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Scientists use "universal language" of gene signatures to match cancer and other diseases with potentially effective drugs

Test of "Connectivity Map" yields information on treatments for cancer, obesity and Alzheimer's

In one of the most ambitious spinoffs of the human genome project, researchers at Dana-Farber Cancer Institute, Children's Hospital Boston, the Broad Institute of Harvard and MIT, and other collaborating centers have unveiled a new, systematic approach to drug discovery that matches diseases with potential treatments using a universal language based on cells' distinctive gene activity profiles, or "signatures."

A set of three articles being published in the September 29 issue of *Science* and in the September 28 advance online edition of *Cancer Cell* unveils the first steps toward what researchers have dubbed a "Human Connectivity Map."

"The Human Connectivity Map works much like a Google search to discover connections among drugs and diseases," explained **Todd Golub, MD**, who is an investigator at Dana-Farber, the head of the Cancer Program of the Broad Institute, an associate professor of pediatrics at Harvard Medical School, and a Howard Hughes Medical Institute Investigator. He is a senior author on two of the papers.



Todd Golub, MD

The paper in *Science* describes the concepts underlying the gene signature catalogue and gives an overview of its initial testing. "This should be particularly useful for pharmaceutical companies, so that academic scientists and companies alike can compare the signatures of diseases and compounds to signatures in the Connectivity Map database, and, from that, generate hypotheses," Golub explained.

The strategy allows scientists to capture distinctive gene signatures of cancer and other disease cells and compare them with signatures of cells that have been treated with a large number of drugs, both old and new. The more closely the disease signature resembles the signature of a reference cell that has been treated by a particular drug, the greater the odds that the drug will be an effective treatment for that disease.

Conversely, the system can reveal the molecular mechanism of a treatment that is effective but whose method of action has been a mystery, and that knowledge can lead scientists to other, similarly-acting drug candidates.

The gene signatures are captured by devices called microarrays, or "gene chips," that take a snapshot of the tens of thousands of genes at the heart of every cell. The Connectivity Map system is based on the difference in gene activity patterns – which genes are active, which are inactive † in a disease cell compared with a normal cell, or a cell before it has been treated with a drug and after the drug has been administered. Usually there is a group of 100 or more genes whose activity differs between one state and the other: That set of genes makes up the signature.

The publications describe how the Connectivity Map, which in its initial edition contained links to 164 different drugs and other chemical compounds, was used to obtain information on treatments for obesity, Alzheimer's disease, and cancer, and to suggest new therapies for drug-resistant leukemia and advanced prostate cancer.

Scott Armstrong, MD, PhD, a pediatric oncologist at Dana-Farber and Children's Hospital Boston, is senior author on a paper in *Cancer Cell* that describes how the method successfully identified a drug that can overcome therapy-resistant cases of acute lymphoblastic leukemia (ALL) in children. So-called "glucocorticoid" drugs like prednisone are very effective in many cases of ALL, but in some patients the cancer cells are resistant to the drugs, which often can lead to fatal results.

"We took cells from ALL patients that were either resistant or sensitive to glucocorticoids and put them through the Connectivity Map database, and it predicted that one of the best drugs would be rapamycin," said Armstrong, who is also an assistant professor of pediatrics at Harvard Medical School. "Then we tested rapamycin to see if it made the ALL cells more sensitive to glucocorticoids, and in some cell lines it appears that it does," he said, adding that a clinical trial is being planned to try rapamycin in children who have had recurrences of initially successfully treated ALL.

Moreover, the comparison of gene signatures revealed that rapamycin's effectiveness was due in part to its action on a molecule that causes cancer cells to self-destruct.

The method also enabled researchers to match up a pair of natural products, known as celastrol and gedunin, with a mechanism by which some advanced prostate tumors continue to grow aggressively despite hormone-blocking treatments. A paper in *Cancer Cell* reports on this work, which made it possible for scientists to connect the action of the two natural products with known biological effects of other drugs. It turned out that celastrol and gedunin inhibit a molecule called HSPH90, which in turn blocks the overactive cell signaling of the androgen receptor in prostate cancer cells that drives their aggressive growth. Dana-Farber researcher **Haley Hieronymus, PhD**, who used the Connectivity Map to sift through thousands of drugs and compounds, is the paper's lead author.

The researchers said that in view of these promising results, they are proposing a large-scale effort – along the lines of the Human Genome Project – to map connections among genes and diseases to accelerate the development of new and improved therapies for a wide range of disorders. Like the data in the current papers, the information garnered in the course of such a project would be freely available to scientists everywhere.

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Dana-Farber Cancer Institute (www.dana-farber.org) is a principal teaching affiliate of the Harvard Medical School and is among the leading cancer research and care centers in the United States. It is a founding member of the Dana-Farber/Harvard Cancer Center (DF/HCC), designated a comprehensive cancer center by the National Cancer Institute.

Founded in 1869 as a 20-bed hospital for children, Children's Hospital Boston today is the nation's leading pediatric medical center, the largest provider of health care to Massachusetts children, and the primary pediatric teaching hospital of Harvard Medical School. In addition to 347 pediatric and adolescent inpatient beds and comprehensive outpatient programs, Children's houses the world's largest research enterprise based at a pediatric medical center, where its discoveries benefit both children and adults. More than 500 scientists, including eight members of the National Academy of Sciences, nine members of the Institute of Medicine and 11 members of the Howard Hughes Medical Institute comprise Children's research community. For more information about the hospital visit: <http://www.childrenshospital.org>.

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