Predicting Mode of Action and Point of Departure from Toxicogenomic Data

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The U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) and National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program (NTP) are embracing gene expression profiling as a means of assessing bioactivity. EPA ORD is using differential gene expression from BioSpyder's TempO-Seq technology and a variety of ontology-based tools (e.g., the Broad Institutes Gene set enrichment analysis (GSEA) conventional ontology enrichment analyses, Benchmark Dose) to address activity and mode of action. These technologies are emerging as a viable way to assess mode of action (MoA) and points of departure (POD) and have the potential to drastically reduce testing costs and compound development time. The first steps in using transcriptional responses as a basis of safety assessment are in progress. Furthermore, opportunities exist for using transcriptomics as the basis for a "read-across"-style assessment of chemical similarity, comparing gene expression signatures, or ontology enrichment profiles to predict putative MoA in the absence of generating new in vivo data. However, several important considerations remain unresolved, including which biological system(s) should be used to query transcriptional responses, how to translate expression changes into adverse outcome pathways or other definitions of mode of action, and the best manner in which to summarize gene expression data into a POD. The manner in which these challenges are addressed over the coming years will have a substantial impact on how these data are used to inform chemical safety decisions. This research is designed to provide clarity about the impact of these and other questions, suggest best practices, and provide the chemical safety community with tools for their implementation.

The specific goals of this research are:

- Goal 1: Deriving and interpreting a point of departure from high-throughput transcriptomics
    - Goal 1A: Determine how decisions about the data analysis pipeline impact point of departure and pathways identified as perturbed
    - Goal 1B: Determine the relationship between transcriptomics-derived PODs and more conventional PODs
    - Goal 1C: Determine whether the cytotoxic burst concept described for ToxCast bioactivity translates to expression analysis
- Goal 2: Defining a domain of applicability for a cell line panel
    - Goal 2A: Determine how similar are different target tissues (in vivo) to cell lines being explored for in vitro screening
    - Goal 2B: Explore how many tissues would need to be represented in a screening battery for adequate coverage
- Goal 3: Defining impact of cell line selection on transcriptomic-based decisions (future activity)
- Goal 4: Develop a graphical toolbox to allow stakeholders to independently bring to bear this best practices pipeline on their datasets (future activity)

Implications: This work is designed to establish the utility of gene expression profiling using in vitro models for predicting adverse outcomes and hazard. By identifying a suite of genes with altered expression after exposure to a compound, transcriptomic studies can yield essential information on potency and mode of action. In the longer term, these technologies are being developed as part of the broader multi-tier safety assessment paradigm being refined at ScitoVation. The efforts will also support validation of the lung and liver toxicity models and the liver bioreactor project. This program will also develop possible application of various machine learning algorithms to predict cellular response to compounds based on previously studied chemicals both in vivo and in vitro. There is a legacy of data already in the public domain using transcriptomics to study dose

response to chemicals, and the application of computational methods and cellular ontologies to predict MoA and possible adverse outcomes could further reduce cost and time of chemical screening approaches, or provide information valuable to designing in vitro exposure experiments for screening new compounds.

Collaborations: BioSpyder

Key words: gene expression, mode of action, point of departure, in vitro transcriptomics, toxicogenomics

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Peer-reviewed publication(s):

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