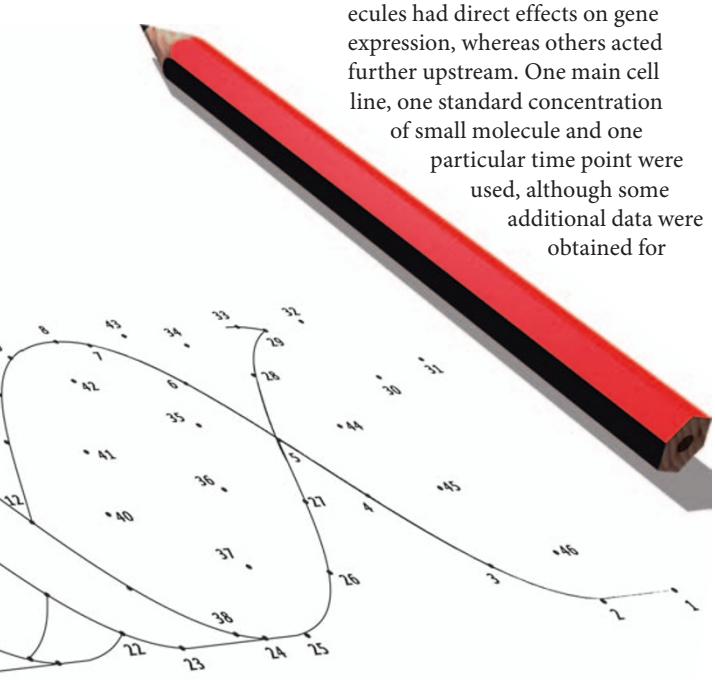
CHEMICAL GENOMICS

Joining the small-molecule dots

A new database of gene-expression responses to small molecules is available for determining the mechanisms of action of new molecules, studying the molecular basis of physiological processes and searching for potential therapies.

The authors of this pilot connectivity map obtained mRNA expression profiles for human cell lines that were challenged with 164 different small molecules, representing a range of Food and Drug Administration (FDA)-approved drugs and non-drug bioactive compounds. Some of these molecules had direct effects on gene expression, whereas others acted further upstream. One main cell line, one standard concentration of small molecule and one particular time point were used, although some additional data were obtained for variations in these parameters. The resulting database of expression profiles — the connectivity map — was formatted so that a query signature could be compared to it, and a score was obtained for the similarity to each signature in the database.



To test the connectivity map, the authors queried it with published signatures from known histone-deacetylase inhibitors. This retrieved the same inhibitors from the database and also some others that are known to have similar mechanisms. Likewise, querying the database with published oestrogen data retrieved oestrogen and its structural homologues, and showed known antagonists of this hormone as having high negative scores. These results were robust with respect to concentration and time point, although, as expected, oestrogen only affected cells that express its receptor, and antagonists required oestrogen in the medium to have an effect. Similar success was achieved with molecules that affect gene expression less directly.

After these tests, the authors went on to use the connectivity map to obtain new information (see further reading for full details). First, they used comparisons with known molecules in the database to generate a plausible and testable hypothesis about the mechanism of action of an uncharacterized small molecule. They then looked at the reverse strategy of querying the database with expression signatures from patients and animal models to find small molecules that are already in the database that might mimic or suppress particular diseases. They identified compounds that might be responsible for inducing obesity (thiazolidindiones), a potential therapy for Alzheimer disease (4,5-dianilinophthalimide) and a possible treatment for dexamethasone-resistant leukaemia (rapamycin). The plausibility of these candidates was confirmed by observations already in the literature.

This pilot connectivity map is still small but it has already demonstrated its utility. By expanding its coverage of small molecules and its range of experimental parameters it should form the basis of a valuable community resource.

Patrick Goymer, Associate Editor,
Nature Reviews Genetics

ORIGINAL RESEARCH PAPER Lamb, J. *et al.* The connectivity map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* **313**, 1929–1935 (2006)
FURTHER READING Hieronymus, H. *et al.* Gene expression signature-based chemical genomic prediction identifies novel class of HSP90 pathway modulators. *Cancer Cell* 28 Sep 2006 (doi:10.1016/j.ccr.2006.09.005) | Wei, G. *et al.* Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL-1 and glucocorticoid resistance. *Cancer Cell* 28 Sep 2006 (doi:10.1016/j.ccr.2006.09.006)
WEB SITE
Connectivity map:
http://www.broad.mit.edu/cmap

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