*Nature Reviews Drug Discovery* | AOP, published online 16 September 2011; doi:10.1038/nrd3565

DRUG REPOSITIONING

# Genetic signatures uncover new uses

Identifying new therapeutic uses for approved drugs — known as drug repositioning — can reduce development costs and accelerate regulatory approval. Two papers by Butte and colleagues in *Science Translational Medicine* used computational analysis of publicly available gene expression data to suggest potential new therapeutic uses for approved drugs. In particular, they showed that the anti-ulcer drug cimetidine could be used for the treatment of lung adenocarcinoma, and the anticonvulsant topiramate could be a new therapy for inflammatory bowel disease.

The authors used two sets of gene expression data; microarray data associated with 100 diseases from the Gene Expression Omnibus, and data from human cancer cell lines treated with 164 small molecules. The authors then used a technique known as 'significance analysis of microarrays' to obtain a signature of genes that were significantly up- and downregulated for each disease. Next, they statistically compared each disease signature to each drug expression signature to create a series of drug gene expression profiles. A score was assigned to each drug–disease pair based on profile similarity, with a negative score indicating that the drug and disease have opposite signatures, suggesting that a drug has the potential to have a therapeutic effect on a disease.

This method identified drug–disease relationships for 53 out of 100 diseases, and each of the 164 small molecules was associated with at least 1 of the 53 diseases. Many cancers showed the highest number of matches to therapies, and the drug predicted to be efficacious for the largest set of diseases was the histone deacetylase inhibitor vorinostat.

The authors found that topiramate — which is currently used to treat epilepsy — had a stronger therapeutic score for Crohn's disease than the established therapeutic prednisolone, and was also one of the strongest predicted therapies for ulcerative colitis. So they tested topiramate in a rat model of inflammatory bowel disease. Rats that were treated with topiramate had less diarrhoea, reduced pathological inflammation and ulceration, and less destruction of the colon mucosal layer; these effects were comparable to those in animals treated with prednisolone.

In addition, the methods predicted several new therapeutic relationships for lung adenocarcinoma. The authors chose to test cimetidine because it is an off-patent, inexpensive drug and has a favorable side-effect profile. Lung adenocarcinoma cells treated with cimetidine showed reduced growth and proliferation, and exhibited extensive apoptosis. In a mouse xenograft model of lung adenocarcinoma, cimetidine reduced tumour growth to levels almost comparable with the chemotherapeutic doxorubicin.

The authors identify several caveats to their work, such as the need to have gene expression profiles for any drug that is being evaluated and the issue of whether the effects of a drug in a breast cancer cell line are relevant in all types of diseases. Although clinical studies will be needed before a drug can be approved for a new indication, these papers show that analysis of public gene expression databases can uncover additional uses for approved drugs.

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**ORIGINAL RESEARCH PAPERS** Sirota, M. *et al.* Discovery and preclinical validation of drug indications using compendia of public gene expression data. *Sci. Transl. Med.* **3**, 96ra77 (2011) Dudley, J. T. *et al.* Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. *Sci. Transl. Med.* **3**, 96ra76 (2011)