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Benes Laboratory

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The Benes laboratory, also known as The Center for Molecular Therapeutics, is engaged in the design and application of personalized therapies for cancer. Targeted cancer treatments have emerged from research studies showing that the biology of cancer cells differs from that of healthy cells, and that each person's cancer has a unique genetic signature. Our goal is to pinpoint the cancer cells' biological weak points and then to attack those weak points with smart drugs that are specifically designed for such an attack. We use a very large collection of previously established tumor cell lines derived from many different cancers as well as newly established lines from patients treated at MGH. To better understand why some patients respond more favorably than others to therapy, we use both cancer cells and other cells found in tumors and study their interplay.

We are studying the molecular basis of response to anticancer agents.

Molecular Basis of Cancer Therapeutic Response

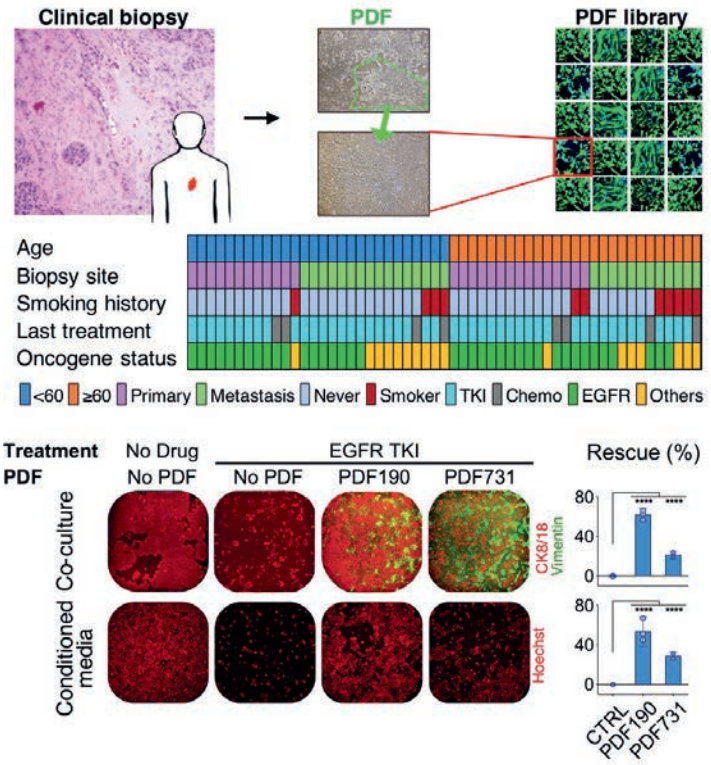
Clinical responses to anticancer therapeutics are often restricted to a subset of cases treated. In some instances, clear evidence is available that correlates clinical responses with specific tumor genotypes. Our goal is to identify tumor cell states that predict sensitivity to anticancer agents. To accomplish this goal, we use historically established cancer cell lines as well as cancer cells obtained from tumor biopsies and study their response to anticancer agents and their combinations using high-throughput approaches. We collaborate with multiple groups at MGH and beyond to identify new treatment options for rare cancers. We use molecular profiling at multiple levels including genetic, epigenetic and proteomic to discover the mechanistic basis of drug response and identify biomarkers predictive of response in patients.

Targeting the Tumor Microenvironment

Tumors contain fibroblasts, endothelial cells and immune cells among others. These cells and the extracellular material they produce constitute the tumor microenvironment. We study how the tumor microenvironment influences therapeutic response. In particular we culture cancer associated fibroblasts from tumor biopsies. Our living collection of Patient Derived Fibroblasts gives us insights into the functional diversity of fibroblasts in tumors, and how they influence cancer cells as well as immune cells. Through these studies we aim to design therapeutic strategies targeting the tumor as a whole by perturbing routes of communication and cooperation between the different cell types present in tumors.

Resistance to Cancer Therapies

Even for the most successful anticancer therapies, drug resistance invariably emerges and limits the impact on patient lives. The molecular mechanisms underlying acquired resistance to cancer therapeutics are not well defined but are likely to be



Top: A collection of Patient Derived Fibroblasts (PDF) established from tumor biopsies of patients at the MGH. Fibroblasts were isolated from biopsies of a diverse population of non-small cell lung cancer patients. Bottom: PDFs impact the response to Epidermal Growth Factor Tyrosine Kinase Inhibitor (EGFR TKI) through secreted factors: cancer cells sensitive to EGFR inhibition are protected by PDFs in co-culture (top) as well as in the presence of culture media conditioned by PDFs (bottom). Cancer cells are labelled red and PDFs green.

different for each therapy and cancer. We are investigating how drug combinations could overcome resistance, and within this context, studying how changes in intracellular signaling pathways affect drug response.

We are tackling the problem of therapeutic resistance using cell lines made resistant in the laboratory or isolated from resistant tumors. Previous results have shown that these cell line models do recapitulate at least some of the mechanisms of resistance at play in patients. We interrogate combinations of a panel of clinically relevant anticancer drugs as a way to quickly identify candidate therapeutic strategies and to jumpstart mechanistic studies that will help characterize the molecular basis of acquired resistance.

Selected Publications:

Amzallag A, Ramaswamy S, **Benes CH**. Statistical assessment and visualization of synergies for large-scale sparse drug combination datasets. *BMC Bioinformatics.* 2019 Feb 18;20(1):83.

Misale S, Fatherree JP, Cortez E, Li C, Bilton S, Timonina D, Myers DT, ... **Benes CH**. KRAS G12C NSCLC Models Are Sensitive to Direct Targeting of KRAS in Combination with PI3K Inhibition. *Clinical Cancer Research* 2018 Oct 16; 25(2):796–807.

Dardaei L, Wang HQ, Singh M, Fordjour P, Shaw KX, ... **Benes CH**. SHP2 inhibition restores sensitivity in ALK-rearranged non-small-cell lung cancer resistant to ALK inhibitors. *Nat Med.* 2018 May;24(4):512-517.

Kodack DP, Farago AF, Dastur A, Held MA, Dardaei L, Friboulet L, von Flotow F, ... **Benes CH**. Primary Patient- Derived Cancer Cells and Their Potential for Personalized Cancer Patient Care. *Cell Rep.* 2017 Dec 12;21(11):3298-3309.

Crystal AS, Shaw AT, Sequist LV, Friboulet L, Niederst MJ, Lockerman EL, Frias RL, ... **Benes CH**. Patient-derived models of acquired resistance can identify effective drug combinations for cancer. *Science*. 2014 Dec 19; 346(6216):1480–86.

Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, Greninger P, ... **Benes CH**. Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature*. 2012 Mar 28;483(7391):570-5.