# Transcriptional Reprogramming Drives Cancer Cell Heterogeneity and Drug Resistance

*Principal Investigator:*

- Charles Sawyers, MD – Memorial Sloan Kettering Cancer Center

*Co-Principal Investigator:*

- Leonard Zon, MD – The Broad Institute of MIT and Harvard

Abstract: Drug resistance is a major issue for successful cancer treatments. Examples include acquired resistance to BRAF or MEK inhibitors in melanoma and to antiandrogen therapy in prostate cancer. A common mechanism of acquired resistance is DNA-based mutation of the drug target, which results in outgrowth of the mutant subclone and clinical relapse. Next generation inhibitors can circumvent mutation-based resistance mechanisms. However, some cancers evade targeted therapies through a mechanism that we refer to as lineage plasticity, whereby tumor cells acquire phenotypic characteristics of a cell lineage whose survival no longer depends on the drug target. At a recent HHMI Investigator meeting, Drs. Zon and Sawyers presented complementary stories of drug resistance associated with lineage plasticity -- in zebrafish models (melanoma) and in human tissue models (prostate cancer) that revealed remarkably parallel themes underlying the resistance phenotype. In zebrafish melanoma, a chromatin factor SATB2 activates a primitive neural crest program and drives resistance to BRAF inhibition. In prostate cancer, the reprogramming factor SOX2 is upregulated and drives cell fate changes, cellular heterogeneity and resistance to antiandrogen therapy. We hypothesize that a common module is transcriptionally activated in such disparate tumors as prostate cancer and melanoma which leads to the expression of reprogramming factors, thereby creating a cellular state of increased plasticity which sets the stage for emergence of drug resistance. The goal of our Starr application is to characterize this common module through detailed analysis of the transcriptional and chromatin changes in our models that drive resistance.