⟶ **DRUG DEVELOPMENT**

Predicting toxicity

More efficient compound safety screening methods are much-needed to help reduce the persistently high attrition rates in clinical development. Now, writing in the *Journal of Proteome Research*, Nicholson and colleagues present the novel approach taken by the Consortium on Metabonomic Toxicology (COMET), which provides the largest validation so far of the potential of metabolic profiling to predict drug toxicity.

Their metabonomics-based method involved profiling compound-induced perturbations in urinary metabolites using ^{1}H nuclear magnetic resonance spectroscopy (NMR). Their study included 80 compounds that were selected to cover a diverse range of structures and toxicities, with an emphasis on

liver and kidney toxins as these are the major organs involved in toxicity.

Urine samples were collected from male rats both prior to and at various time points over 7 days following treatment with a single dose of compound. This culminated in 6,260 control and 6,675 treated urine samples from 1,652 rats. Histopathology and clinical chemistry evaluations were carried out at 48 and 168 hours post-dose, respectively, to monitor toxicity.

To assess the effect of compounds on urinary metabolites, the authors first built a multivariate model of normal urine based on pre-processed ^{1}H NMR spectra of the samples. Classification of samples from dosed animals as normal or abnormal using this model revealed a high correspondence between toxicity and abnormal metabolic profiles, with 67 out of the 80 treatments showing agreement as to the presence or absence of an effect. Compared with the normal model, 62 treatments exerted an effect and these were used for subsequent studies.

Next, Nicholson *et al.* set out to determine whether urinary metabolite analysis could be used to detect specific organ toxicity. To do this, they used a density estimation method — Classification of Unknowns by Density Superposition (CLOUDS). This combines NMR data obtained from all animals across all time points within the studies for a

particular treatment, which can then be compared as a single unit with the signatures of other treatments.

Using the CLOUDS method in blind tests the authors could correctly identify the target organ of the liver toxin azathioprine and the kidney toxin maleic acid, even at sub-toxic levels. Assessment of the system across all 62 treatments showed that it had a sensitivity — the proportion of all treatments affecting a given organ that are classified to that organ — to liver and kidney toxins of 67% and 41%, respectively. The corresponding specificities — the proportion of all treatments predicted to affect a given organ that truly affect that organ — were 77% and 100%, respectively.

These promising results indicate that this metabonomics-based method provides a non-invasive, sensitive, rapid and cost-effective approach for preclinical toxicology, and it is currently in use by several of the COMET pharmaceutical partners. Such an approach could also have potential in studying drug efficacy in preclinical studies and clinical trials.

Sarah Crunkhorn

ORIGINAL RESEARCH PAPER Ebbels, T. *et al.* Prediction and classification of drug toxicity using probabilistic modeling of temporal metabolic data: the consortium on metabonomic toxicology screening approach. *J. Prot. Res.* **6**, 4407–4422 (2007)
FURTHER READING Lindon, J. *et al.* The Consortium for Metabonomic Toxicology (COMET): aims, activities and achievements. *Pharmacogenomics* **6**, 691–699 (2005)