SYSTEMS TOXICOLOGY MODULE

SYSTEMS TOXICOLOGY KNOWLEDGEBASE AND DATA ANALYSIS FOR METACORE™ AND METADRUG™

USE THE SYSTEMS TOXICOLOGY MODULE TO:

- Investigate toxic liabilities of xenobiotics and identify biomarkers of organ toxicity
- Assess target safety liabilities
- Evaluate compounds for in-licensing
- Compare in-house development vs. competitor compounds
- Mechanistically evaluate pre-clinical toxicity findings, and assess clinical relevance
- Differentiate on and off-target effects
- Develop screening strategy for follow-up compounds

WHO CAN BENEFIT

- Safety assessment researchers working in molecular, mechanistic and discovery toxicology groups.
- Environmental safety scientists evaluating chemical risk from a molecular or pathway perspective.
- Academic researchers in toxicology groups in universities and hospitals.

SYSTEMS TOXICOLOGY MODULE OVERVIEW

A knowledge base and data analysis module designed for the assessment of safety liabilities of drugs, environmental contaminants and other xenobiotics at all stages of discovery and development.

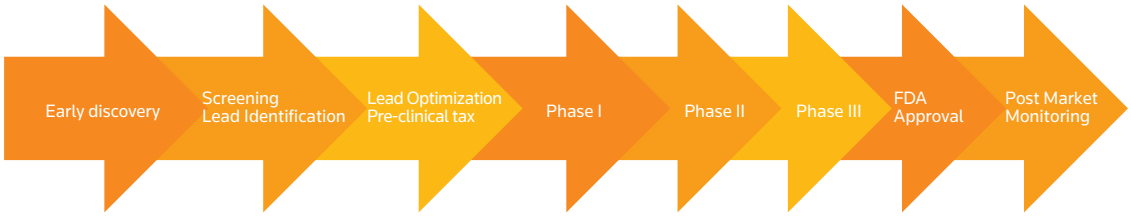
Available as an add-on module for MetaCore or MetaDrug systems biology and systems pharmacology solutions, it seamlessly integrates a database of safety-related information and analytical tools.

Adding to the existing information mining and data analysis power of MetaCore and MetaDrug, the Systems Toxicology Module includes a comprehensive, searchable database of gene, protein and metabolite associations to chemical toxicity, new toxicity-related pathway maps, and tools for visualization and filtering of toxicity information on pathway maps and biological interaction networks.

Developed with leading drug safety experts, the Systems Toxicology Module brings together the relevant molecular data types generated as part of the safety assessment process and the tools and supporting information to make the best use of these data. Experiments can easily be designed to model specific pathologies, to investigate mechanisms and pathways of toxicity, or to identify safety biomarkers. Molecular safety data can be analyzed in the context of previously reported effects and known signalling and metabolic networks, and automated data analysis and reporting workflows enable rapid interpretation and reporting of experimental results.

KEY CAPABILITIES

- Browsable toxicity ontology of highly-detailed terms covering multiple target organs, with organ substructures and pathology subtypes differentiated
- High quality, manual full-text literature curation of gene, protein and small molecule associations to toxicity terms
- Simple key-word or multi-parameter Boolean searching across toxicity categories for pathology terms, toxicants, and gene, protein or metabolite biomarkers of toxicity



- Comprehensive target safety assessment
- In silico toxicity evaluation of scaffolds/lead compounds
- Comparative analysis of competitor safety profiles

- Analysis of in vitro and early *in vivo* systems toxicology experiments
- Toxicity pathways exploration
- Identification and validation of translational biomarkers
- Corelation of target relationship to observed toxicity
- Ranking of candidates by safety profiles

- Understanding of unexpected safety issues and identification of clinical safety biomarkers

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HARDWARE REQUIREMENTS

CLIENT (FOR WEB PORTAL AND IN-HOUSE INSTALLATIONS):

- P4 CPU and 1GB RAM
- Internet Explore 6.0 or higher
- Macromedia Flash Player 8 or higher
- Java Runtime Environment (JRE) 1.5.0
- ChemDraw ActiveX / Plugin Net 9.0 Download Edition

SERVER (FOR IN-HOUSE INSTALLATIONS):

- 2 or more P4/XEON CPU's with 4GB of RAM recommended
- 3.2 GHz CPU and higher recommended
- SCSI HDD with minimum of 250GB of storage recommended
- RAID recommended
- RedHat Enterprise Linux 3, 4, or 5.1; SuSE 9.2; CentOS 4.4
- X development package installed
- Oracle 10.2 DBMS and client tools
- MetaCore and MetaDrug support x86-64 bit architecture

- Ability to flag specific classes of toxicity associations on maps alongside data, and visualize and filter networks for specific pathologies
- Automated analysis and reporting of experimental data with unique enrichment calculations for specific pathologies, xenobiotic metabolism, and toxicity processes
- QSAR-based prediction of pathological outcomes from chemical structures (with MetaDrug)

EXPERIMENTAL DATA

You can import molecular structures*, experimental data such as genomic, proteomic, metabolomic data, and screening data. This unique feature of MetaCore and MetaDrug permits the concurrent integration and visualization of multiple types of chemical and biological data on pathways and networks. With the Systems Toxicology Module, these data can be analysed and visualized in the context of pathological findings, biomarkers and pathways. Addressable data types include:

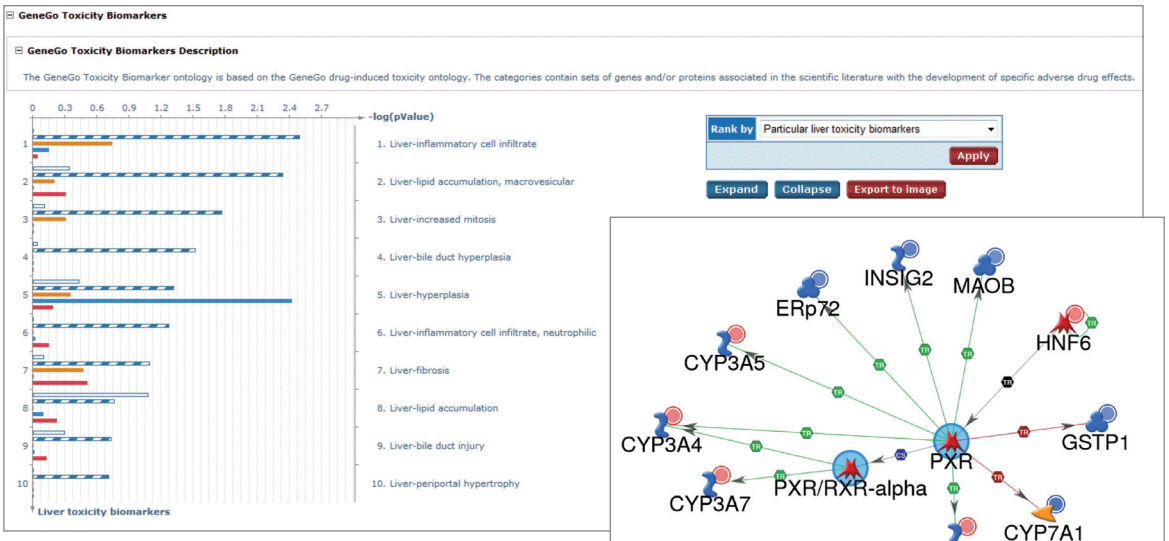
- MOL, SD & CDX structure files*
- NMR or MS metabolite data, via CAS numbers, SMILES or brutto formulas
- Gene expression data: whole genome arrays, focused arrays, QPCR and SAGE
- Proteomic data
- MicroRNA data
- siRNA assays
- HTS and HCS data

(*requires MetaDrug)

CONTENT

The Systems Toxicology Module adds to the existing content of MetaCore and MetaDrug with:

- 29 new pathway maps representing toxicologically relevant processes
- > 11,000 highly-detailed pathology terms covering 11 target organs (liver, kidney, heart, nose, trachea, lung, esophagus, forestomach, glandular stomach, epididymis, testis), organized into a browsable ontology with organ substructures and pathology subtypes differentiated
- > 17,000 toxicant-pathology associations
- > 7,700 gene and >3,900 protein-toxicity annotations
- > 5,100 small molecule metabolite-toxicity annotations
- 11 additional MetaDrug QSAR models for structure based prediction of pathological and safety pharmacology outcomes.



GeneGo toxicity biomarkers enrichment

Protein interaction network showing differential gene expression in transcriptional targets of Pregnane-X receptor (PXR)

Contact us to find out more about MetaCore, MetaDrug and the Systems Toxicology Module or visit thomsonreuters.com/diseaseinsight

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