Cancer Target Discovery and Development (CTD^2)

Specific Aims

Institution: Broad Institute

Specific Aims

The Broad/CTD^2 Center goal is to determine the relationship of the genetic features uncovered in human cancers to acquired dependencies found in the cancers and to identify small molecules that target the dependencies comprehensively. Toward this goal, the Broad/CTD^2 aims to:

I. Assemble an "Acquired Cancer Dependency Small-Molecule Probe Kit" of new and existing small-molecule probes whose members modulate many candidate targets/processes important for cancer, and use this probe kit to identify the dependencies associated with a given cancer genotype.

We have measured the sensitivity of 243 genetically characterized cancer cell lines to 355 small- molecule probes and drugs, and have applied enrichment analysis to identify genetic features that predict the observed response. We will expand our cancer cell-line profiling efforts to test a wider set of cancer cell lines (~850 lines) against compounds of high interest. The compounds selected for testing will include:

- Compounds identified in our pilot phase dataset as having selective sensitivity in cancer cells lines based on their genetic features. Expanding our sample size for compounds of high interest will allow us to confirm the significance of the results, as well as better understand whether the genetic feature/sensitivity relationship is affected by other factors, such as cancer lineage.
- Rational combinations defined based on the specific genetic feature/small-molecule sensitivity relationships discovered during the pilot phase.
- Novel probes discovered during the pilot phase that target novel oncogenes (e.g. IDH1-R132H) or pathways that may constitute dependencies.

In addition, we will continue to adapt and develop a number of analytical methods for the prediction of small-molecule sensitivities based on genetic features of cancer. Together these efforts will allow us to demonstrate the value of our CCD Catalog as a hypothesis-generating resource for the academic community.

II. Develop HTS assays for the discovery and development of novel small-molecule probes targeting cancer dependencies.

We have developed assays and executed high-throughput screens for 10 projects (of which 2 were trans-network projects) against a collection of stereochemically and skeletally diverse small molecules synthesized at the Broad Institute. We are targeting a May 1 public release of primary screening data onto the CTD^2 portal. We will continue follow-up chemical optimization and biological characterization of leads to yield high-quality probes.