



SU2C–National Science Foundation Convergence Research Team:

“Genetic, Epigenetic, and Immunological Underpinnings of Cancer Evolution Through Treatment”



[This abstract was provided by the scientists when their application was accepted.]

The last two decades have seen the development of increasingly effective cancer therapies which target different vulnerabilities of cancer cells. In a subset of cancers, including acute myeloid leukemia (AML) and non-small cell lung cancer with activating *EGFR* mutations, these therapies can induce significant clinical responses, however most patients subsequently relapse such that these responses do not lead to long-term cures. We propose to investigate the process of response to treatment, the basis for persistence of a subset of cells during clinical response, and the mechanisms driving subsequent therapeutic relapse in these two tumor types. This will involve combining genomic, computational, and laboratory studies at the various stages of therapeutic response and resistance with mathematical modeling approaches to understand the evolution of drug resistance and to develop novel therapeutic strategies aimed to prevent the emergence of clinical resistance. We have assembled a collaborative team of cancer biologists, physician scientists with expertise in clinical oncology, and mathematical modelers. The overall goal is to use studies of patient samples and accurate preclinical models to understand and to build quantitative dynamical models of the therapeutic response and the emergence of clinical resistance.

The understanding gained from the studies will be used to develop and test innovative therapeutic strategies with informed, multimodality therapeutic regimens that include tumor-directed therapies and immunotherapy. The goal is to inform the use of combination therapies which are aimed to prevent therapeutic resistance and to maximize clinical response, in order to improve outcomes for cancer patients. Although the efforts will focus on lung cancer and AML, the results and approaches will have broader relevance to oncology and are aimed to uncover general principles and models, which are relevant to the spectrum of human cancers.

