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A NIBR-led clinical trial (ClinicalTrials.gov identifier NCT04294160) will assess select combinations of MAPK pathway inhibitors in patients with BRAF-mutant CRC. While we hope one of these combinations will lead to responses in the majority of patients, we know not all patients will respond and the ones that do will ultimately develop resistance.

The current research proposal aims to identify mechanisms of resistance of BRAF-mutant CRC to MAPK pathway inhibition and explores ways to overcome them. Specifically, the project focuses on two proposed mechanisms of resistance: 1. MAPK pathway activation via RAS mutations and 2. cancer cell survival through cellular differentiation.

Academic publications and in-house data describe the emergence of RAS mutations in BRAF-mutant CRC patients treated with MAPK pathway inhibitor combinations. We will mimic the emergence of clinical resistance pre-clinically by mixing RAS mutant variants with RAS wild-type BRAF-mutant cells. These studies will determine if: 1. specific RAS mutants are intrinsically more or less resistant to certain MAPK pathway inhibitors and 2. RAS mutants affect the sensitivity of RAS wild-type BRAF-mutant cells, in trans. To address the 2nd potential mechanism of resistance, cellular differentiation upon MAPK pathway inhibition, we will analyze expression patterns of these “persistent” cells that survive MAPK pathway inhibition. To complement expression signatures, we also plan to run whole-genome dropout studies in “persistent” models to identify functional genes involved in this cellular differentiation.

Selected Publications

Primary patient-derived cancer cells and their potential for personalized cancer patient care.
Kodack DP, Farago AF, Dastur A, Held MA, Dardaei L, Friboulet L, von Flotow F, Damon LJ, Lee D, Parks M, Dicecca R, Greenberg M, Kattermann KE, Riley AK, Fintelmann FJ, Rizzo C, Piotrowska Z, Shaw AT, Gainor

JF, Sequist LV, Niederst MJ, Engelman JA, Benes CH.
Cell Rep. 2017 Dec 12;21(11):3298-3309.

PF-06463922, an ALK/ROS1 Inhibitor, Overcomes Resistance to First and Second Generation ALK Inhibitors in Preclinical Models.
Zou HY, Friboulet L, Kodack DP, Engstrom LD, Li Q, West M, Tang RW, Wang H, Tsaparikos K, Wang J, Timofeevski S, Katayama R, Dinh DM, Lam H, Lam JL, Yamazaki S, Hu W, Patel B, Bezwada D, Frias RL, Lifshits E, Mahmood S, Gainor JF, Affolter T, Lappin PB, Gukasyan H, Lee N, Deng S, Jain RK, Johnson TW, Shaw AT, Fantin VR, Smeal T.
Cancer Cell. 2015 Jul 13;28(1):70-81.

The brain microenvironment mediates resistance in luminal breast cancer to PI3K inhibition through HER3 activation.
Kodack DP, Askoxylakis V, Ferraro GB, Sheng Q, Badeaux M, Goel S, Qi X, Shankaraiah R, Cao ZA, Ramjiawan RR, Bezwada D, Patel B, Song Y, Costa C, Naxerova K, Wong CSF, Kloepper J, Das R, Tam A, Tanboon J, Duda DG, Miller CR, Siegel MB, Anders CK, Sanders M, Estrada MV, Schlegel R, Arteaga CL, Brachtel E, Huang A, Fukumura D, Engelman JA, Jain RK.
Sci Transl Med. 2017 May 24;9(391).

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