The overarching aim of research in the **Engelman laboratory** is to develop new and more effective therapeutic strategies for the treatment of cancer, with a particular emphasis on lung cancer. Cancer therapies are changing from general chemotherapeutic agents to drugs that target specific proteins and signaling pathways (i.e., targeted therapies). Our laboratory aims to understand the biological underpinnings of cancer sensitivity and resistance to this emerging class of therapies. We are particularly interested in the regulation of the PI3K pathway, a signaling network that is crucial for the growth and survival of many epithelial cancers. The ultimate goal of our research is to develop therapies that are more effective and less toxic for patients with cancer.

**Targeted therapies**

The research goal of my laboratory is to advance targeted therapies to benefit patients with cancer. Our research focuses on understanding the biological underpinnings of sensitivity and resistance to specific kinase inhibitor targeted therapies in cancers with specific genetic abnormalities. In particular, we focus on the regulation of key signaling networks that regulate cancer cell growth and survival, such as the PI3K-AKT and MEK-ERK signaling pathways. We study how perturbation of specific signaling pathways (alone or in combination) impairs cell growth and induces cell death in the context of specific genetic abnormalities. More recently, our research has also begun to focus on how one should model responsiveness to therapies in the laboratory to optimally inform what will occur in the clinic. Our studies encompass biochemistry, molecular biology, cell culture models, mouse models and assessment of clinical specimens. Our laboratory studies encompass established targeted paradigms such as EGFR-, ALK-, and ROS-mutant lung cancers as well as cancers for which no effective targeted therapy currently exists, such as KRAS mutant cancers.

**Resistance mechanisms to targeted therapies**

Unfortunately, clinical experience has taught us that we cannot yet cure even the simple cancers that are addicted to a single kinase. Although targeted therapies are often initially very effective for such cancers, these cancers almost always develop resistance. For example, EGFR-mutant lung cancers that are sensitive to EGFR inhibitors invariably develop resistance, and the same is true for EML4-ALK lung and BRAF-mutant cancers treated with ALK and BRAF inhibitors respectively. Resistance usually develops within one year in each of these cancer paradigms. My laboratory is highly focused on understanding how resistance develops in patients so we can devise strategies to overcome it or thwart its emergence. To understand how resistance to these therapies develops, we culture genetically defined, sensitive cancer cell line models until resistance emerges (in vitro and
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in vivo). We then use these models to figure out how resistance develops. Using these methodologies, we have discovered resistance mechanisms that occur in patients, and these findings have led to novel therapeutic strategies that are being explored in the clinic.

These laboratory efforts leverage complementary efforts in the clinic in which we actively biopsy tumors from patients upon the development of resistance. These patient-tumor-derived models have proven invaluable for elucidating results from clinical trials and developing new ideas for future therapeutic strategies. By developing patient-derived models in the laboratory, we are able to determine how cancers become resistant to therapies in the clinical trial and to identify new treatment strategies to overcome resistance.