Mechanism of Action:

discover your small molecule's interactions and targets

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Knowing the cellular targets of a small molecule can help researchers better understand the biological basis of a disease and develop new drugs to treat that disease. Whether it is an FDA-approved drug with an unknown mechanism of action, a natural product, or a novel small molecule identified from a laboratory screen, researchers must understand how a molecule of interest exerts its effects. These insights can pave the way for development of a compound as a molecular probe or possibly a new drug with well-characterized on- and off-target effects.

A team of researchers at the Broad can help realize this goal. With deep expertise in key scientific areas, the Mechanism of Action team brings state-of-the-art tools and a highly integrated approach to bear on small molecules with unknown cellular targets. Their approach combines the strengths of four complementary strategies: proteomics, RNAi screening, expression profiling, and computational analysis.

Proteomics Broad researchers use mass spectrometry to identify the protein targets that bind to a small molecule.

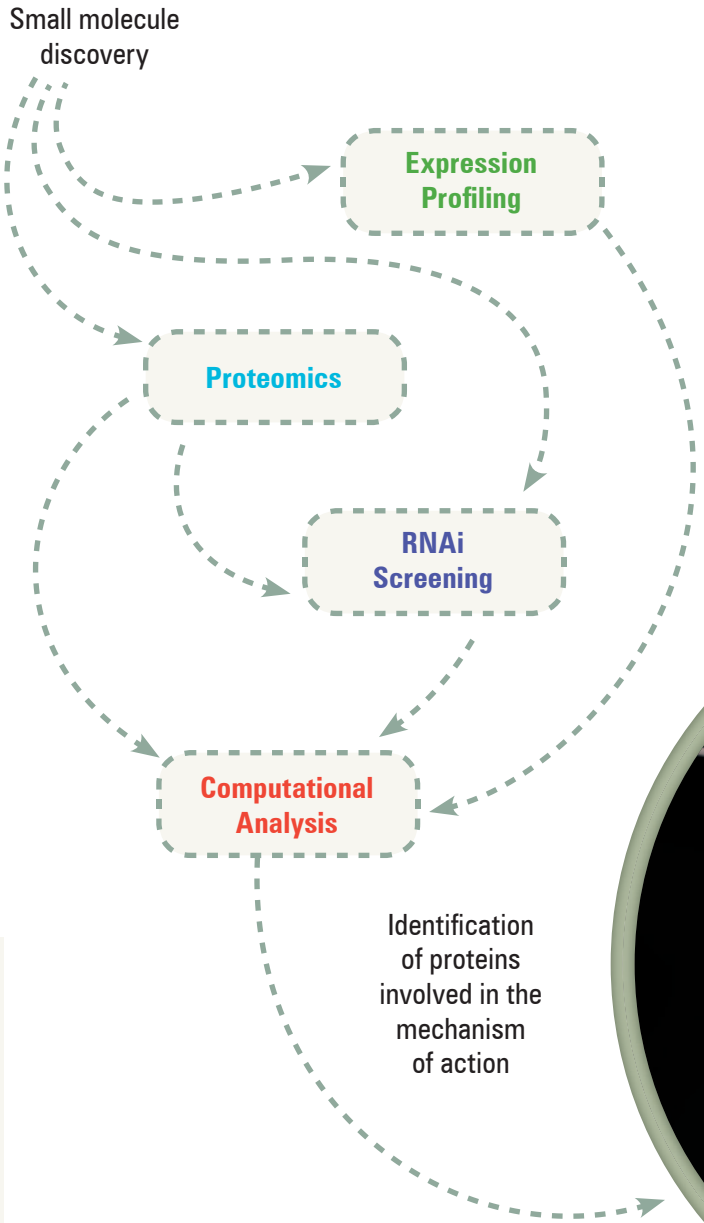
RNAi screening Genetic perturbations offer researchers insights into the individual genes and pathways involved in a small molecule's effects.

Expression profiling By looking at the expression of thousands of genes after treatment with a small molecule, researchers can glean a small molecule's gene-expression signature, which can in turn be compared to an extensive library of signatures from other small molecules (The Connectivity Map) to draw connections to compounds with known mechanisms of action.

Computational analysis
The Broad Mechanism of Action team brings together all of the data generated through these approaches using computational analyses. The team can further inform these analyses using the rich set of historical Broad Institute screening data (including, *e.g.,* from ChemBank).

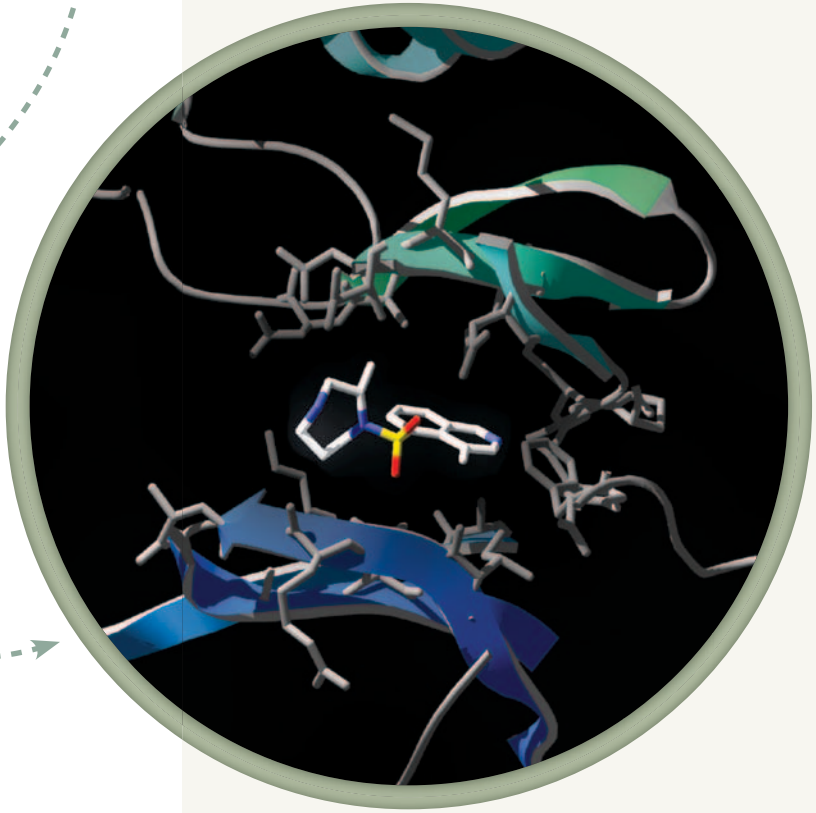
"Our collaboration with the Broad Institute has been essential for the identification of new small molecules that selectively target a rare subtype of leukemia. The target ID group did an outstanding job of identifying the targets of our lead compound and facilitated the development of optimal second generation compounds."

John Crispino, Associate Professor of Medicine, Northwestern University



"This is a team that invests a great deal of time and diligence to understand the science behind the collaborative projects it works on. They are willing to invest the time that's necessary to understand an investigator's needs and objectives. That kind of collaboration ensures the trust that people need to work with each other in an open and transparent way."

Randall Peterson, Associate Professor of Medicine at Massachusetts General Hospital, Senior Associate Member of the Broad Institute



"Deciphering the mechanism of action for natural products is devilishly difficult since many influence multiple cellular targets. Mechanism of Action has provided an amazing opportunity for us to get a comprehensive picture of compound-target interactions and generate a broad view of a compound's impact on cellular systems."

Susan Lindquist, Member of the Whitehead Institute, Professor of Biology at MIT, Investigator of the Howard Hughes Medical Institute, Senior Associate Member of the Broad Institute

"The only thing more exciting than finding a new bioactive compound is discovering that it acts through a new and unanticipated molecular mechanism. With the help of the Broad Institute's RNAi, proteomic, computational and gene expression platforms, we are able to significantly accelerate this difficult process."

Brent Stockwell, Associate Professor, Columbia University

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