Team Progress Updates

SU2C–National Science Foundation Drug Combinations Convergence Research Team:

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

Decades of cancer research and therapeutic development have made it clear that achieving durable control of metastatic solid tumors will usually require complex therapeutic combinations. Unfortunately, there are far too many possible combinations to test in clinical trials. Instead, new conceptual frameworks and approaches are needed to design and deliver high-order therapeutic strategies.

To address this urgent need, a collaborative team has been assembled from a broad swath of disciplines. Researchers include theoretical physicists and clinical investigators who are integrating dynamic network modeling and evolutionary analyses with systematic cell death and therapeutic resistance data. The goal is to predict the impact of complex drug combinations and to determine safe and effective dosing including how the doses should be scheduled.

More specifically, the team is constructing dynamic models for estrogen-receptor positive breast cancer, testing the robustness of these models, and using molecular data obtained from breast cancer patients to characterize and interpret how sensitivity and resistance to treatment evolves over time.

The team reported the following progress:

April 2019

- The team has completed dynamic models of signal transduction for ER+, HER2+, and/or PI3KCA-mutant breast cancer. Team members have used these models to map out resistance mechanisms and to identify drug combinations that are clinically relevant in breast cancer.
- Genetic screening has identified genes that, when lost, can confer resistance to PI3K inhibitors, as well as genes that, when lost, may confer hypersensitivity to these same drugs. These findings are now being developed into a test that will be able to predict whether a patient will benefit from chemotherapy.
- Studies have revealed that in most breast cancer cases, the evolution of acquired drug resistance shares driver mutations, albeit at different time points. The team has identified one metastatic-specific mutation that may be related to acquired resistance in the final stage of the tumor.

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January 2018

- Discrete dynamic network model predicted combinatorial inhibition of PIK3CA and anti-apoptotic proteins MCL1 and BCL2 would prime cells for apoptosis was confirmed. Model used to identify which combination of a set of drugs that are clinically relevant to breast cancer are synergistic.
- Implementation of a genome wide CRISPR-CAS9 screen to identify genes that may confer sensitivity to PIK3a inhibitors or the combination of a PI3Ka inhibitor plus an ER degrader.
- Extensive genomic analysis of pre- and post-treatment breast cancer tumor samples is in progress.
- Whole exome sequencing and RNA-seq analysis of the tumor samples is underway.

September 2017

- Completed a comprehensive discrete dynamic network model of signal transduction in ER+, HER2+ and/or PIK3CA-mutant breast cancer.
- Analysis of tumor evolution in setting of primary and acquired resistance to PIK3CA inhibitors in ER+ breast cancer.
- Genome wide CRISPR screen looking for mechanisms of resistance to PIK3CA inhibitors in ER+ breast cancer cell lines
- A novel discrete dynamic network model of signal transduction in ER+, Her32+ and/or PIK3CA mutant breast cancer was developed.
- Dynamic BH3 Profiling was applied to melanoma cell lines and showed that measured apoptotic priming was correlated with efficacy of BRAF inhibitor treatment.

December 2016

- Constructing dynamic and interactive models of the PI3K and BRAF signal transduction pathways.
- Carrying out gain of function and synthetic lethal screens in cell culture using CRISPER/CAS9, ShRNAs, and drug libraries with cells that are drug resistant (to PI3K and BRAF) and drug sensitive that has uncovered several synthetic lethals and gain of function phenotypes.
- Biopsy samples from patients with tumors resistant to PI3K drugs being analyzed for the evolution of mutations that arise before and after drug treatment.