New genomic tool makes connections between drugs and human disease

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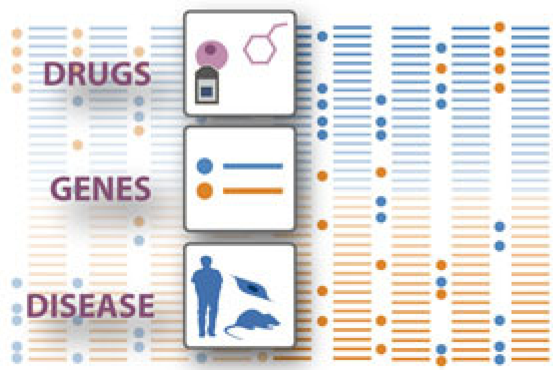


Image by Maria Nemchuck and adapted from an illustration by Bang Wong.

In three papers appearing in Science and Cancer Cell, Broad researchers describe the "Connectivity Map" and its scientific applications to cancer and other diseases

While the ultimate goal of biomedicine is to connect each human disease with drugs that can effectively treat or cure it, the paths toward this goal are often circuitous. The earliest steps, in particular, can be hindered by a lack of basic knowledge about how drugs and diseases work — for example, the biology that underlies a particular disease or the molecules that are targeted by a drug's action. What is needed to accelerate this "match-making" process is a relatively quick and systematic method for comparing different drugs and diseases based on their biological effects.

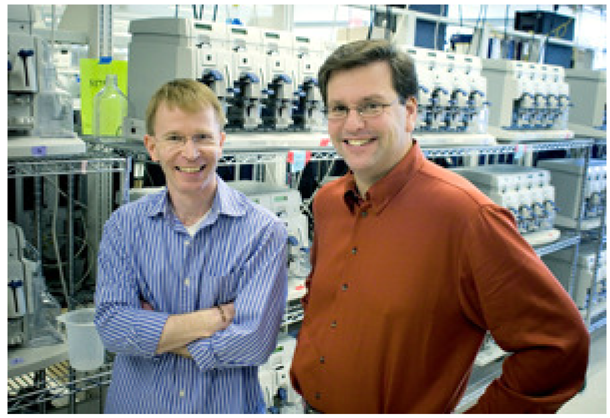
Toward this end, a research team led by Broad Institute scientists has developed a new kind of tool that relies on genes to connect diseases with potential drugs to treat them and to predict how new drugs function in cells. Called the "Connectivity Map," the new tool and its first uses are described in the September 29 issue of *Science* and in separate publications in the September 28 immediate early edition of *Cancer Cell*. The three papers demonstrate the map's ability to accurately predict the molecular actions of novel therapeutic compounds and to suggest ways that existing drugs can be newly applied to treat diseases such as cancer.

"The Connectivity Map works much like a Google search to discover connections among drugs and diseases," said senior author Todd Golub, the director of the Broad Institute's Cancer program, an investigator at the Dana-Farber Cancer Institute, an associate professor at Harvard Medical School and an investigator at the Howard Hughes Medical Institute. "These connections are notoriously difficult to find in part because drugs and diseases are characterized in completely different scientific languages."

To build the Connectivity Map, the scientists described the effects of different drugs and diseases using the common language of "genomic signatures" — the full complement of genes that are turned on and off by a particular drug or disease. The scientists compiled the genomic signatures of more than 160 drugs and other biologically active compounds, forming a database of biological "barcodes" that denote cells' responses to the different drugs. Then, they developed a computer program that matches the barcodes based on the patterns shared among them. Together, these features enable the first-generation Connectivity Map to directly compare the biological effects of different drugs with each other, and also with those seen in diseases.

Like other scientific databases, the Connectivity Map can be queried by nearly any researcher with a computer, where the search "word" is the genomic signature of a particular human disease, drug or other biological response of interest, and the search results consist of a rank-ordered list of reference compounds that have matching signatures. These comparisons can yield new scientific insights, particularly when a connection exists between a poorly understood drug (or disease) and a drug whose effects have been extensively characterized — the case for many of the compounds currently referenced in the database. This potential is underscored by two cases where the Connectivity Map has already been used: one, to discover the mechanisms underlying a novel drug candidate for prostate cancer and another, to reveal that a drug currently used to treat one disease may be useful in another.

"This is a powerful discovery tool for the scientific community," said Justin Lamb, the lead author of the Science paper and a senior scientist in the Broad Institute's Cancer program. "By analyzing just a small fraction of available drugs, we have already confirmed several biological connections between drugs and human disease, and made entirely new ones, too."



Justin Lamb and Todd Golub
Photo courtesy of Justin Ide/Harvard News Office

One of the surprising results to emerge from the use of the Connectivity Map involves gedunin, a plant derivative that, despite a long history of medicinal use, is not well understood molecularly. Described in *Cancer Cell* by first author Haley Hieronymus, a researcher at the Broad and the Dana-Farber Cancer Institute, and her colleauges, gedunin was first identified in a high-throughput chemical screen for molecules that disrupt hormone signals in prostate cancer cells. Then the researchers used the Connectivity Map to help uncover its molecular action, which as confirmed through additional work, disrupts a key quality control mechanism in the cell, mediated by the heat shock 90 protein (HSP90).

Another key finding suggests a new way to overcome drug resistance in cancer. Using the Connectivity Map, a scientific team led by Scott Armstrong, an assistant professor at Harvard Medical School and Children's Hospital Boston and an investigator at the Dana-Farber Cancer Institute, identified the FDA-approved immunosuppressant drug, sirolimus (also known as "rapamycin"), as a therapeutic candidate for overcoming drug resistance in a form of human leukemia. These findings are described in *Science* and in a separate *Cancer Cell* paper by first author Guo Wei, a research fellow at the Broad and the Dana-Farber Cancer Institute, and his colleagues.

Although the first version of the Connectivity Map is limited mainly to drugs, the same concepts could be applied to almost any aspect of human biology, including diseases, genes and even RNA-based gene inhibitors (RNAi). "Expanding this initial map to encompass all aspects of human biology would provide a valuable public resource for the scientific community," said Eric Lander, an author of the *Science* paper and the director of the Broad Institute. "Such an effort would parallel the sequencing of the human genome, both in its scope and in its potential to accelerate the pace of biomedical research."

Other Broad Institute scientists who participated in these studies include Irene Blat, Jean-Philippe Brunet, Steve Carr, Jon Clardy, Paul Clemons, Emily Crawford, Stephen Haggarty, William Hahn, Jim Lerner, Joshua Modell, David Peck, Xiao Peng, Srilakshmi Raj, Michael Reich, Kenneth Ross, Aravind Subramanian, David Twomey, Ru Wei and Matthew Wrobel.

—Nicole Davis, Communications
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Papers cited:

Lamb *et al*. (2006) The Connectivity Map: using gene-expression signatures to connect small molecules, genes and disease. *Science*; doi:10.1126/science.1132939

Hieronymus *et al.* (2006) Gene expression signature-based chemical genomic prediction identifies novel class of HSP90 pathway modulators. *Cancer Cell*; doi:10.1016/j.ccr.2006.09.005

Wei *et al.* (2006) Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL-1 and glucocorticoid resistance. *Cancer Cell*; doi: 10.1016/j.ccr.2006.09.006

Additional resources:

Listen to *Science* Magazine's podcast with Todd Golub on the Connectivity Map

Listen to NPR Science Friday featuring the Connectivity Map

For more information, contact:
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Related Links

- The Connectivity Map
- Dana-Farber Cancer Institute press release
- Broad Institute press release