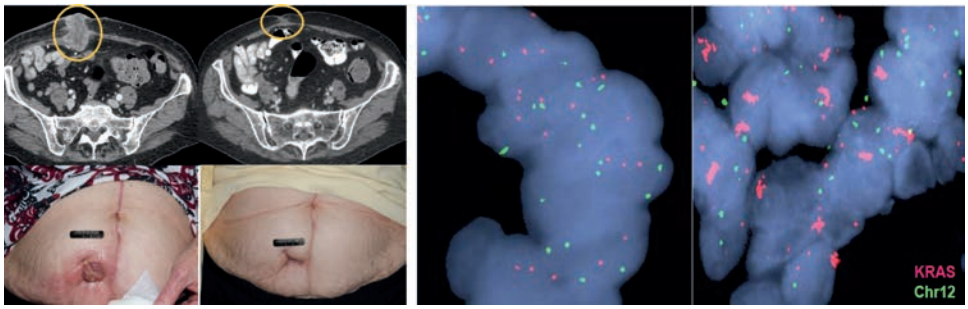
The Corcoran laboratory focuses on developing new and effective therapies for gastrointestinal cancers, including colorectal, pancreatic, stomach, and esophageal cancers, by targeting the specific survival signals that are active in a given patient's cancer. Our research utilizes targeted therapies, which are drugs that inhibit signaling pathways activated by the specific mutations that drive individual tumors. Since 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.

Targeted therapy strategies for gastrointestinal cancers

Historically, the standard clinical approach for patients with advanced cancers has been to treat all patients with the same tumor type with the same generalized chemotherapy strategy. However, even among patients with the same type of tumor, the genetic mutations driving tumor growth in each individual patient can be vastly different. As an alternative approach, by identifying the key gene mutations present in an individual patient's tumor, we can "personalize" therapy by matching each patient with specific therapies that target those mutations essential for tumor growth. Our laboratory focuses on developing targeted therapy strategies directed against specific mutations commonly found in gastrointestinal cancers, including cancers with BRAF and KRAS mutations. However, while targeted therapy strategies can lead to dramatic tumor responses, clinical benefit is often limited by the ability of tumor cells to evolve and develop resistance to therapy. By identifying and understanding the key signals driving resistance, our laboratory aims to devise combinations of targeted agents that can overcome or even prevent resistance.

BRAF-mutant colorectal cancer

BRAF mutations occur in 10-15% of colorectal cancers and confer poor prognosis. While BRAF inhibitors have shown dramatic anti-tumor activity in melanomas harboring BRAF mutations, these agents are 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 found that reactivation of the MAPK signaling pathway (often mediated through EGFR), contributes to the relative insensitivity of BRAF mutant colorectal cancers to BRAF inhibition. However, we found that combining BRAF inhibitors with EGFR and/or MEK inhibitors can overcome resistance, leading to improved efficacy (*Cancer Discovery*, 2012). We have also identified multiple mechanisms of resistance that can arise to these newer BRAF inhibitor combinations, and are utilizing this information to develop therapeutic strategies to surmount resistance (*Cancer Discovery*, 2015; *Cancer Discovery*, 2018).



Pre-treatment Week 16 Pre-treatment Post-progression

Response and resistance in BRAF-mutant colorectal cancer. (Left) Example of a dramatic tumor response in a patient treated with the combination of a BRAF and a MEK inhibitor. (Right) KRAS amplification (red probes) can lead to BRAF inhibitor resistance in BRAF mutant colorectal cancer patients.

KRAS-mutant cancers

KRAS is the most commonly mutated oncogene in human cancer, mutated in ~20% of all cancers, including pancreatic (~90%) and colorectal cancers (~40%). 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 through hypothesis-based and large-scale pooled RNA interference screening approaches, with the goal of developing new targeted therapy combination approaches for KRAS-mutant cancers. Recently, through a pooled RNA interference drug screen, we identified combined targeting of BCL-XL and MEK as a promising therapeutic strategy that leads to dramatic tumor regressions in KRAS-mutant mouse tumor models. We have also identified adaptive feedback signals that impede the ability of MEK inhibitors to suppress MAPK signaling. We have expanded these approaches to identify other potentially effective targets 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 to bringing new therapeutic strategies into the clinic for evaluation in novel clinical trials. Based on our observations, we have launched several clinical trials of BRAF inhibitor combinations in BRAF-mutant colorectal cancers that are showing increased efficacy (*J Clinical Oncology*, 2015). We have also developed a clinical trial combining the BCL-XL/BCL-2 inhibitor navitoclax with the MEK inhibitor trametinib in KRAS-mutant cancers.

To guide our laboratory investigations, we are utilizing key clinical specimens, including tumor biopsies and patient-derived tumor models to understand how tumors become resistant to therapy. We also utilize serial blood collections for circulating tumor DNA analysis to monitor the tumor heterogeneity and clonal dynamics associated with the emergence of therapeutic resistance (*Cancer Discovery* 2015, *Nature Medicine* 2015, *Cancer Discovery* 2016, *Cancer Discovery* 2017, *Cancer Discovery* 2018.)

Selected Publications:

Parikh AR*, Leshchiner I*, Elagina L*, Goyal L, Levovitz C, Siravegna G , Livitz D, Rhrissorrakrai K, Martin EE, Van Seventer EE, Hanna M, Slowik K, Utro F, Pinto CJ, Wong A, Danysh BP, Fece de la Cruz F, Fetter IJ, Nadres B, Shahzade HA, Allen JN, Blaszkowsky LS, Clark JW, Giantonio B, Murphy JE, Nipp RD, Roeland E, Ryan DP, Weekes CD, Kwak EL, Faris JE, Wo JY, Aguet F, Dey-Guha I, Hazar-Rethinam M, Dias-Santagata D, Ting DT, Zhu AX , Hong TS, Golub TR, Iafrate AJ, Adalsteinsson VA, Bardelli A, Parida L, Juric D, Getz G, **Corcoran RB**. Liquid versus tissue biopsy for detecting acquired resistance and tumor heterogeneity in gastrointestinal cancers. *Nature Medicine*, in press (2019).

Corcoran RB, André T, ... , Rangwala F, Van Cutsem E. Combined BRAF, EGFR, and MEK Inhibition in Patients with BRAFV600E-Mutant Colorectal Cancer. *Cancer Discovery*. 2018, 8: 428-443.

Hazar-Rethinam M, Kleyman M, ... , Iafrate AJ, Van Allen EM, **Corcoran RB**. Convergent Therapeutic Strategies to Overcome the Heterogeneity of Acquired Resistance in BRAFV600E Colorectal Cancer. *Cancer Discovery*. 2018; 8: 417-427.

Strickler JH, Loree JM, Ahronian LG, Parikh AR, Niedzwiecki D, Pereira AAL, McKinney M, Korn WM, Atreya CE, Banks KC, Nagy RJ, Meric-Bernstam F, Lanman RB, Talasaz A, Tsigelny IF, **Corcoran RB**, Kopetz S. Genomic Landscape of Cell-Free DNA in Patients with Colorectal Cancer. *Cancer Discovery*. 2018; 8: 164-173.

Goyal L, Saha SK, Liu LY, Siravegna G, Leshchiner I, Ahronian LG, ... , Tiedt R, Bardelli A, Juric D, **Corcoran RB***, Bardeesy N*, Zhu AX*. Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in FGFR2 fusion-positive cholangiocarcinoma patients. *Cancer Discovery*. 2017; 7: 252-263.

Russo M, Siravegna G, Blaszkowsky LS, ... , Iafrate AJ, Bardelli A, **Corcoran RB**. Tumor heterogeneity and lesion-specific response to targeted therapy in colorectal cancer. *Cancer Discovery*. 2016; 6: 147-53

*Denotes equal contribution