ScitoXpress™

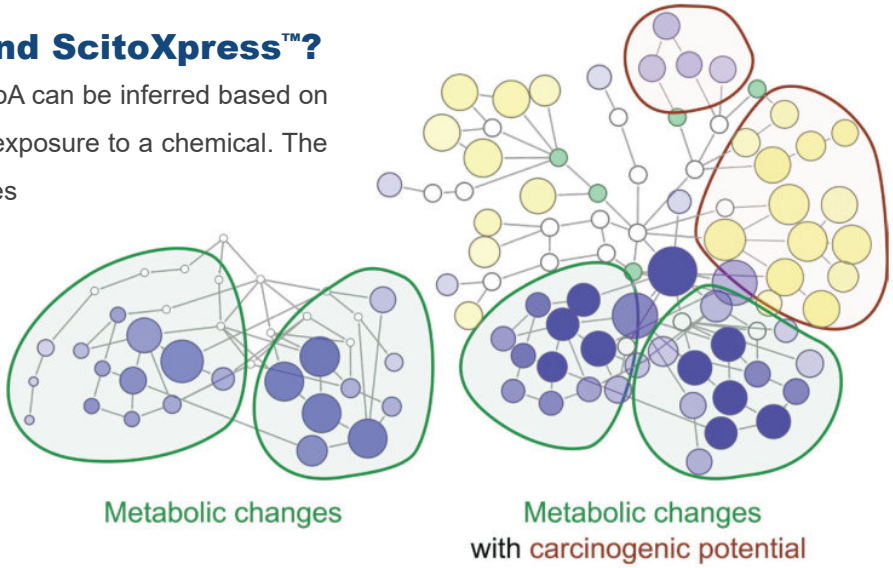
Identifying Mode of Action and Bioactivity Effect Levels

ScitoVation
PIONEERS IN CHEMICAL SAFETY ASSESSMENT

Transcriptomics analysis offers a cost-efficient and rapid means of categorizing chemical risk. With our newly introduced ScitoXpress™ package, we conduct in vitro transcriptomics studies on client compounds to provide answers about: 1) Points of departure (POD)—the lowest dosage at which bioactivity occurs—and 2) Potential modes of action (MoA) based on the subsets of genes that are expressed at various doses. Possible applications of our ScitoXpress™ package are as a screening tool for a small subset of compounds or to identify possible modes of action for outcomes observed in vivo.

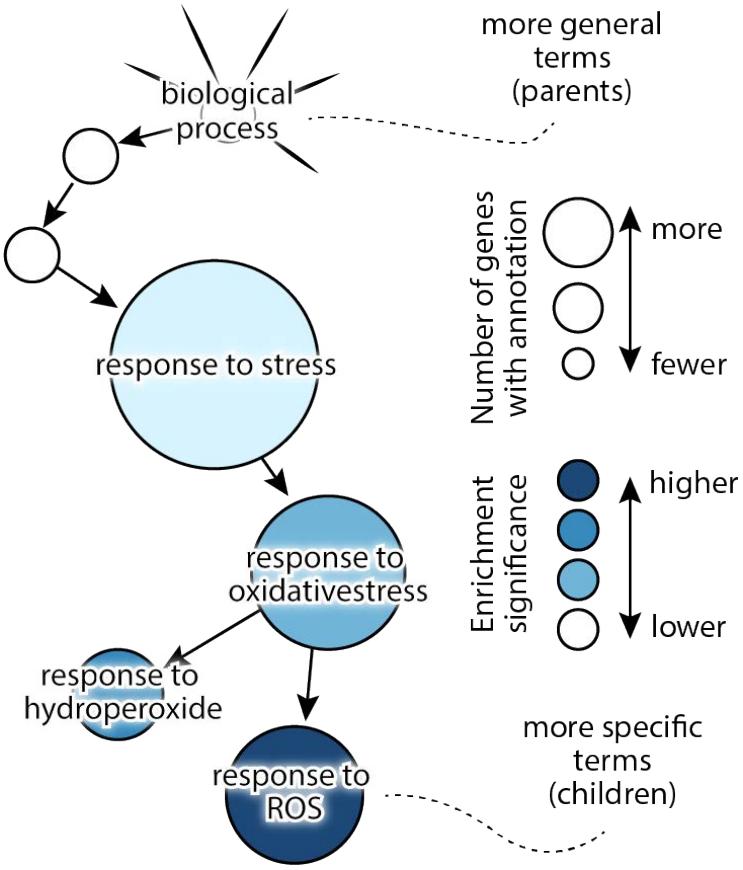
Why Use Transcriptomics and ScitoXpress™?

With the use of transcriptomics, POD and MoA can be inferred based on changes in gene expression in response to exposure to a chemical. The rationale behind this approach is that changes in gene expression must precede the observed changes in phenotype (e.g.,tumor formation, liver hypertrophy). Thus, dose-response changes in gene expression are likely to be observed at lower doses compared to endpoints such as disease or tumors that would be observed in in vivo studies.



Our ScitoXpress™ package delivers additional value by:

- **Guiding additional studies:** The information can be used for guiding additional studies including study design and possible endpoints or organs of interest. This saves clients both time and money.
- **Being a rigorous approach, applied by experts:** ScitoVation brings a wealth and depth of expertise in analyzing these data. Once these methods are widely adopted, this increases the possibility of acceptance of the interpretation of the results by our peers, including regulators.
- **Already having support from government groups:** The methods used are currently under adoption by U.S. EPA, the National Toxicology Program and Health Canada.



What's Provided

The standard output includes the following:

- POD estimate: Doses at which bioactivity are observed
- MoA: Output from our proprietary software tool MoAviz showing perturbed pathways.
- Documentation of analysis consistent with the OECD Transcriptomic Reporting Framework.
- Excel spreadsheet of differentially expressed genes for customers desiring to conduct additional analysis

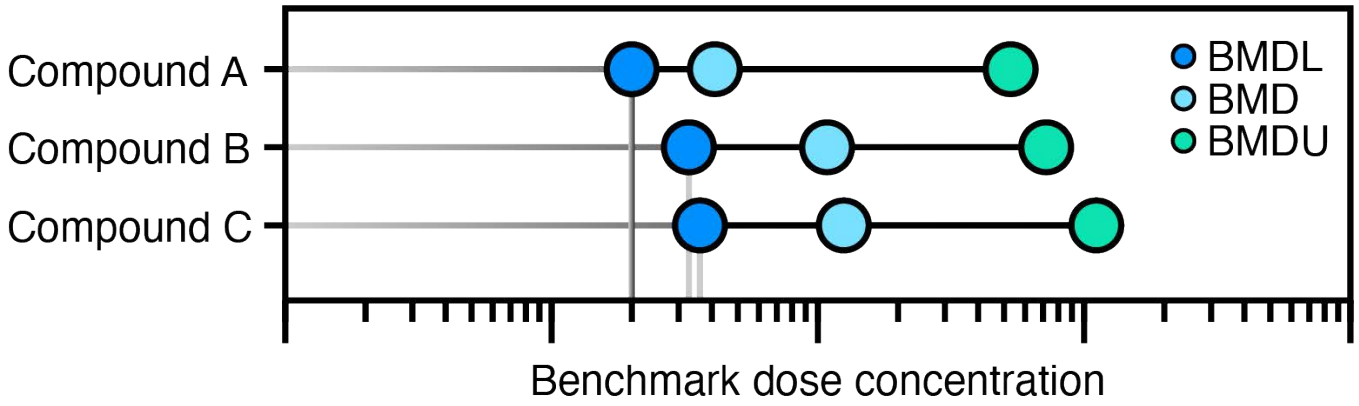
The ScitoVation Promise

- We promise to partner with you to define metrics for success at the beginning of the project and outline a clear plan to achieve them.
- We promise to meet the timeline pending receipt of client materials or approvals within the pre-agreed timeframes.
- We promise to stand behind our pricing unless there is a change in scope. Any changes in scope that affect the price will be promptly communicated and discussed as appropriate.
- We promise to perform our work with the highest level of scientific rigor and scrutiny.
- We promise that all deliverables including experimental designs, protocols, data, analyses, and reports will be reviewed before submission to the client.

Using Transcriptomic Points of Departure to Determine Compound Toxicity

Conventional concepts of points of departure for adverse effects (e.g., NOAEL/LOAEL) do not translate directly to gene expression data. The benchmark dose approach offers a robust alternative method, and has been adapted to transcriptomics. Benchmark Dose is a data driven mathematical approach to determine a dose at which a significant change in response is detected. It is applicable to continuous data such as gene expression data where changes in the abundance of gene transcripts can be detected for all genes expressed in a cell using fluorescence detection (as in microarray technology) or via counts of sequenced transcripts per gene (as with RNA-Seq).

Chemicals with different potencies lead to apical effects at different exposure levels (i.e., have different points of departure, POD). It has been similarly established that compounds with lower points of departure also induce transcriptomic changes at lower concentrations. This observation has led to the concept of the transcriptomic point of departure as a proxy for compound toxicity. The impact of a compound on the transcriptome can be quantitatively determined and used to compare potency (Figure). We are using this concept with clients in applications related to compound screening and down-selection. There are also potential applications in product stewardship, such as alternatives assessment.



Benchmark dose estimates for gene expression for three hypothetical compounds. Lower (BMDL, dark blue) and upper (BMDU, green) confidence intervals for the estimate for reference.

CONTACT US

For additional information, please contact customerservice@ScitoVation.com

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