

Mechanism of Toxicity Reports

Mechanistic predictive toxicogenomic analyses to discovery gene expression patterns and complex pathway and gene relationships.

With ToxExpress® Mechanisms of Toxicity (MOT) Reports, it's possible to:

- Gain a deeper understanding of human risk due to toxicity-related adverse events
- Frame species-specific and biomarker discovery efforts
- Compress development time and effort to explain toxicity issues and to implement secondary screens
- Develop rational drug rescue strategies

Drug issues often present complex biological interactions among multiple pathways and frequently require multiple sequential experiments to identify (Figure 1). Now with one rapid *in vivo* experiment, Gene Logic's MOT Reports enable you to see toxicity issues with more clarity than you ever imagined.

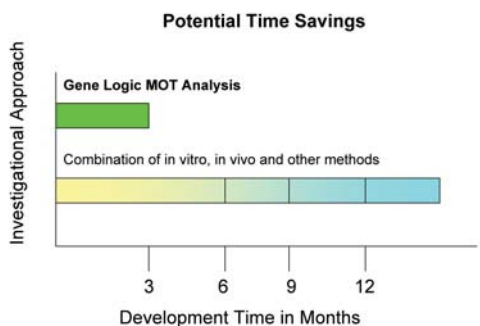


Figure 1: An illustration comparing development time when both *in vivo* and *in vitro* conventional methods are employed to elucidate toxicity versus gene expression analysis. The microarray experiment includes in-life studies and genomic analysis.

A rapid, detailed assessment within weeks.

Gene Logic's MOT Reports provide a deeper, richer understanding of your compound's effect by examining thousands of regulated and co-regulated pathway genes simultaneously, thus enabling more informed drug development decisions in just weeks.

MOT Reports are generated using extensive gene expression reference content and sophisticated analysis tools within Gene Logic's ToxExpress® System. Toxicogenomic analysis works cohesively with other safety assessment data (Figure 2) to provide a detailed analysis of the underpinning biology that drives predicted or observed toxicity.

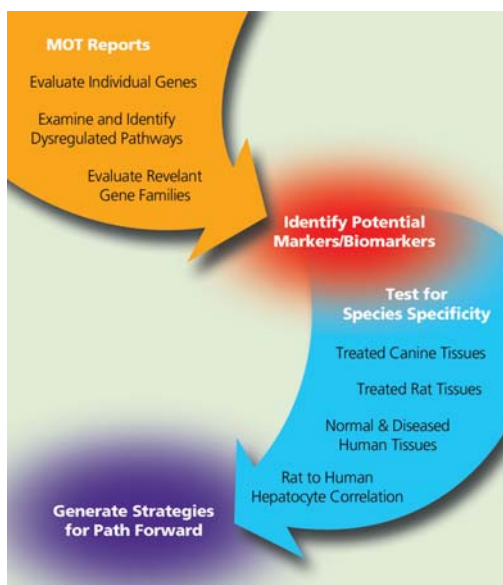


Figure 2: Mechanism of Toxicity (MOT) using gene expression illustrates a process for developing strategies to advance compounds. MOT Reports provide an in-depth analysis of individual genes, pathways and relevant gene families. From this analysis potential markers/biomarkers can be identified. Species-specific analysis can be completed on these marker by testing expression data from treated canine tissues, treated rat tissues, treated human hepatocytes or normal and disease human tissues.

Each project begins with an in-depth scientific discussion to determine the scope of the project. Using data from in-life studies and gene expression profiling, Gene Logic evaluates relevant gene sets, pathways and functional activity to unravel the biology behind the toxicity. Gene Logic's expert molecular toxicologists systematically uncover and clarify a road map that helps explain the adverse event. MOT results provide the information, the strategies, and the potential answers you need to move your compound forward.

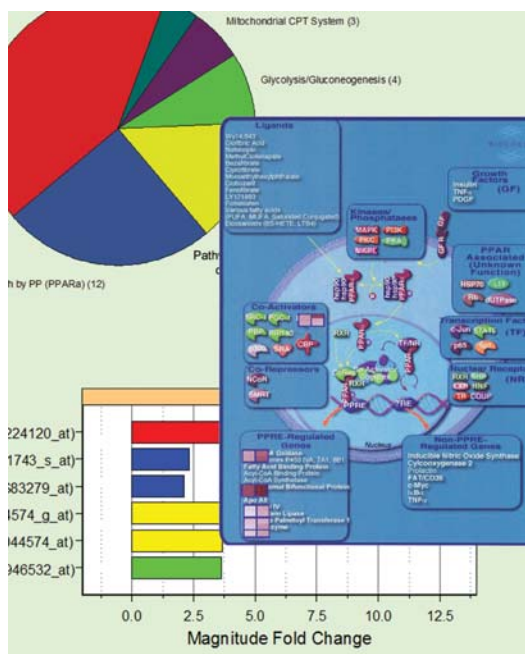


Figure 3: Some examples of MOT Report findings generated on Clofibrate. Top toxicity relevant pathways are identified using standard and proprietary tools. These pathways are further interrogated on a gene-by-gene basis, and results are placed directly into pathways as illustrated in the blue figure. Selected gene sets are examined further for dysregulation, and supporting evidence from similar compounds in the ToxExpress® Reference Database helps confirm findings (not shown).

Endless possibilities and flexibility in analysis approaches.

MOT Reports can be applied to a wide variety of efforts, such as those to:

- Explore and understand the biological changes of adverse events in the context of genes and pathways
- Determine molecular mechanisms and relevance of dysregulation being triggered by toxicity
- Elucidate unforeseen, anticipated or observed toxicity

- Compare your compound's profile to those within the ToxExpress® System for further evidence that patterns are associated with specific phenotypes
- Examine effects of a set of compounds at the gene and pathway level
- Explore dose- and time-dependent responses
- Investigate archived tissues for look-back studies when toxicity occurs

Gene Logic has the capability to develop custom analyses designed to:

Discover potential candidates and novel biomarkers:

- Identify potential candidate biomarkers (screening or diagnostic)
- Utilize the power of both toxicological and human disease-based genomic databases
- Test relationships between gene expression, clinical pathology and histopathology, across all ToxExpress® System reference compounds and BioExpress® System tissues or on a select few
- Survey multiple organs for off-target effects
- Examine cross-species relationships:
 - Determine differential expression between rodent, canine, or human-specific (in vitro only) experiments to help explain species-specific responses
 - Canine microarray data-hundreds of samples representing liver, kidney, and heart tissues
 - Rat microarray data-thousands of samples in the ToxExpress® System derived from *in vivo* and *in vitro* studies completed using well characterized pharmaceuticals and reference chemicals
 - Human microarray data-thousands of normal and diseased human tissue samples in the BioExpress® System and hundreds of in vitro human hepatocyte sample data in the ToxExpress® System

MOT Reports. Faster answers. Greater detail.

For more information about how MOT Reports can help you answer perplexing toxicity issues, call 1-800-GENELOGIC to talk to your Business Development or Customer Support representative, email us at info@genelogic.com, or visit us at www.genelogic.com.



www.genelogic.com

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