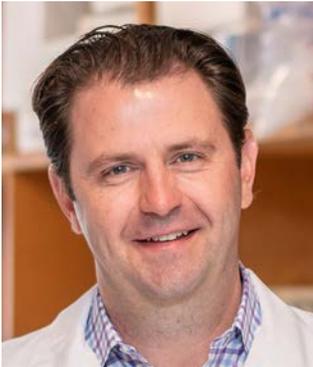


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Corcoran Laboratory

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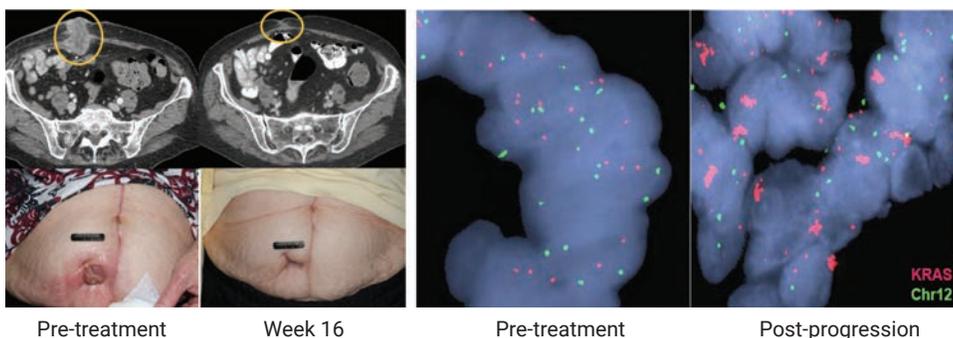
The Corcoran laboratory focuses on developing new and effective therapies for gastrointestinal cancers, including colorectal, pancreatic, stomach, and esophageal cancers, by targeting the specific survival signals that are active in a given patient's cancer. Our research utilizes targeted therapies, 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).



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 because KRAS itself has proven difficult to target directly with small molecules. Currently, our 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. We have identified adaptive feedback signals that impede the ability of MEK inhibitors to suppress MAPK signaling and have explored the role of novel agents (ERK inhibitors) or convergent signaling nodes to overcome feedback. We have expanded these approaches to identify other potentially effective targets in KRAS-mutant cancers, including direct KRAS inhibitors. Despite promising clinical responses in KRAS-G12C mutant NSCLC, there has been limited efficacy of G12C inhibitors as single agents in colon cancer. To address this limitation, we have defined key mechanisms of adaptive feedback resistance in response to KRAS inhibition and have employed vertical pathway inhibition strategies targeting the RAS-MAPK pathway as described in a recent publication (*Clinical Cancer Research*, 2020).

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:

Tian J, Chen JH, Chao SX, Pelka K, Giannakis M, Hess J, Burke K, Jorgji V, Sindurakar P, ..., Demehri S, Leary R, Campbell CD, Yilmaz O, Getz GA, Parikh AR, Hacohen N, **Corcoran RB**. Combined PD-1, BRAF and MEK inhibition in BRAF^{V600E} colorectal cancer: a phase 2 trial. *Nat Med*. 2023 Feb;29(2):458-466.

Ryan MB, Coker O, Sorokin A, Fella K, Barnes H, Wong E, Kanikarla P, Gao F, Zhang Y, Zhou L, Kopetz S, **Corcoran RB**. KRASG12C-independent feedback activation of wild-type RAS constrains KRASG12C inhibitor efficacy. *Cell Rep*. 2022 Jun 21;39(12):110993. doi: 10.1016/j.celrep.2022.110993.

Tanaka N, Lin JJ, Li C, Ryan MB, Zhang J, Kiedrowski LA, Michel AG, Syed MU, Fella KA, Sakhi M, Baiev I, Juric D, Gainor JF, Klemptner SJ, Lennerz JK, Siravegna G, Bar-Peled L, Hata AN, Heist RS, **Corcoran RB**. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. *Cancer Discov*. 2021 Aug;11 (8):1913-1922.

Ryan MB, Fece de la Cruz F, Phat S, Myers DT, Wong E, Shahzade HA, Hong CB, **Corcoran RB**. Vertical pathway inhibition overcomes adaptive feedback resistance to KRASG12C inhibition. *Clin Cancer Res*. 2020. 26:1633-1643.

Parikh AR*, Leshchiner I*, Elagina L*, Goyal L, Levovitz C, Siravegna G, ..., 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*/2019 Sep;25(9):1415-1421.

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*Denotes equal contribution