⇥ **ANTICANCER DRUGS**

Forecasting drug responses

The US National Cancer Institute has screened more than 100,000 anticancer compounds using a panel of 60 diverse human cancer cell lines (NCI-60), which has provided a rich database of the *in vitro* effects of these compounds. A key question, however, is whether such data might be used to predict drug responses for important tumour types that are not represented in the panel, and more ambitiously, in patients. Writing in *PNAS*, Theodorescu and colleagues present a novel *in silico* algorithm — termed co-expression extrapolation or COXEN — that exploits the NCI-60 database to accurately predict the effectiveness of chemotherapeutic agents both *in vitro* and in patients.

The COXEN algorithm is composed of several steps, instigated by the determination of a drug's activity in a first set of cells. Microarray analysis of gene expression levels is then used to identify a set of genes that are most closely associated with drug sensitivity — chemosensitivity markers. Next, the expression levels of these markers are determined in a second set of cells or tumour and patterns of concordant co-expression are established. Multivariate analysis of the concordantly expressed genes is then used to predict the drug sensitivity of this second set of cells or tumour. The final result — the COXEN score — is on a scale that is equivalent to standard GI_{50} values, the drug concentration required for 50% growth inhibition.

To confirm whether this method could be used to accurately predict the drug sensitivity of cell lines not included in the NCI-60 panel, the authors first applied this algorithm to predict the activities of two common chemotherapeutic agents, cisplatin and paclitaxel, in the BLA-40 bladder cancer cell panel. Exposure of BLA-40 cell lines to these two drugs confirmed their predictions — with accuracies of 85% for cisplatin and 78% for paclitaxel.

To address the potential clinical use of this approach, the authors applied COXEN to forecast patients' chemotherapeutic response. By aligning the NCI-60 gene expression data with that of patients' tumours, they were able to predict the clinical response of patients with breast cancer to two commonly used chemotherapies, docetaxel and tamoxifen. Interestingly, many of the COXEN biomarkers were found to belong to pathways related to DNA replication, recombination, repair and cell-to-cell signalling, consistent with the molecular functions of these compounds. Clinical response was measured by residual tumour size for docetaxel and disease-free survival time for tamoxifen, with respective COXEN prediction accuracies of 75% and 71%.

Last, they set out to determine whether COXEN could be applied to drug discovery. They predicted chemosensitivity patterns for cells in the BLA-40 panel for 45,545 compounds whose NCI-60 drug
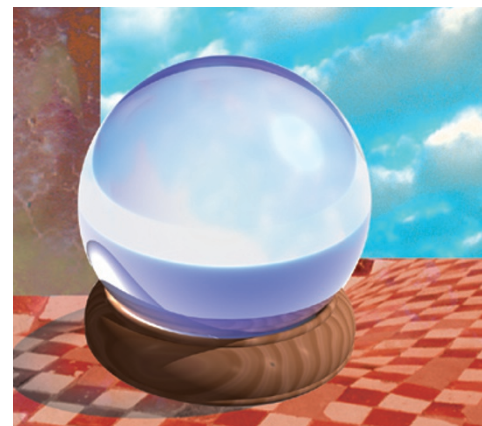
screening data were available. Ranking compounds in order of the number of cell lines predicted to be sensitive allowed them to identify a top hit, the imidazoacridinone NSC637993. This compound, when tested for growth inhibition in the BLA-40 panel, was found to be effective against a higher percentage of BLA-40 cell lines than the current most potent bladder cancer chemotherapy, cisplatin.

It is hoped that COXEN may prove to be a valuable tool in the treatment of cancer and the discovery of novel agents for specific cancer types. Accurate compound pre-screening could also substantially reduce the failure rates in clinical trials, in addition to being a potential strategy to personalize cancer therapy.

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ORIGINAL RESEARCH PAPER Lee, J. *et al.* A strategy for predicting the chemosensitivity of human cancers and its application to drug discovery. *Proc. Natl Acad. Sci. USA* **104**, 13086–13091 (2007)

FURTHER INFORMATION
Coxen: http://www.coxen.org
National Cancer Institute: http://www.cancer.gov