

## Comprehensive Elucidation of the Mechanisms of Action of Anticancer Molecules

### *Principal Investigator:*

- Olivier Elemento, PhD, Weill Cornell Medical College

### *Co-Principal Investigators:*

- Tarun Kapoor, PhD, The Rockefeller University

**Abstract:** The goal of this proposal is to identify the mechanisms of action of anticancer molecules using a novel chemical genomic approach developed in our laboratories. Understanding mechanisms of action is key to improving the efficacy of anticancer molecules and to developing strategies to overcome the resistance that will otherwise occur in most treated patients. Our strategy involves: (a) Isolating and expanding multiple clones that are drug resistant and excluding those clones in which general drug efflux is increased to gain resistance. (b) Using high-throughput sequencing along with dedicated computational algorithms to identify the resistance signature of each drug. (c) Using chemical biology, biochemistry and cell biology approaches to determine direct and indirect mechanisms underlying drug resistance and action. In Aim 1, we will expand our existing genomic and bioinformatic methodology to derive a drug's resistance signature. In Aim 2, we will demonstrate how our approach can be used to study anticancer compounds with incomplete knowledge of mechanisms of action and that have failed in the clinic due to low efficacy. This aim is expected to provide a comprehensive elucidation of the mechanisms of action of Tasisulam, an antimetabolic drug whose direct target is currently unknown, and will thus provide strategies to improve its efficacy. In Aim 3, we will analyze several breast cancer drugs whose mechanisms of action are partially characterized and whose resistance signature is unknown. We will use the resistance signatures to predict which drugs can be combined to maximize efficacy and slow down the acquisition of resistance.