“Systematic Studies of Resistance to Targeted Anticancer Therapeutics and Combinations”

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Abstract: Despite the considerable promise of targeted anticancer agents, the development of therapeutic resistance-or its presence *de novo*-invariably undermines their clinical efficacy. Discerning the mechanisms of resistance in a manner that informs the design of more durable cancer treatment regimens therefore constitutes one of the great challenges in oncology. This collaborative project will employ a genome-scale, gain-of-function screening approach to identify genes whose activation/aberrant expression can drive tumor drug resistance. Specifically, we will overexpress each of >16,000 human genes in cancer cell lines that harbor particular genetic features, and perform functional screens for resistance to eight targeted anticancer agents and three therapeutic combinations currently in oncology clinical trials. Top candidate resistance genes for each drug or drug combination will be subjected to pharmacological and biochemical validation studies. Leading candidate genes from these screens will also be queried in the context of intensive genomic and pathological characterization in tumor samples from patients receiving several representative agents. The long-term objective of this project is to define the most prominent mechanisms of tumor drug resistance and disseminate them to the scientific and medical community to inform lasting anti-cancer treatment strategies in the clinic. As such, this effort is expected to have far-reaching scientific and clinical significance. The categorical nature and magnitude of potential impact makes this project highly compatible with the goals of the Starr Cancer Consortium.