Scientific Abstract

SU2C–National Science Foundation Drug Combinations Convergence Research Team:

"Rational Design of Anticancer Drug Combinations with Dynamic Multi-Dimensional Input"

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

Achieving durable control of metastatic solid tumors will require high-order targeted therapeutic combinations, due to the inevitable emergence of resistance to single-agent therapeutics. However, design of combinatorial regimens cannot be done by empirical trial and error in the clinical setting. The guiding hypothesis is that dynamic network modeling and evolutionary analyses might be integrated with systematic cell death and therapeutic resistance data to predict high-order combinations. The goal of the research is to apply to and test this approach to PIK3CA-mutant, estrogen receptor positive (ER+) breast cancer.

The project is designed to integrate dynamic modeling of signal transduction pathways relevant to cell proliferation and apoptosis, genomic and evolutionary analyses of tumor cells, and systematic cell death and therapeutic resistance studies. The dynamic models will then be informed, tested, and iterated using experimental approaches, including genome-wide open reading frame screens, dynamic BH3 profiling of cancer cells apoptotic state, and whole exome sequencing and single cell RNA-seq analysis. The models will recapitulate steady state signaling network activation, acute adaptive effects of treatment, and the range of drug-resistant states that may emerge following longer-term drug exposure. They will be used to prioritize drug combinations and dosing and scheduling principles for *in vitro* and *in vivo* testing.

The research will lead to an improved understanding of adaptive and acquired drug resistance mechanisms. It will make a significant contribution toward a major goal of cancer precision medicine, namely the identification of optimal high-order combinations for individual cancer patients.