Genetic 'roadmap' charts links between drugs and human disease

September 28 2006

A research team led by scientists at the Broad Institute of MIT and Harvard announced today the development of a new kind of genetic "roadmap" that can connect human diseases with potential drugs to treat them, as well as predict how new drugs work in human cells. Called the "Connectivity Map," the new tool and its 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 show 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. Based on the results, the papers propose a public project to expand this initial human Connectivity Map -- in the spirit of the Human Genome Project -- to accelerate the search for new drugs to treat disease.

"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 of pediatrics 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."

A key challenge in biomedicine is to connect each human disease with drugs that effectively treat it and to understand the molecular basis for

such drugs' effects. To solve this problem systematically, the scientists described the effects of drugs and diseases in the common language of "genomic signatures," meaning the full complement of genes that the drugs turn on and off.

To create a first-generation Connectivity Map, the scientists measured the genomic signatures of more than 160 drugs and other biologically active compounds. They next developed a computer program to compare the signatures of the drugs with each other and also with the signatures seen in diseases. Using the Connectivity Map, the scientists were able to discover the mechanisms underlying a novel drug candidate for prostate cancer, and 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."

Like other scientific databases, the true value of the Connectivity Map lies in its capacity to be queried by nearly any researcher with a computer. The genomic signature of a particular human disease, drug or other biological response of interest serves as the search "word" and potential functional connections are revealed through a rank-ordered list of reference compounds in the database that have matching signatures.

One of the surprising results to emerge from the Connectivity Map involves gedunin, a plant derivative that, despite a long history of medicinal use, is not well understood molecularly. The researchers identified gedunin in a high-throughput chemical screen for molecules that disrupt hormone signals in prostate cancer cells and then used the

Connectivity Map to help uncover its precise molecular action. As confirmed through additional work, gedunin disrupts a key quality control mechanism in the cell.

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, as well as those for gedunin, are described in Science and in separate Cancer Cell publications.

"Although this first version of the Connectivity Map is limited mainly to drugs, the same concepts could be applied universally across all facets of human biology." said Eric Lander, an author of the Science paper and the director of the Broad Institute. "Expanding this initial map to encompass all aspects of human biology would provide a valuable public resource for the scientific community. 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."

Data from the study are made publicly available at www.broad.mit.edu/cmap . A web-based tool for scientists to perform their own analyses using the Connectivity Map is also freely available at this site.

Citation:

-- 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

Source: Broad Institute of MIT and Harvard