

## Metabolomics for understanding adverse drug effects

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Metabolite profiling has been used in physiological investigations of microorganisms, mammalian cells and even organs and tissues. The method holds a promise in toxicity research especially for drugs in preclinical safety evaluation. Metabolomics has potential to give insights into mechanisms of toxicity and maybe useful in off-target toxicity identification. We studied a small set of drugs and compared the metabolite profiles using PCA. We were able to classify the drugs correctly according to their mechanisms of action. Using similar approach we investigated the long term adverse effects of diclofenac on human hepatic cells. In other studies, we looked into detailed metabolome and calculated fluxes in presence of verapamil and doxorubicin on HL-1 cardiomyocytes. Verapamil has shown effects independent of its  $\text{Ca}^{+2}$  channel blocking effect and its possible application to inhibit proliferation explaining its reported anti-cancereffects. Doxorubicin produces multiple and complex effects. Although extensively studied, clinically relevant concentrations were not used as probably these low concentrations do not show any effect in commonly used endpoint assays. We studied the glycolysis and TCA cycle activity in presence of very low but clinically relevant concentration of Doxorubicin. Metabolomics has proved to be a very sensitive method to assess effects of drugs at sub toxic pharmacological concentrations. Changes in the cellular metabolism may already indicate eventual disruption of functions that probably lead to toxicity manifestation. As such alert flags and whistles can be put on drug candidates which alter process that lead to toxicity.