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COMET and the Challenge of Drug Safety Screening

Every few months we get the same old story: a new platform technology, tool, program, or scheme to search for biomarkers for use in drug safety screens or as new diagnostics. Most of these supposed solutions fade away after a few years, and after a lot of money is spent we are often none the wiser. The fact of the matter is that despite all the developments in modern technology, the pharmaceutical industry is no more efficient at producing drugs than it was 30 years ago. In an ideal world, researchers who are involved in optimally designed drug testing would use technologies that exert a quasi-Darwinian selection pressure (survival of the fittest) so that only the best drug candidates would enter the expensive development process. Currently, only ~11% of drugs that proceed into development get to market (*Nat. Rev. Drug Discov.* **2004**, *3*, 711–715), so clearly either Darwin is not helping us much in compound selection or we are not applying the right tools to select the best compounds.

Of course, transcriptomic methods have been used for nearly a decade now to help us understand gene regulator responses to drug toxicity. However, questions such as "what tissue do you sample and when?" always must be considered with these techniques. Typically, toxicogenomic screening involves the measurement of liver or possibly leukocyte transcript levels, but these measurements do not necessarily tell us about the functional capacity of other tissues or organs. For example, why should we assume that such data give information that is pertinent to kidney pathology? The expensive solution is to screen every tissue, but determining the correct time to sample is difficult, particularly as there are slow or fast and weak or strong responders to any drug treatment. Another problem is related to understanding toxic mechanisms: how do you divine which are the genuine transcript responses that reflect mechanisms of toxicity and which are the adaptive or homeostatic responses that are occurring on the same timescale (*Nat. Biotechnol.* **2004**, *22*, 1268–1274)? Similar problems affect other —omics metrics, and of course proteomic methods have been put forward as being one step closer to reality than transcriptomics. In many ways this statement is true, but the same basic problems apply, in addition to the problem that proteomic data do not carry information on enzymatic activities. In toxicology this is a real issue because many toxins act by enzyme inhibition, which may not be reflected in a protein concentration change per se.

We have long advocated the use of metabonomic and related methods to help describe the temporal metabolic responses of complex systems, such as test species and humans, to drug interventions (*Nat. Rev. Drug Discov.* **2002**, *1*, 153–161). Initially, these studies were largely phenomenological, but increasingly they have become mechanistically informative and are becoming more widely used in the pharmaceutical industry. The advantage of metabonomics (NMR- or MS-based screening of body fluids collected over time after drug dosing) is that these methods are analytically highly reproducible, relatively inexpensive, and most importantly capture a lot of real-world endpoint data on a huge number of pathways. Because these studies can be performed noninvasively (e.g., urine sampling), they can be repeated on individual animals so that fast or slow responders can be identified and appropriate statistics can be applied to discover biomarkers.

One of the largest projects undertaken in metabonomics to date was the Consortium on Metabonomic Toxicology (COMET; *Pharmacogenomics* **2005**, *6*, 691–699). This project was funded by several major pharmaceutical companies and undertaken in collaboration with Imperial College London. The aim was to perform a large number (n = 147) of drug interventional and physiological experiments (7-day studies and, in some cases, 28-day studies in rats) to build a database of time-related metabolic response data that could be related to conventional clinical chemical and histopathological outcomes. These data sets were used to construct a series of mathematical models to describe how compounds with different sites and mechanisms of action produce char-

acteristic biomarker patterns that can be used as the basis of an in vivo screening process. The construction of these models is described in this issue of *JPR* (pp 4407–4422).

With this project, we found that urinary metabolite profiles could be highly revealing of toxicity class when the metabolic responses over time were taken into account and compared by using novel combined probabilistic and similarity index methods. COMET was a highly successful project with a working metabolic expert-screening-system shell delivered to each company for augmentation with in-house data unique to each of the COMET company partners. We learned a lot from COMET and have gone on to form the COMET 2 project (again pharma-funded) to investigate toxic mechanisms by using metabolism-driven top-down systems biology tools, and publications are now starting to emerge from that project as well (*J. Proteome Res.* **2007**, *6*, 2711–2719).

We also learned that the so-called gold standard of histopathology is perhaps not the best endpoint with which to compare —omics data. Because —omics data are by definition biochemical data and biochemical changes precede pathological changes, a temporal disconnection will always exist between them. Also, there are many serious conditions that are not necessarily associated with gross pathological changes (acute cyanide poisoning leaves no histopathological evidence!). So, in the future, we will have to learn to use the metabolic trajectories themselves as endpoints in toxicological screens, and to do this effectively we will require the assistance of all the other —omics sciences to help us interpret the metabolic fluctuations that relate to toxic mechanisms. We think there is now light at the end of the —omics safety screening tunnel, but the technology is still some way from widespread practical implementation. We hope that some of the answers will be found in the COMET 2 project, so watch this space. . .

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