The Benes laboratory, 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. Using a large collection of human cancer cell lines, we have made major advances in identifying molecular genetic features, or biomarkers, of a tumor that predict responsiveness to targeted therapies. We are focused on developing molecular diagnostics that will reveal the best treatment course for each patient and on discovering how gene mutations in cancer can be exploited to develop new treatments.

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

Genetics 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 (i.e., genotypes, gene expression) that predict sensitivity to anticancer agents. To accomplish this goal, we use high-throughput screening and expose 1,000 cell lines derived from a broad spectrum of cancers to known and potential anticancer therapeutic agents. For each compound, we characterize the variation in response across the cell line collection and correlate response to genomic and transcriptomic information, including cancer gene mutations, genome-wide copy number information, and mRNA expression data. We then translate these findings to clinical use by analyzing clinical specimens to possibly inform the design of clinical studies.

The use of a very large cell line collection allows us to capture some mutational events that—although relatively rare—are very important for therapeutic response. In addition, while some patient selection strategies have proven quite successful, a wide range of variation in response to treatment exists in almost all cases. Similar to this clinical observation—and perhaps related mechanistically—our large cell line collection allows us to observe important variation in drug response within a given sensitizing genotype. For example, among BRAF-mutant cell lines which are, as a group, remarkably sensitive to BRAF inhibitors, some lines do not respond significantly. Based on these observations, we aim to identify additional biomarkers that will permit more accurate prediction of drug response in the clinic.
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 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.

We are also approaching the problem of resistance using a very different and complementary approach. We systematically identify genes that can cause resistance to a given drug in a given context using a transposon-based genetic screen. Transposons are mobile genetic elements that can insert into a host genome—in our case, the genome of cancer cells. We use an engineered version of a transposon so we can control its mobility and identify genes with expressions that are modified by its insertion, leading to drug resistance.

Selected Publications:


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