

## Toxicogenomics and Biomarker Discovery for the Prediction of Long Term Toxicity

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### ABSTRACT

Toxicogenomics is a novel approach for predicting a compound's toxicity using gene, protein and metabolite expression information. Changes to the molecular expression profiles following exposure to a drug together with conventional clinical endpoints are used to build reference libraries of known compounds against which novel compounds can be tested. Biomarker candidates are then deduced from such libraries and characterized further to determine the causal relationship between the biomarker and toxicity in animal models and humans, respectively.

The basic steps in generating a toxicogenomics knowledge base for the evaluation of novel compounds include the collection of data from conventional toxicology, establishing quality-checked and normalized expression data, construction of a reference database with a number of well-known and well-characterized compounds, and the selection of toxicological marker genes based on statistical methods. After validating and refining the reference compendium it is used to classify novel, uncharacterized compounds. Inclusion of related functional genomics data enables the characterization of gene function and regulatory mechanisms to determine the compounds' mechanisms-of-action at various toxicological endpoints.

Gene data in collaboration with 13 pharma and three academic partners will apply this approach to a series of proprietary compounds that have been dropped from development after they failed conventional toxicology tests. The efforts by the PredTox consortium are actively supported by the European Commission as part of the 'Innovative Medicines for Europe' (InnoMed) programme. During the project high throughput molecular techniques will be combined with conventional toxicology methods to build a unique toxicity profile of each compound. These profiles will be used to predict the likelihood that a drug candidate will fail during toxicological testing phases. Advanced statistical methods, including machine

learning algorithms, will be applied and analysis results will be maintained and accessible to the consortium members.

## PERSONAL HISTORY

Dr. Gmuender has 26 years of experience in molecular biology, including 11 years at Hoffmann-La Roche during which he became acquainted with the microarray technology and participated in various collaborations. In 2001 he joined Genedata as a senior scientific consultant. At Genedata, he analyzes genomics data for a variety of applications and has collaborated with several pharmaceutical companies on the analysis of microarray data in toxicology, including a consortium of three pharmaceutical companies and several EU projects. One of them is the InnoMed consortium, being led by the European Federation of Pharmaceutical Industry and Associations (EFPIA). The goal of this project is to deliver new biomarkers of toxicity, a greater understanding of mechanisms of toxicity and to predict toxicity using transcriptomics, proteomics, metabonomics technologies and conventional toxicology parameters.

## PUBLICATION

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