



Developing Biomarkers for Adverse Response to Drugs or Chemicals

June 2007

Drug-induced liver injury is the leading reason that drug candidates fail. Identifying a suite of toxicity biomarkers for use in preclinical screening of drug candidates will allow drugs with harmful side effects to be identified earlier. Biomarkers that can be used to monitor or stage diseases will also offer insight into the net metabolic effect of a drug and can provide information for developing new drugs or adjusting treatment. Chenomx software offers powerful tools to aid in identifying these biomarkers.

Problem

Drug-induced liver injury is the leading cause for drug candidates to fail during clinical trials and to be pulled from market following approval. Identifying a suite of toxicity biomarkers for use in pre-clinical screening of drug candidates will allow drugs with harmful side-effects to be identified earlier.

Study Design

Researchers at RTI International are using metabolomics to develop markers predictive of liver injury induced by compounds used in the clinical management of tuberculosis, epilepsy, lipid disorders and pain. An example study followed rats that were dosed with vehicle or 100 or 300 mg/kg isoniazid for 1 or 14 days. Urine was collected pre-dose and 0-6 and 6-24 h following the dose. For each sample, 400 μ L of urine was mixed with 200 μ L of a buffer solution containing D₂O, and the mixture was pH adjusted prior to analysis.

ABOUT CHENOMX INC.

Chenomx, Inc. is a privately-held Canadian company that specializes in developing complex mixture analysis technology for broad application in life science technologies. With world-class expertise in chemistry, pharmaceutical sciences, and computer software, Chenomx offers a broad range of software products, compound libraries, and services to support researchers worldwide.

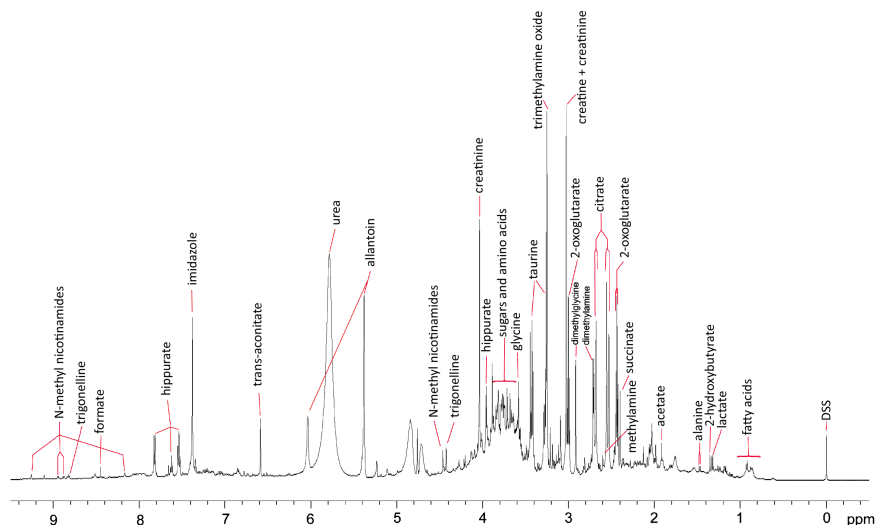


Figure 1. Example spectrum annotated with some identified metabolites

Metabolomic Analysis

For the metabolomics portion of this study, ¹H NMR spectra were acquired on a Varian INOVA 600 MHz spectrometer. Using Chenomx software, RTI scientists identified and quantified metabolites in the urine samples (Figure 1). RTI scientists then assessed the standard deviation of test samples from time-matched control samples, and were able to identify a number of metabolites that differentiated test from control samples in a dose-dependent manner (Figure 2).

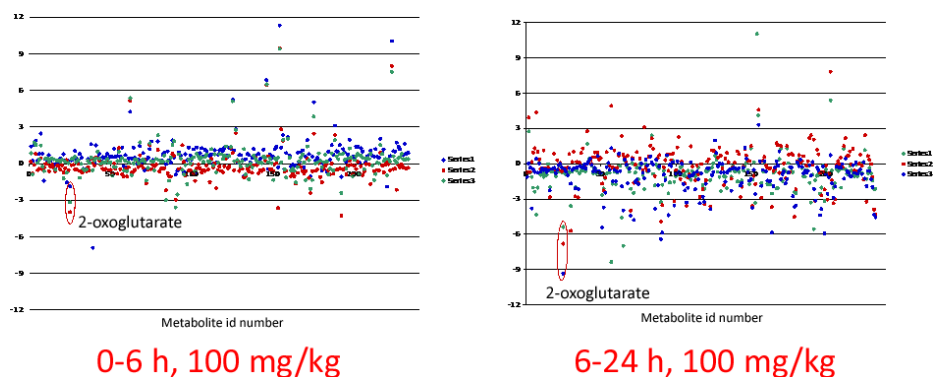


Figure 2. Processing NMR data with Chenomx software allowed identifying and quantifying over 200 metabolites in urine. When viewing standard differences from the control, endogenous metabolites were identified that were associated with isoniazid treatment by dose and time, including 2-oxoglutarate (shown).

Results

RTI scientists were able to study the effects of drugs on the metabolic profiles of rats to begin development of putative biomarkers for drug-induced liver injury. This work will also help in understanding the causal relationships inherent in this type of injury.

Acknowledgements

This case study describes an application developed by the metabolomics group at RTI International, with funding by the National Institutes of Health. The study, including figures and data, appears courtesy of Dr. Susan Sumner (PI, Grant #5R21GM75903) of RTI International.