

# Mapping Human Toxicity and Disease Pathways in ToxCast™

*ToxCast Data Analysis Summit*

*EPA, RTP*

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



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# ToxCast Pathway Approach

- **Bioinformatics**

  - database building and data analysis

- **Systems Biology**

  - mathematical modeling and reasoning to describe/infer biological phenomena

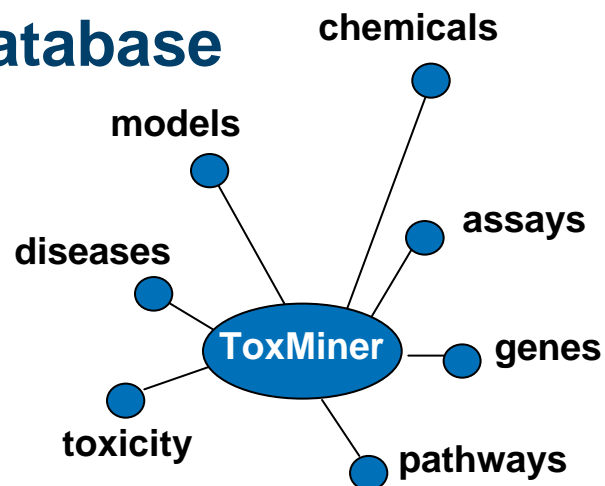
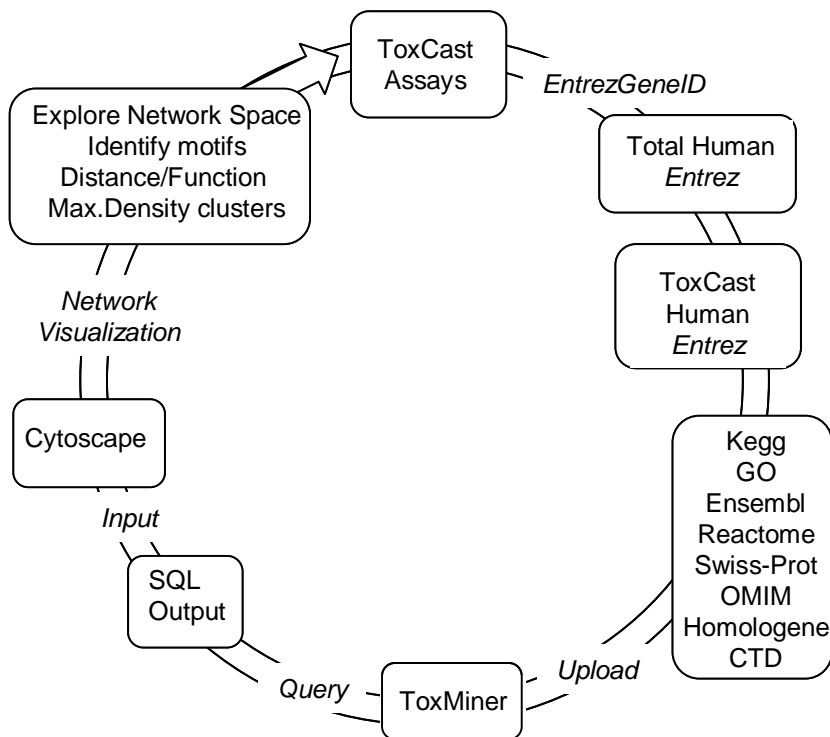
- **Computational Chemistry**

  - mathematical modeling of physical-chemical properties at the molecular level

- **Molecular Biology**

  - HTS technologies-genomics, proteomics, and metabolomics

# ToxMiner Pathway Database



## ACToR Aggregated Computational Toxicology Resource

U.S. ENVIRONMENTAL PROTECTION AGENCY

**ACToR: Aggregated Computational Toxicology Resource**

**Data Collection: EPA CCL3**

**Name:** EPA CCL3 [Link out](#)

**Description:** EPA has drinking water regulations for more than 90 contaminants. The Safe Drinking Water Act (SDWA) includes a process that we must follow to identify and list unregulated contaminants which may require a national drinking water regulation in the future. EPA must periodically publish this list of contaminants (called the Contaminant Candidate List or CCL). In February 2008 we announced the draft CCL3.

**ID:** 139

**Institutional Source:** EPA



**Source Type:** Chemicals

**Number of Substances:** 93

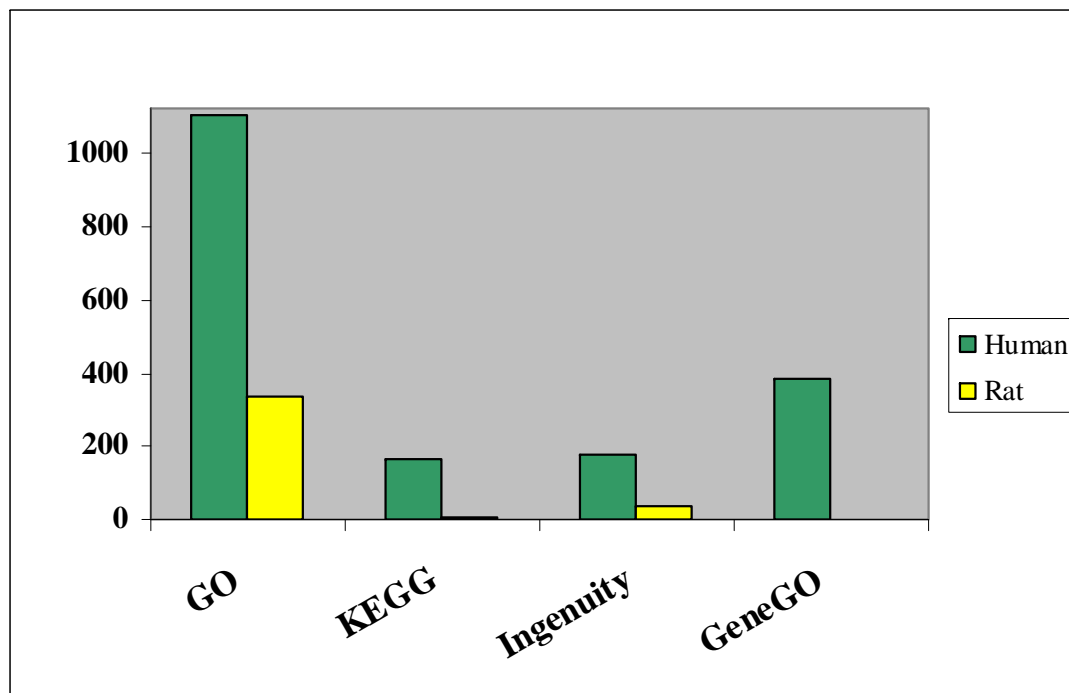
**Number of Genetic Chemicals:** 92

**Chemical Table**

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Structure	Name	CASRN	Generic Chemical Details	Hazard	Outdoorsensitivity	Toxicity	Genotoxicity	Developmental Toxicity	Reproductive Toxicity	Chemical Toxicity	Final Status
	1,1,1,2-Tetrachloroethane	630-29-6	<a href="#">Details</a>	H <sub>3</sub>	C <sub>3</sub>	G	D	R	R	C <sub>1</sub>	
	1,1-Dichloroethane	75-34-3	<a href="#">Details</a>	H <sub>3</sub>	C <sub>3</sub>	G	D	R	R	C <sub>1</sub>	

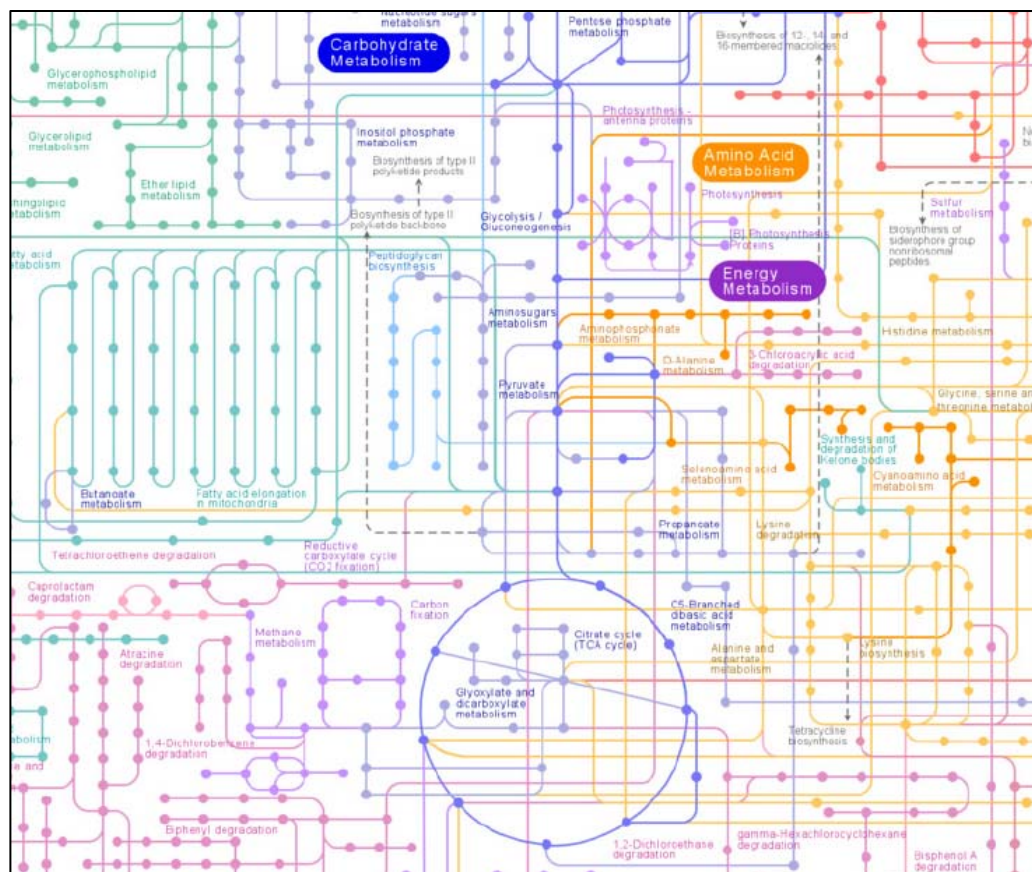
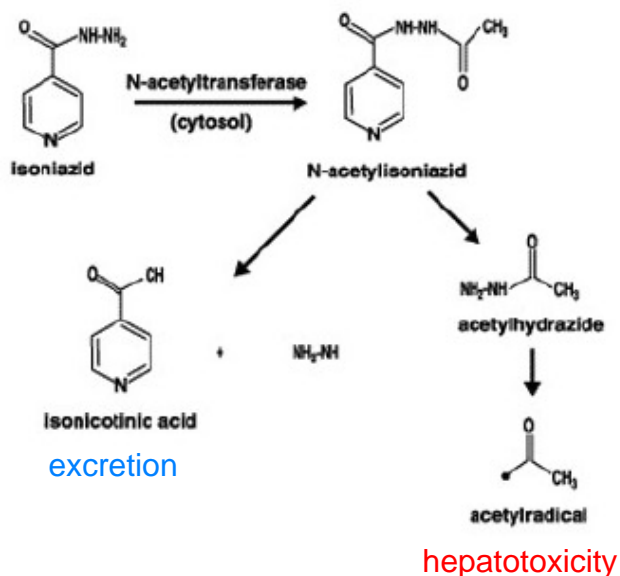
## Pathways/Processes Identified by Analyses of ToxCast Data



	<i>Human</i>	<i>Rat</i>
GO	1104	336
KEGG	166	9
Ingenuity	180	39
GeneGO	385	-
Total Unique Entrez GeneID	236	51

# What is a Pathway?

## Pathway for Isoniazid Metabolism



adapted from KEGG Global Pathway Map (<http://www.genome.jp/kegg/>)

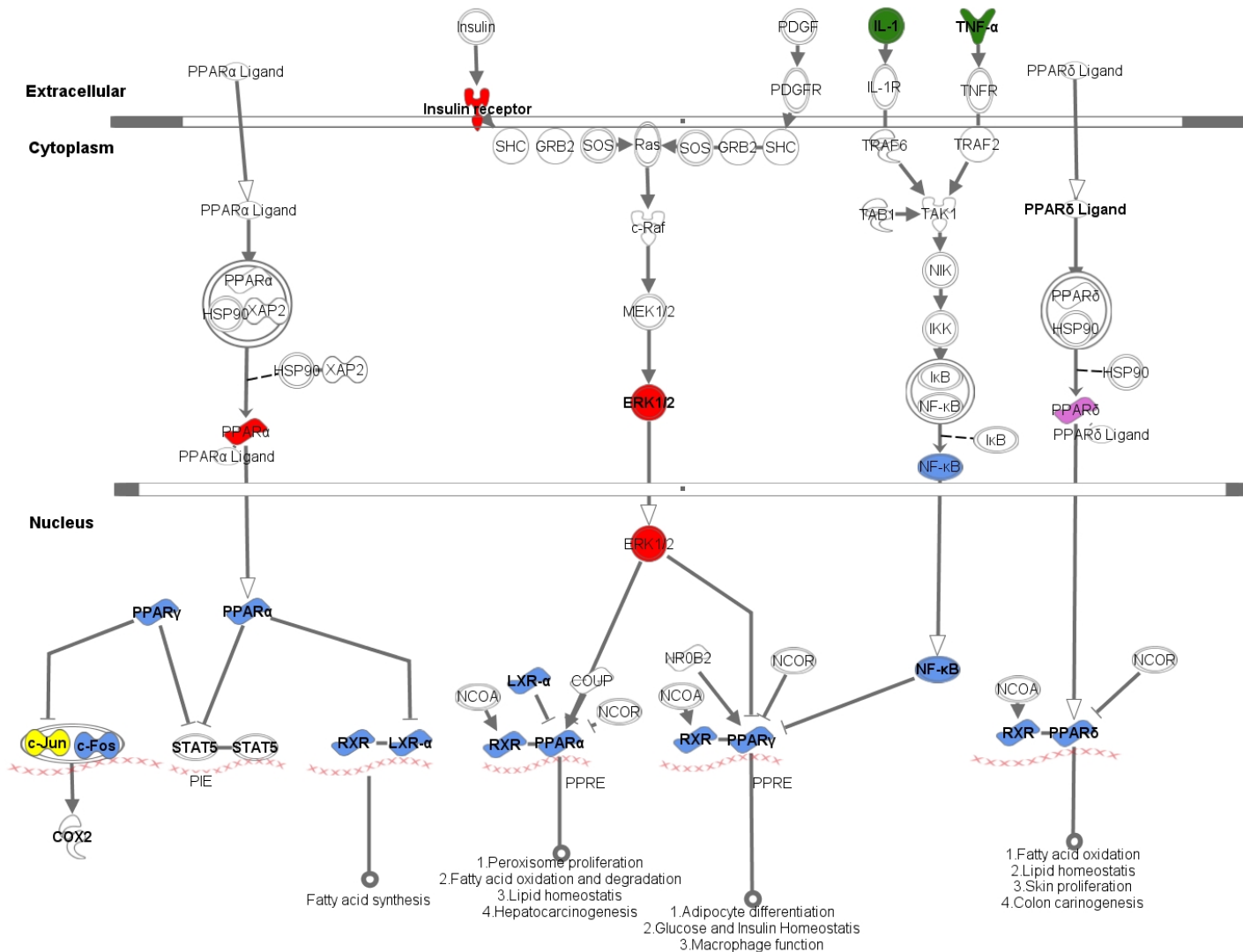
## molecular pathway (muh-LEH-kyoo-ler...)

A series of actions among molecules in a cell that leads to a certain endpoint or cell function.

(taken from the NCI Dictionary of Cancer Terms)

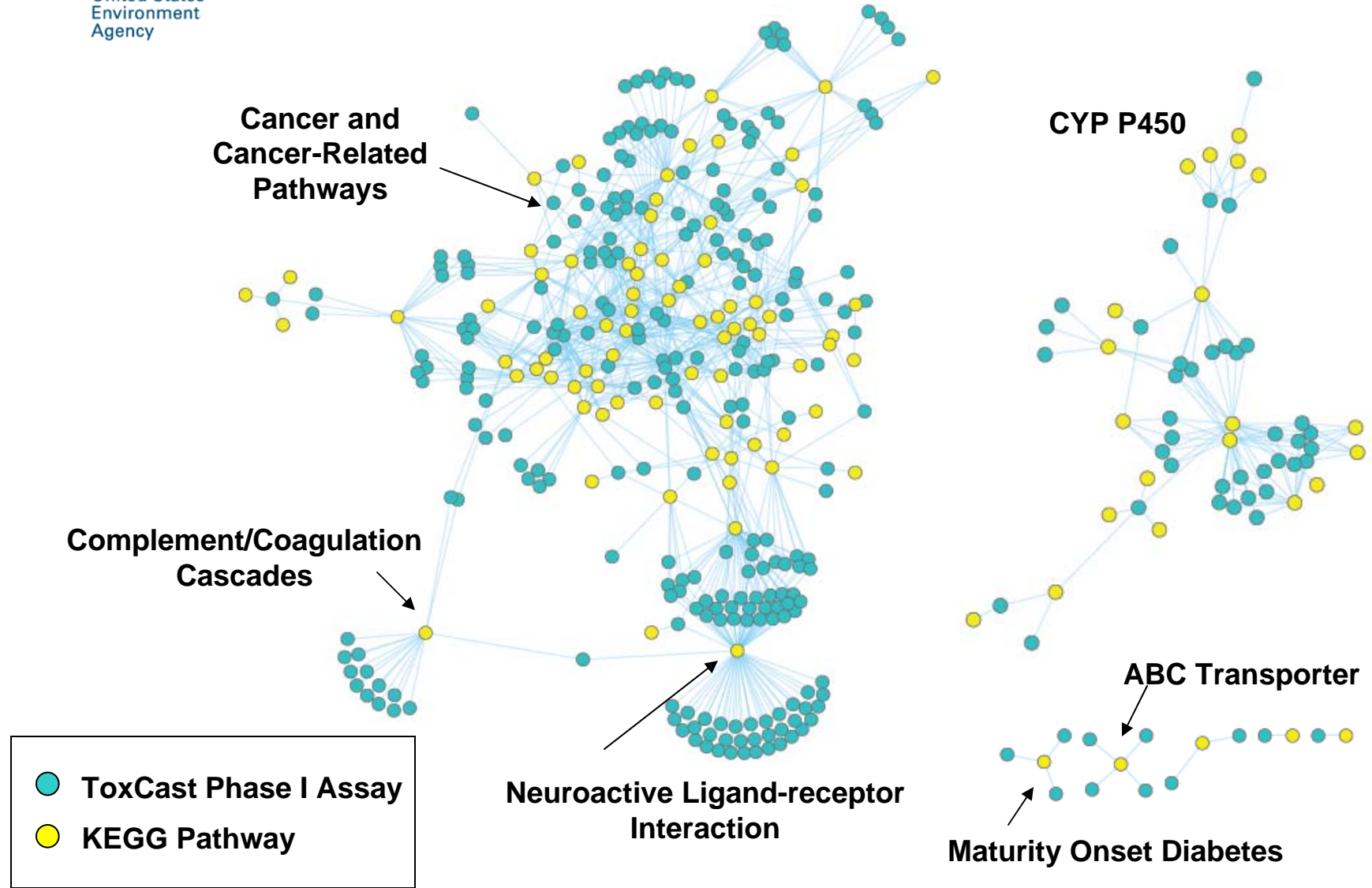
# ToxCast Assay Targets in the PPAR Signaling Pathway

- Biologically Multiplexed Activity Profiling (BioMAP)
- Multiplex Transcription Reporter Assay
- Cell-based HTS Assays
- Cell-free HTS Assays
- High Content Cell Imaging Assays

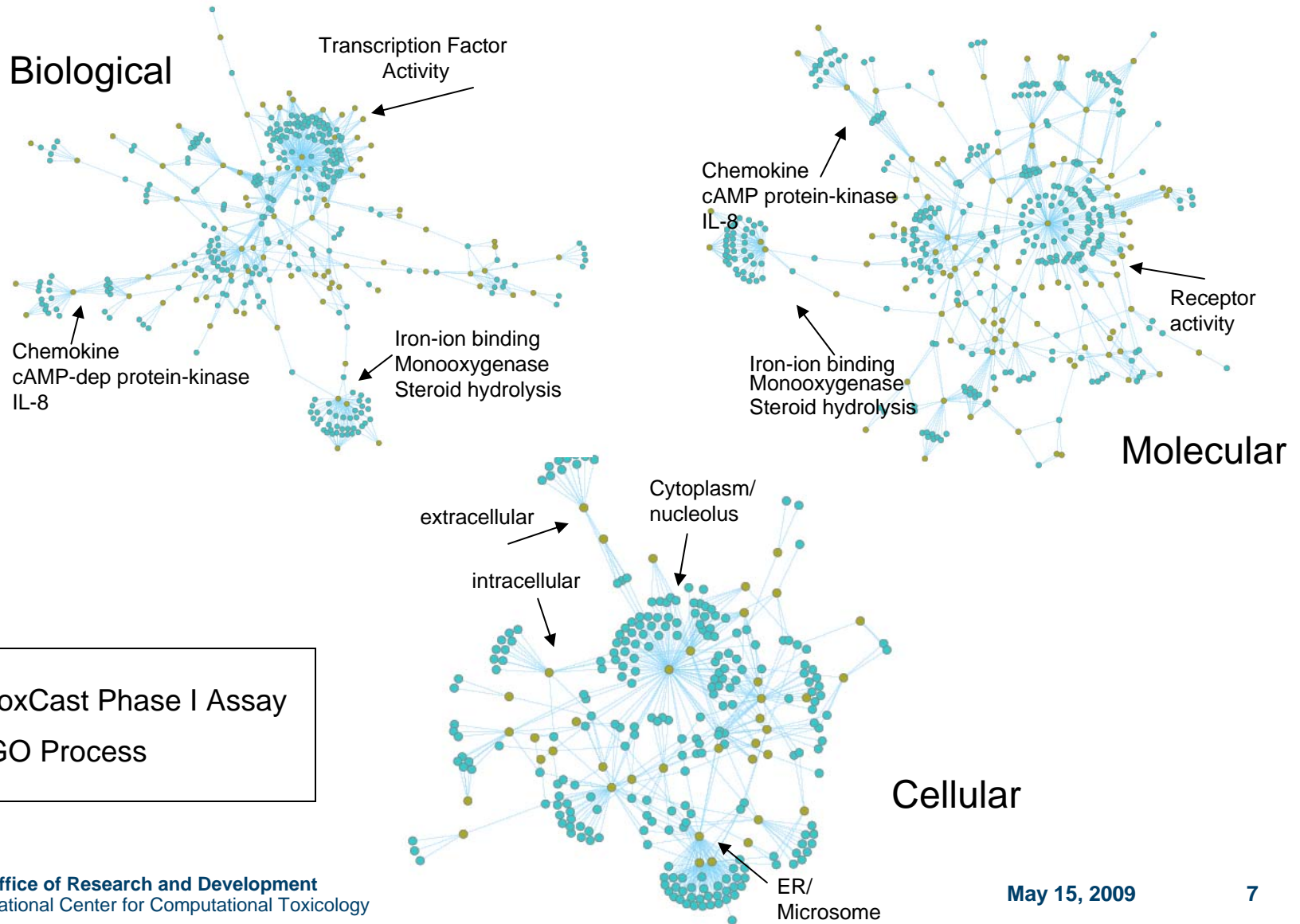


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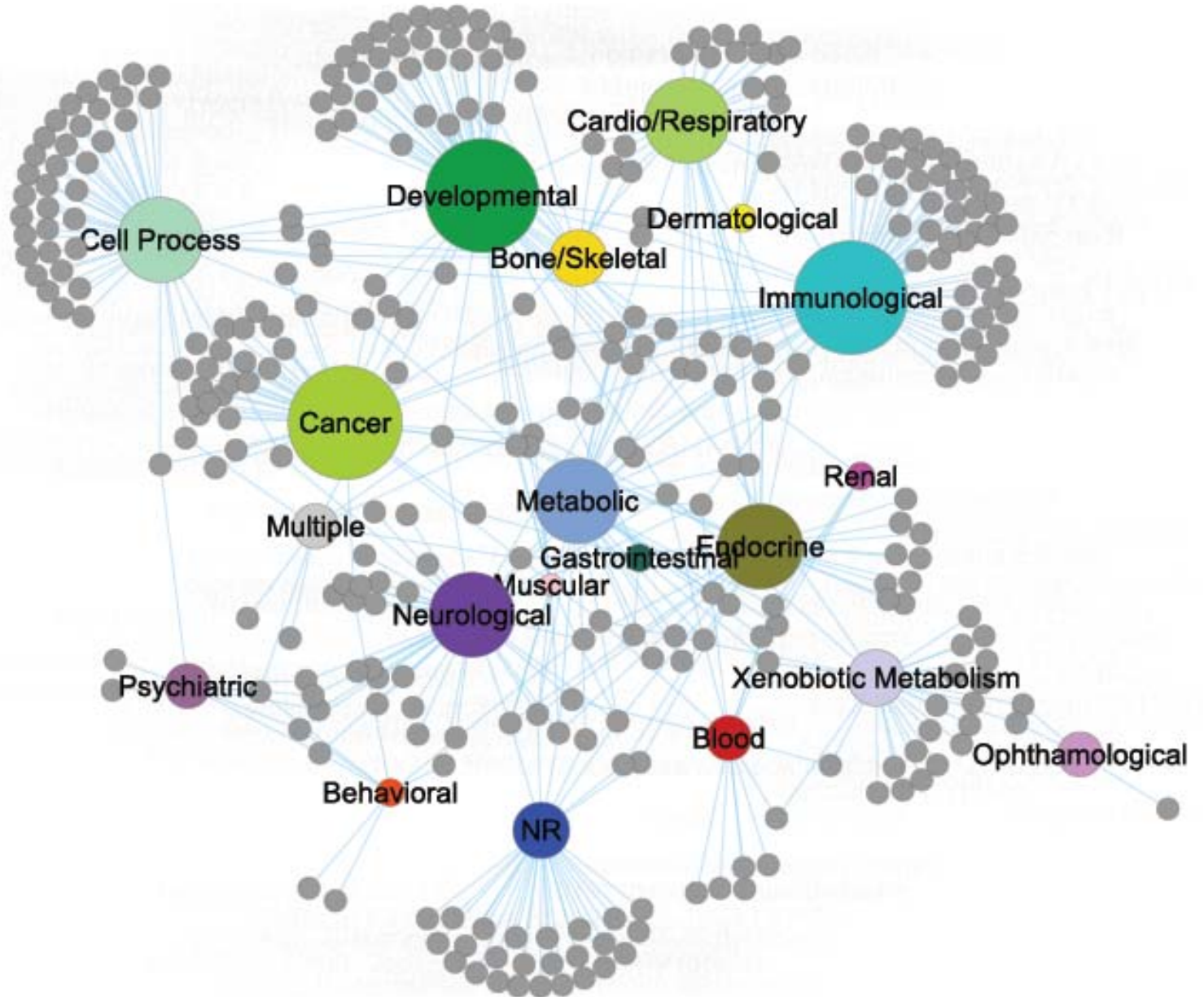
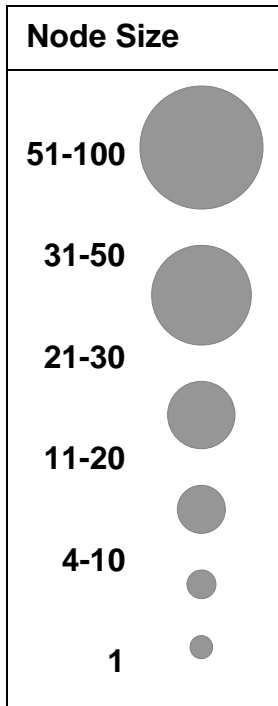
# KEGG Pathways



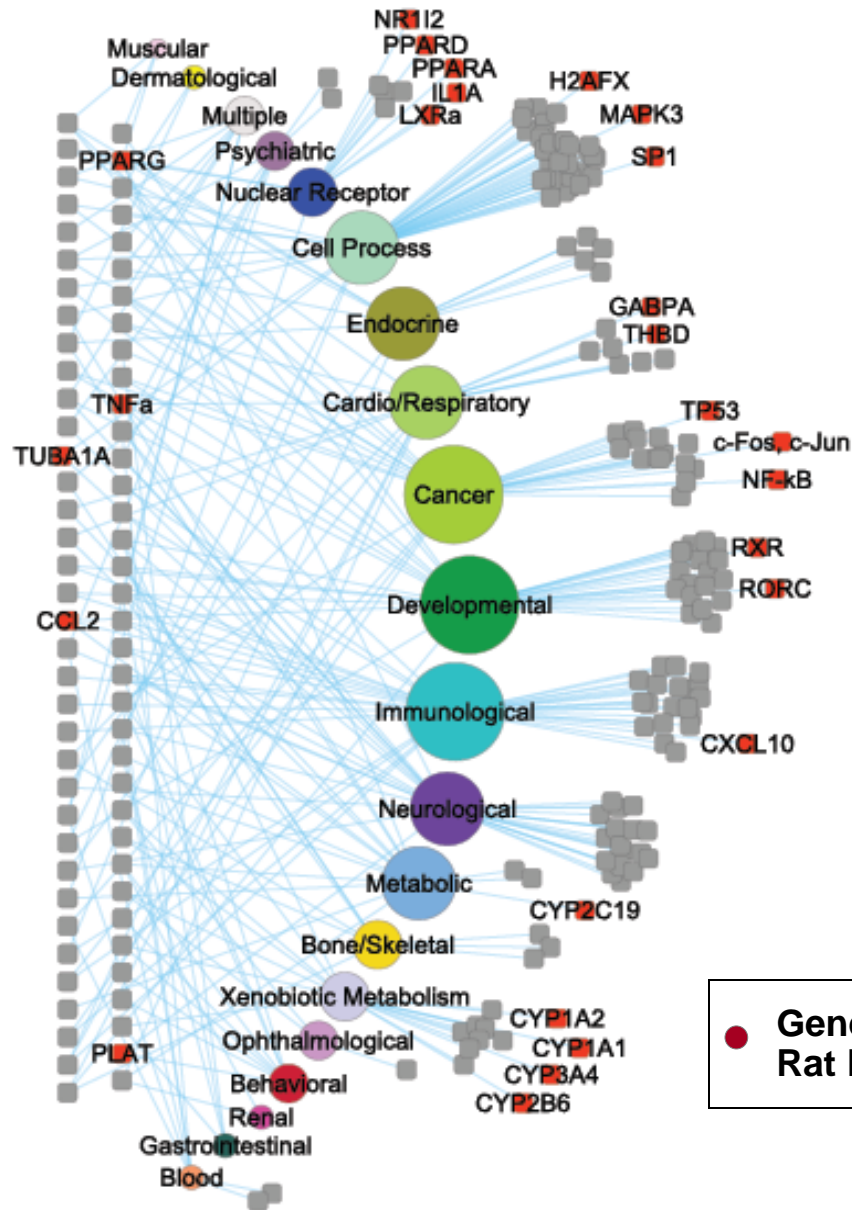
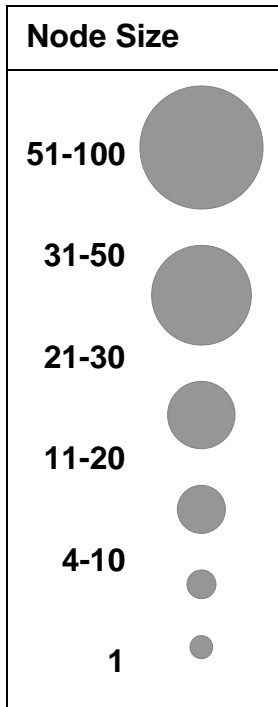
# Gene Ontology Processes



# Disorder Classes Probed by ToxCast Assays



# Genes Probed with ToxCast Assays by Disorder Class



● Genetic Loci Associated with Rat Liver Proliferative Lesions

## Future Directions

- Statistical Sound Approaches to Network Estimation
  - clustering coefficients
  - aggregate bootstrap
- Additional Data to Understand Toxicity Pathways
  - other HTS assays
  - direct testing of failed pharmaceuticals
  - *in vivo* data
  - modular networks/unsupervised methods

