

Virtual Liver: Computational Systems Model of Chemical-Induced Perturbations

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

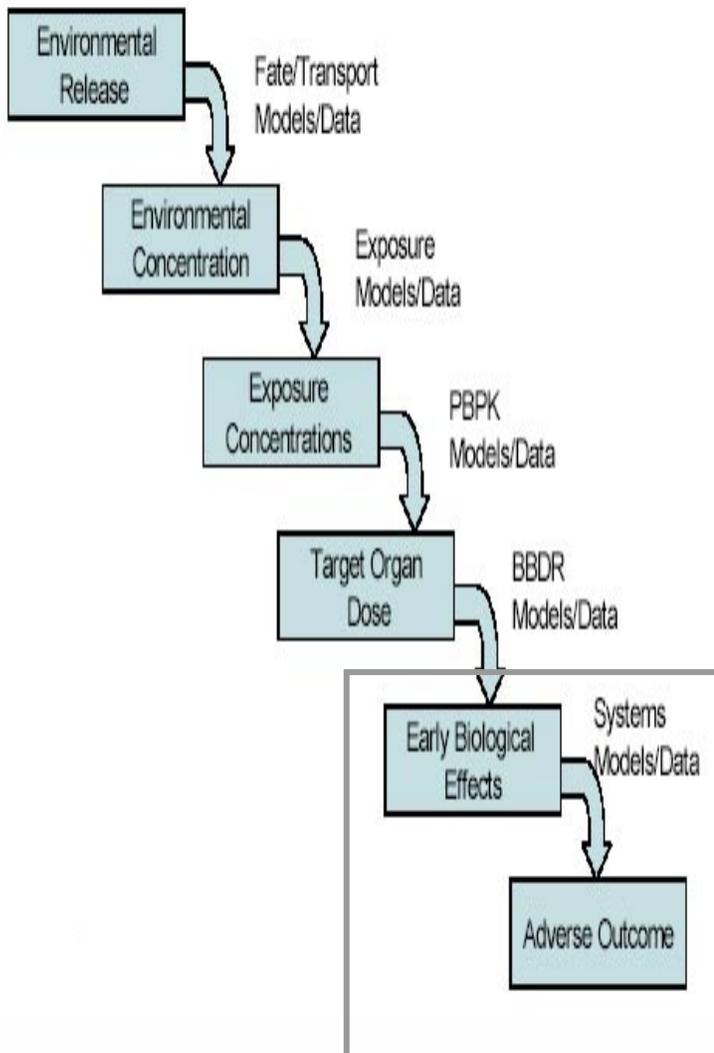




“...to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals”

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Improving Links in Source to Outcome Prediction



Risk Assessment Challenges

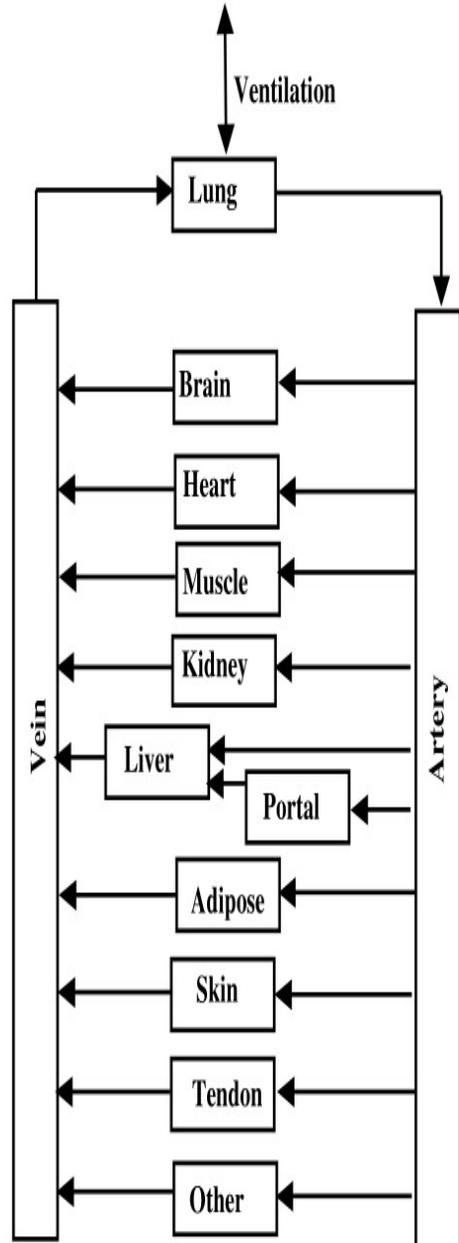
Elucidating the mechanisms of long-term chemical-induced toxicity

Understanding species-specific nature of toxicity: rodents vs. humans

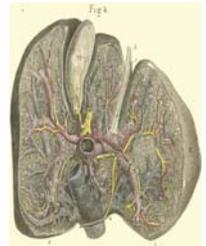
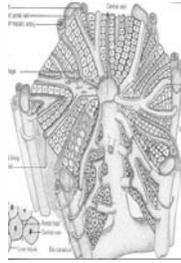
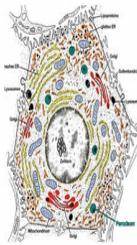
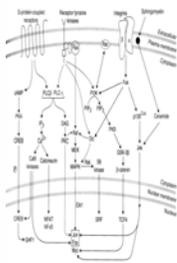
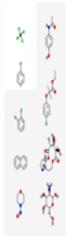
Predicting toxicity at low doses

Physiological Modeling of Chemical Exposure

- Pharmacokinetic modeling predicts organ dose
- Pharmacodynamic modeling predicts adverse outcomes
- **Why model the liver?**
 - The liver plays a key role in removal of xeno-chemicals from the organism (detoxification)
 - The liver shows some of the earliest signs of toxicity
 - The relevance of chronic chemical-induced liver toxicity in rodents needs



Linking Chemicals to Organ Injury



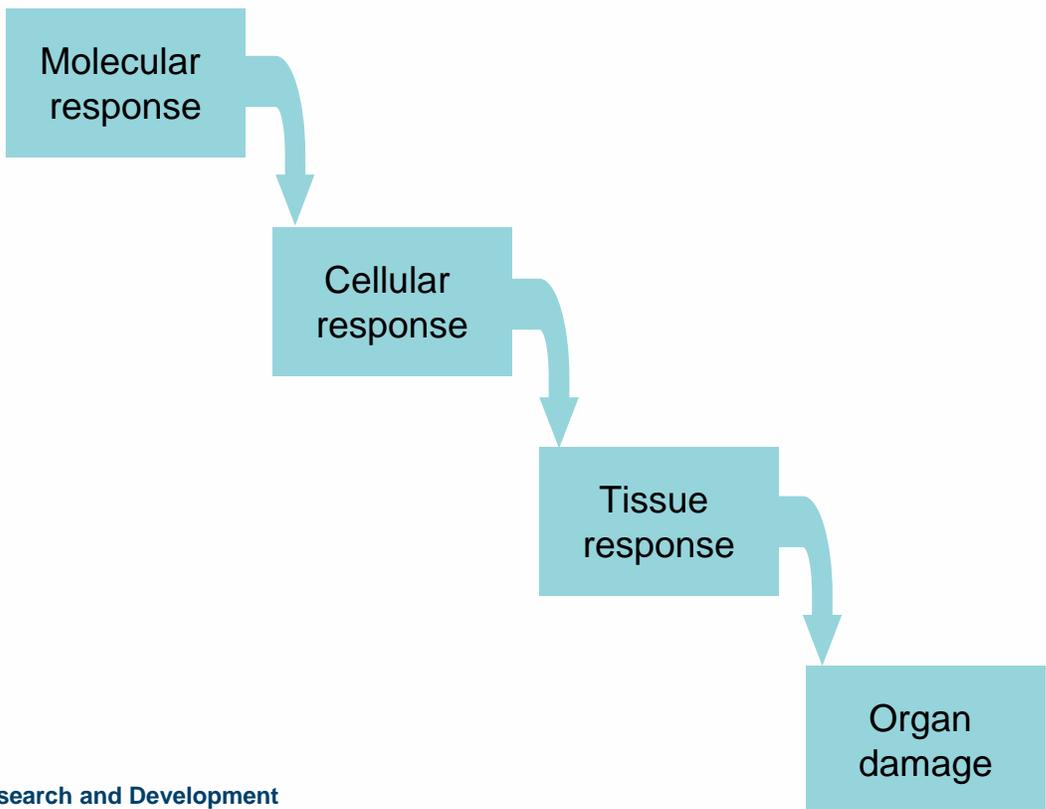
Env.
Chemicals

Molecular
interactions

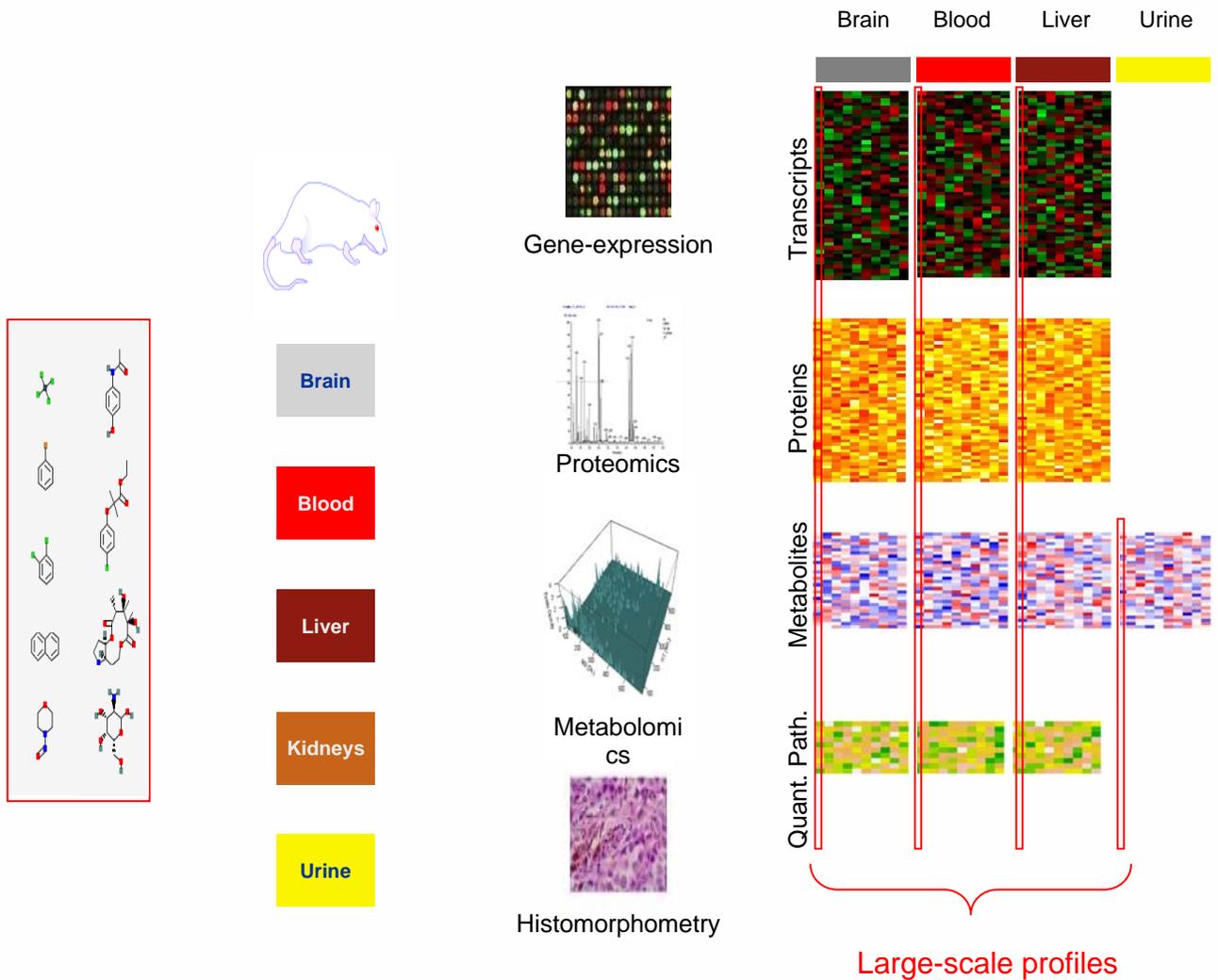
Cellular
Fate

Tissue
Change

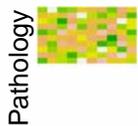
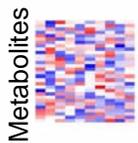
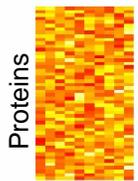
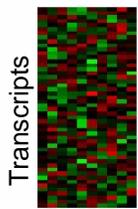
Organ
Injury



Assaying the *Global* State of a Living System: High-throughput Biology



Data Processing and Analysis: Finding The Relevant Biology



Statistics

Machine Learning

Functional Annotation

Pathway Analysis

Significant entities: genes, proteins or metabolites

Empirical models of toxicology end-points / Biomarkers

Functional categorization of significant changes

Explain mechanistic context of perturbations

Large-scale Data sets

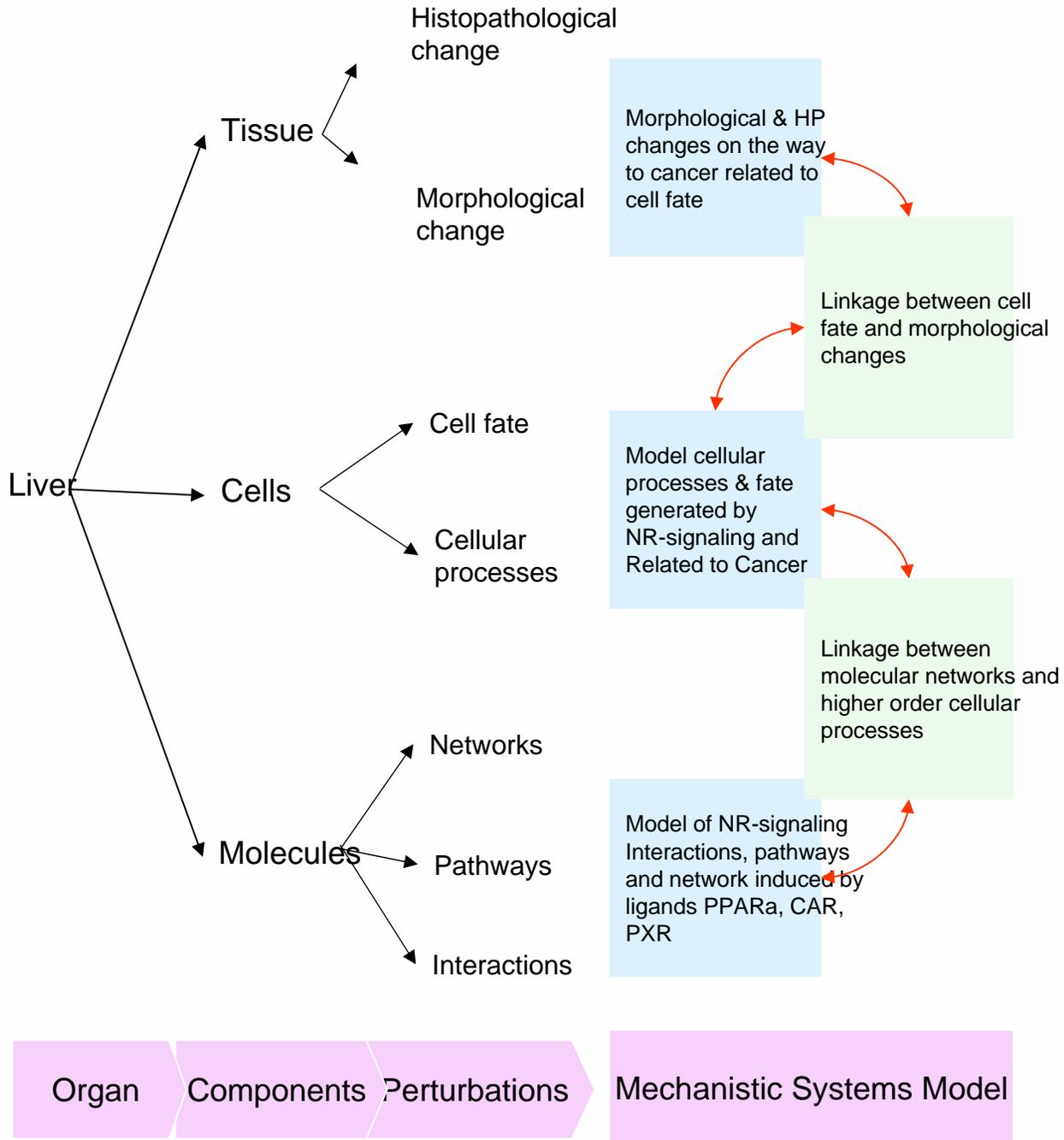


Statistical & Informatics methods

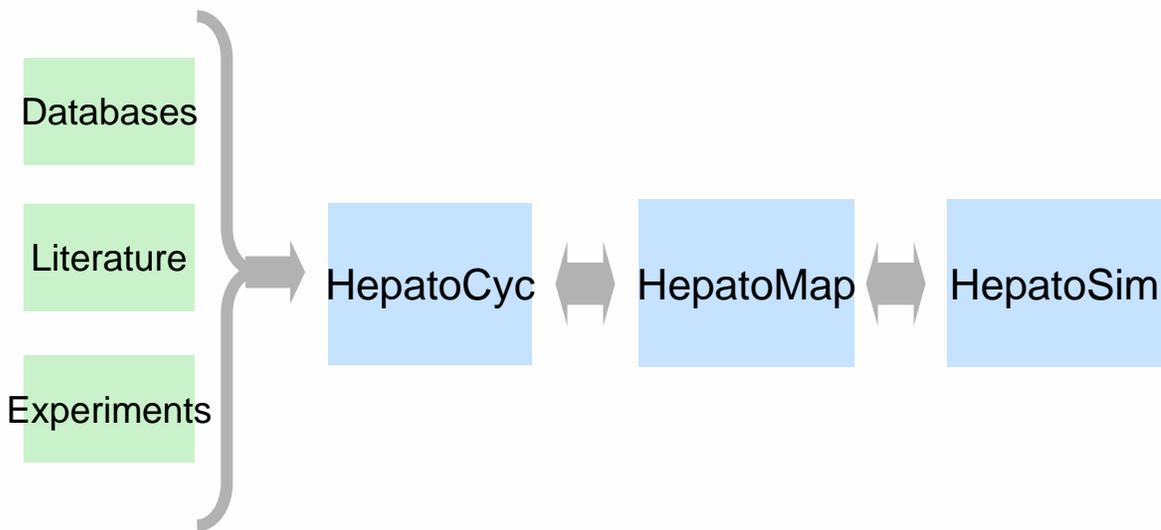


Biologically relevant results

Modeling Large-Scale Perturbations: Systems Biology

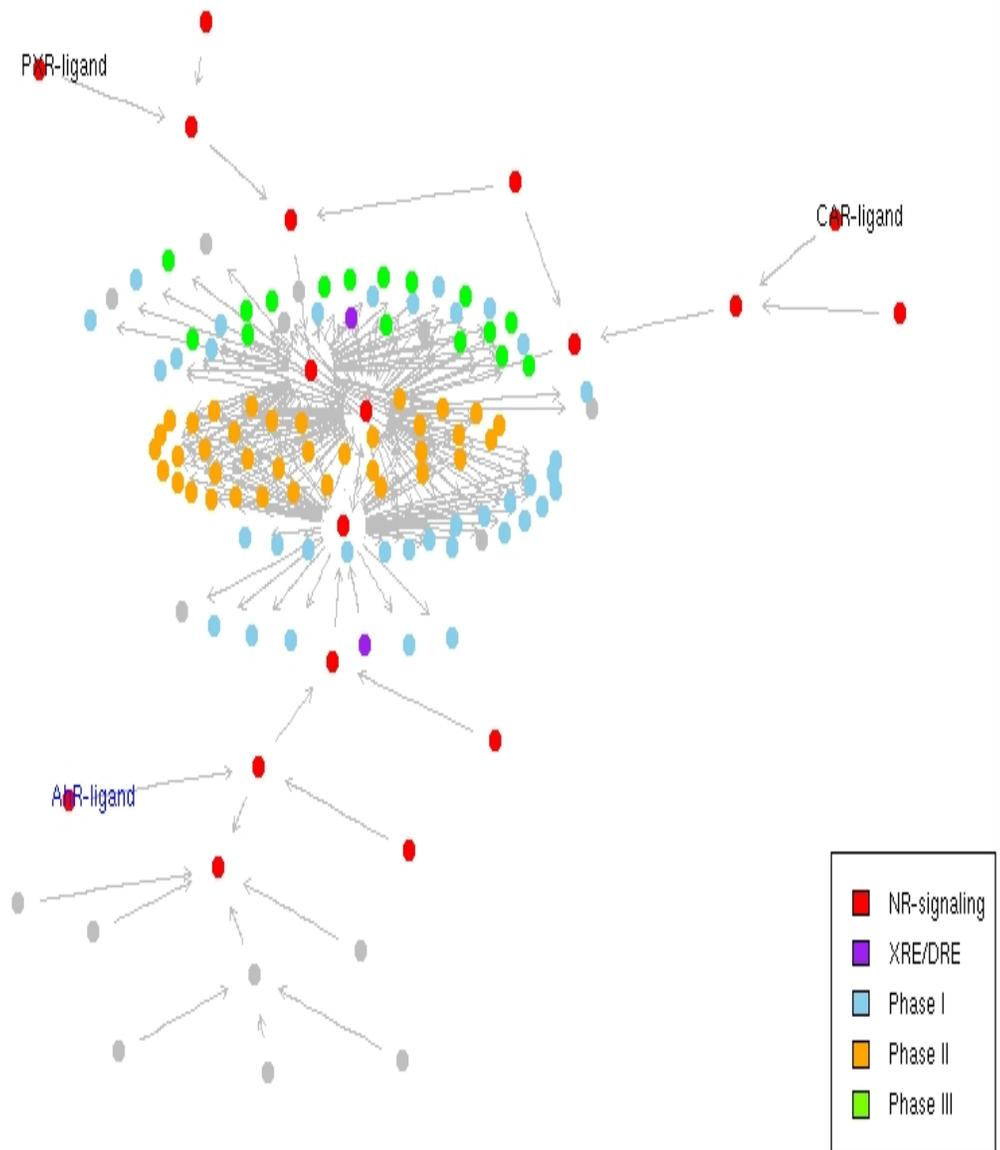


Virtual Liver: Computational Framework for Multiscale Modeling of Chemical-Induced Biological Perturbations



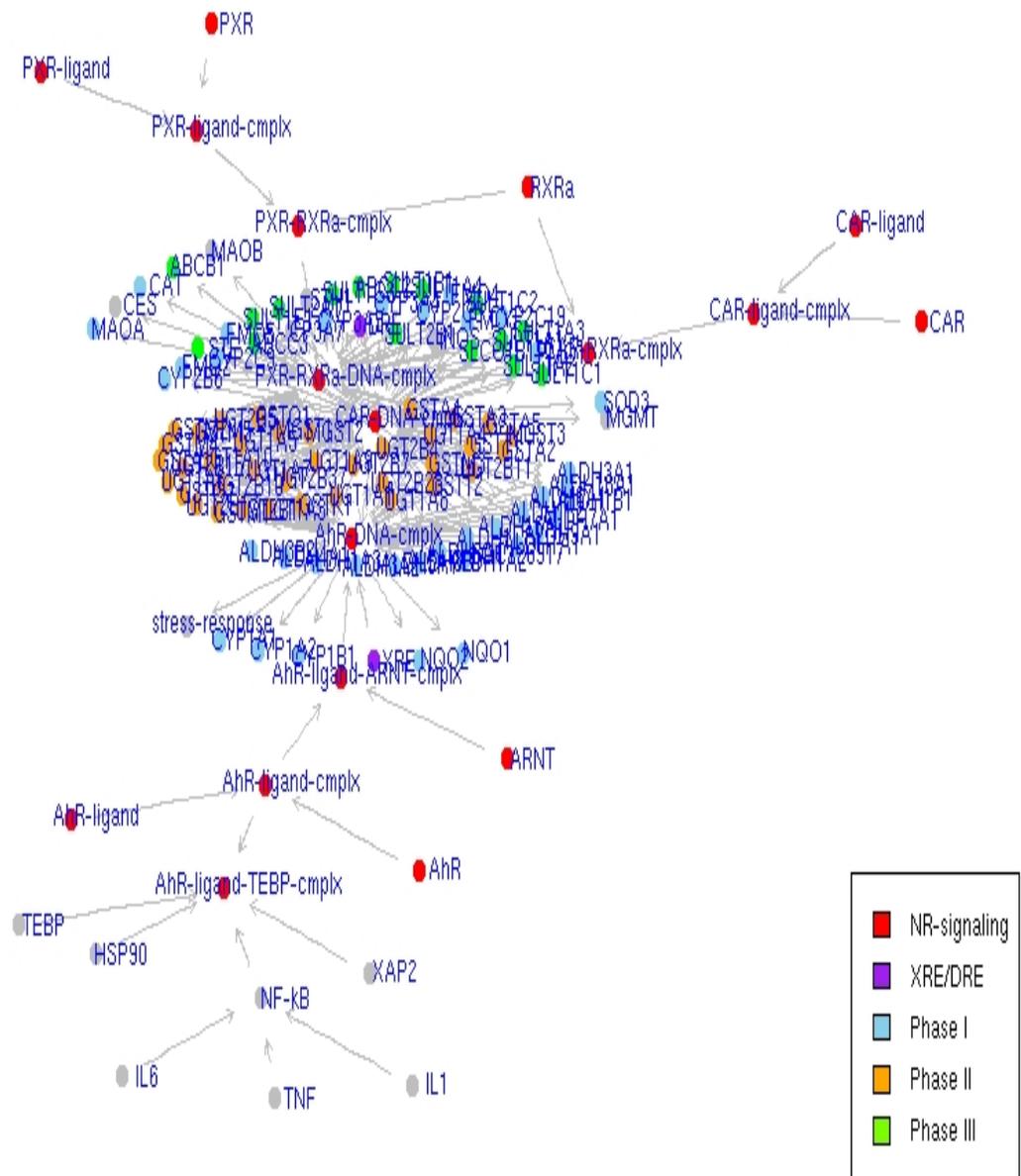
Nuclear Receptor Signaling Regulates Xenobiotic Metabolism

NR-mediated XME Induction



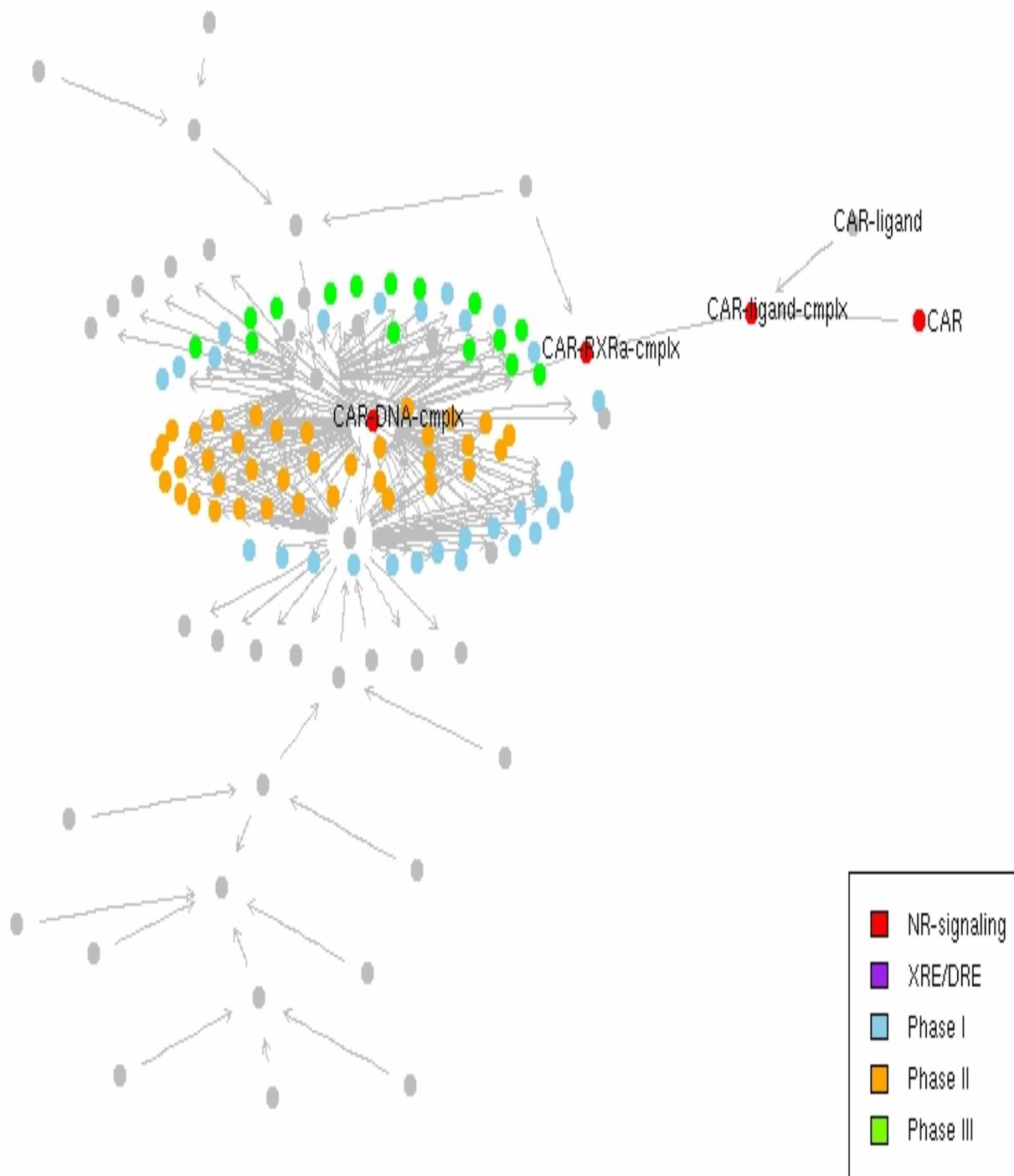
Nuclear Receptor Signaling Regulates Xenobiotic Metabolism

NR-mediated XME Induction

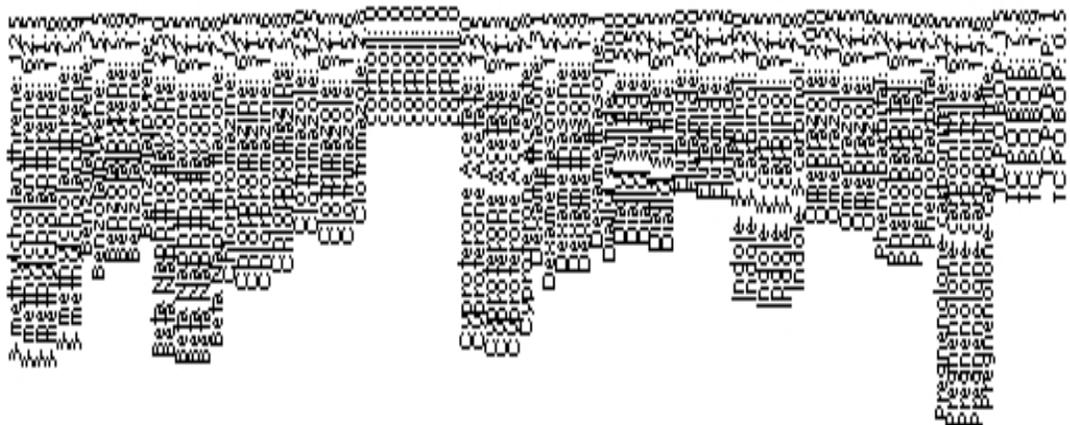
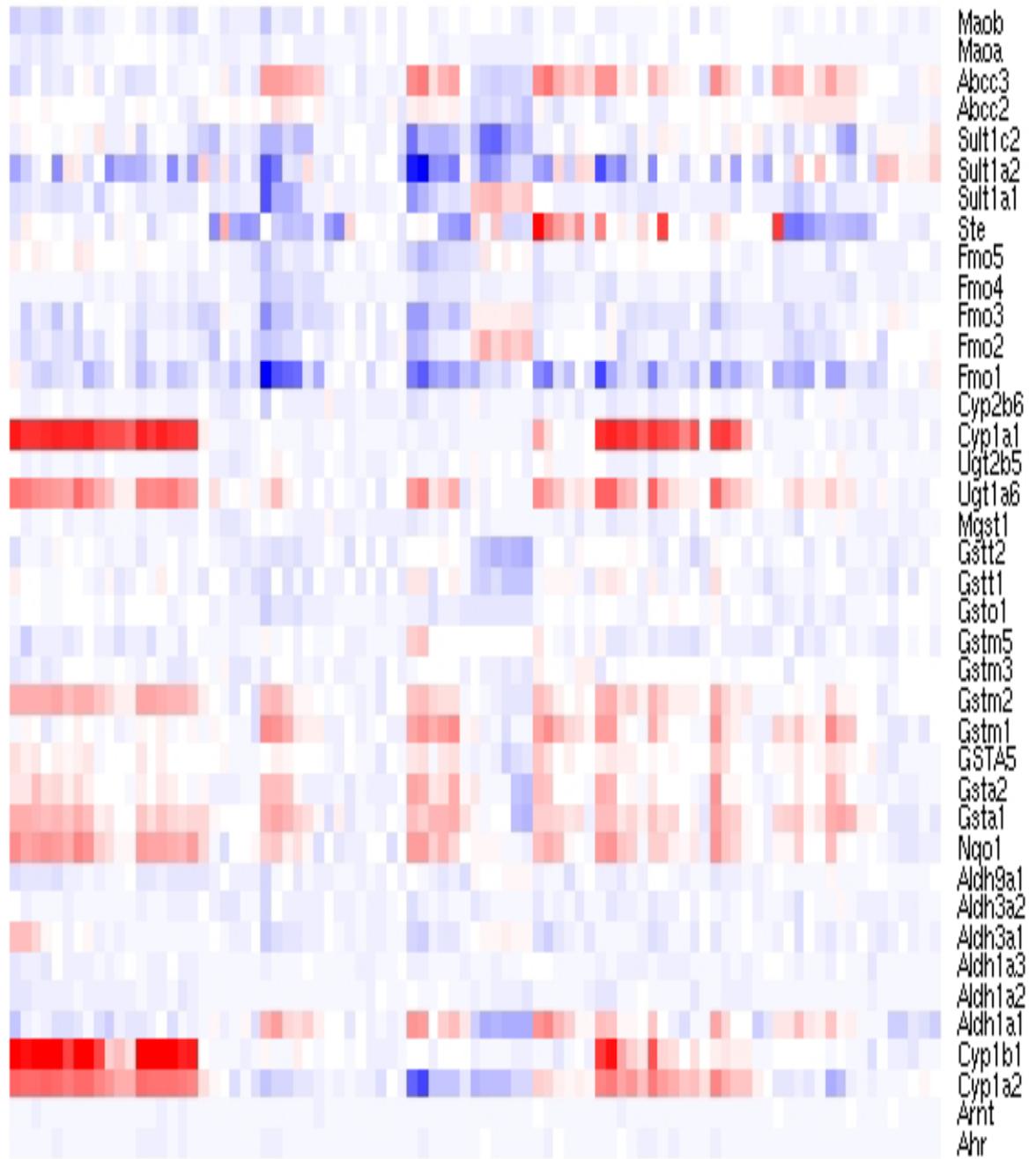




CAR-mediated XME Induction

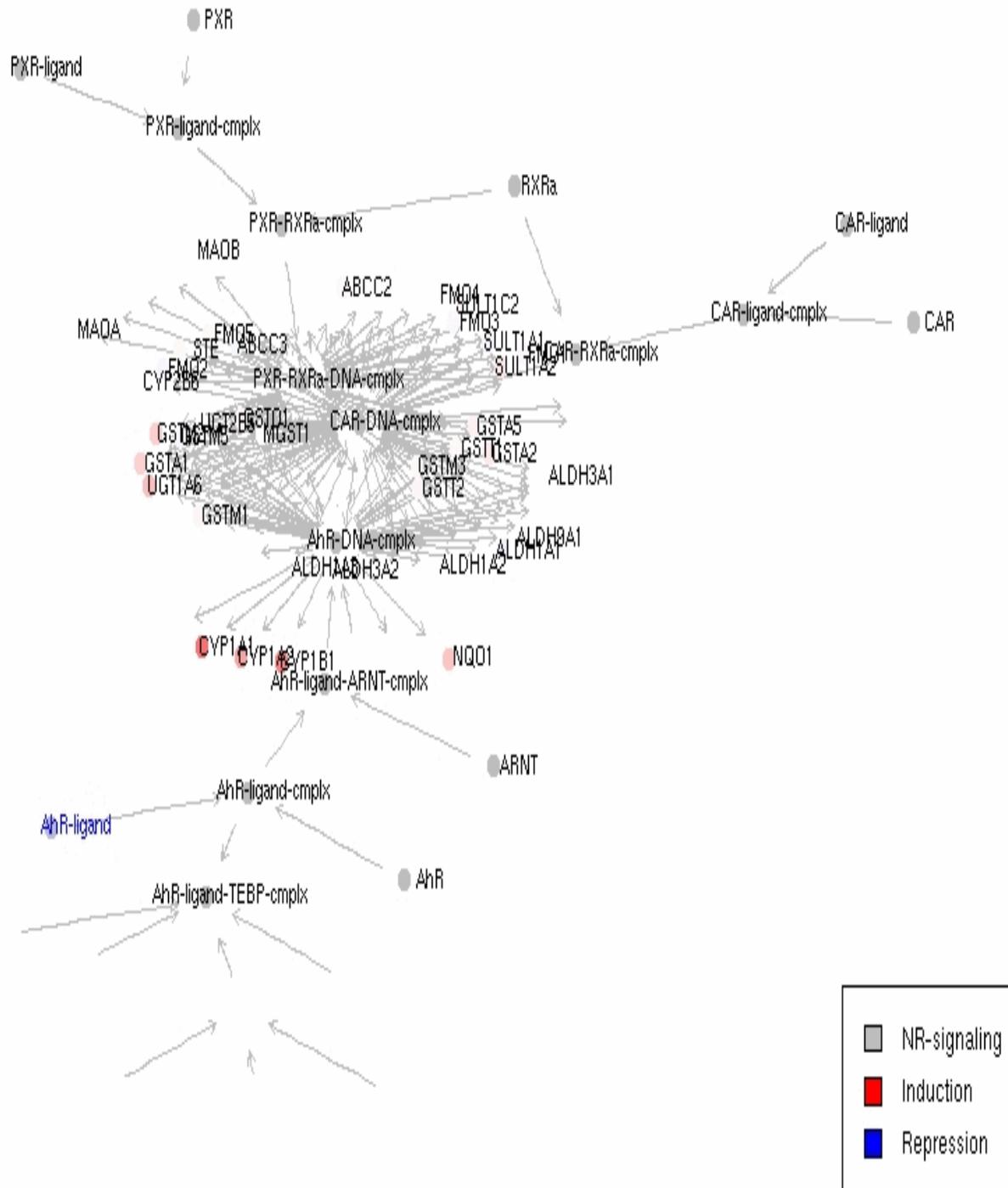


XME induction by NR Activators



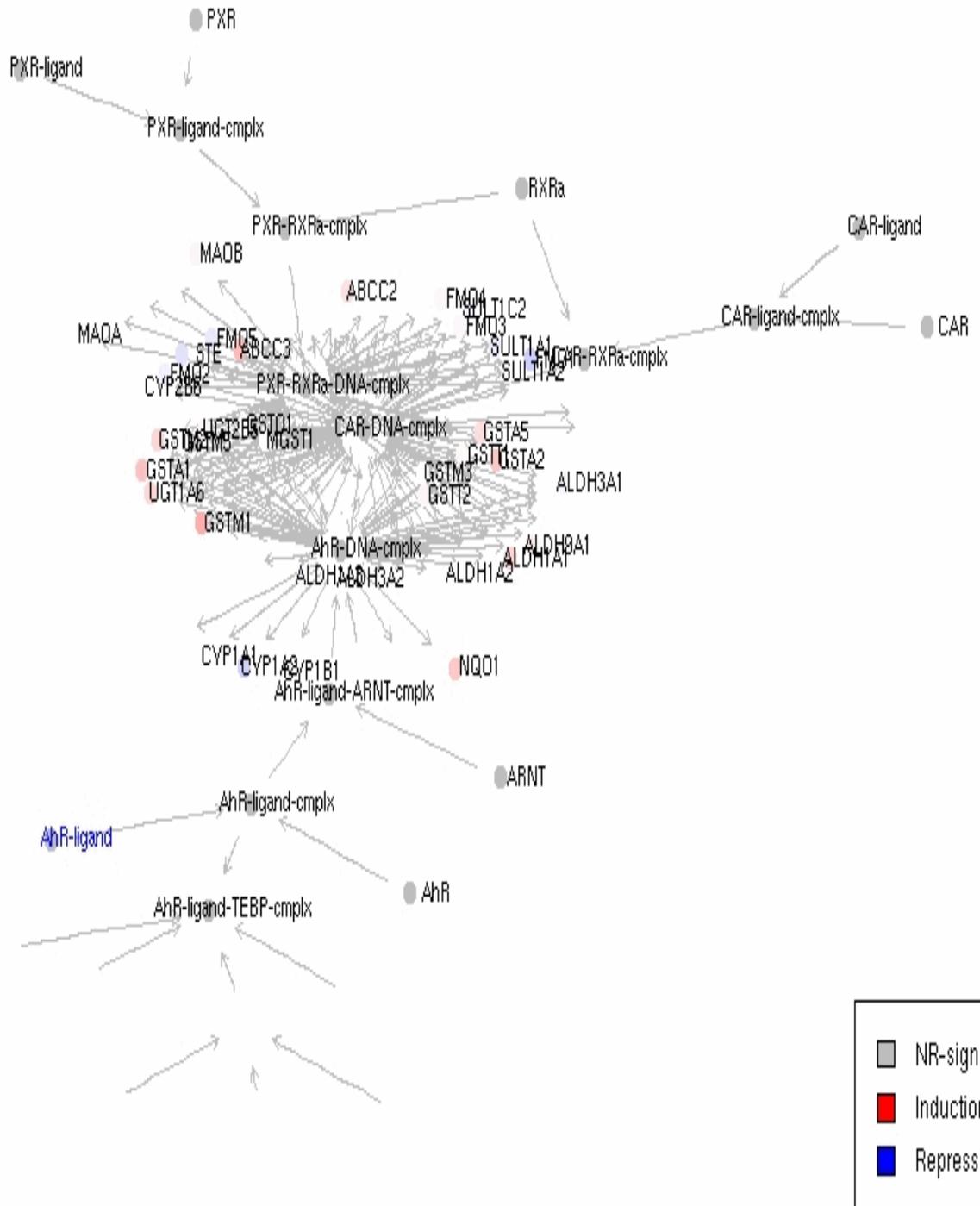


3-methylcholanthrene (3.9 mkd) XME Expression



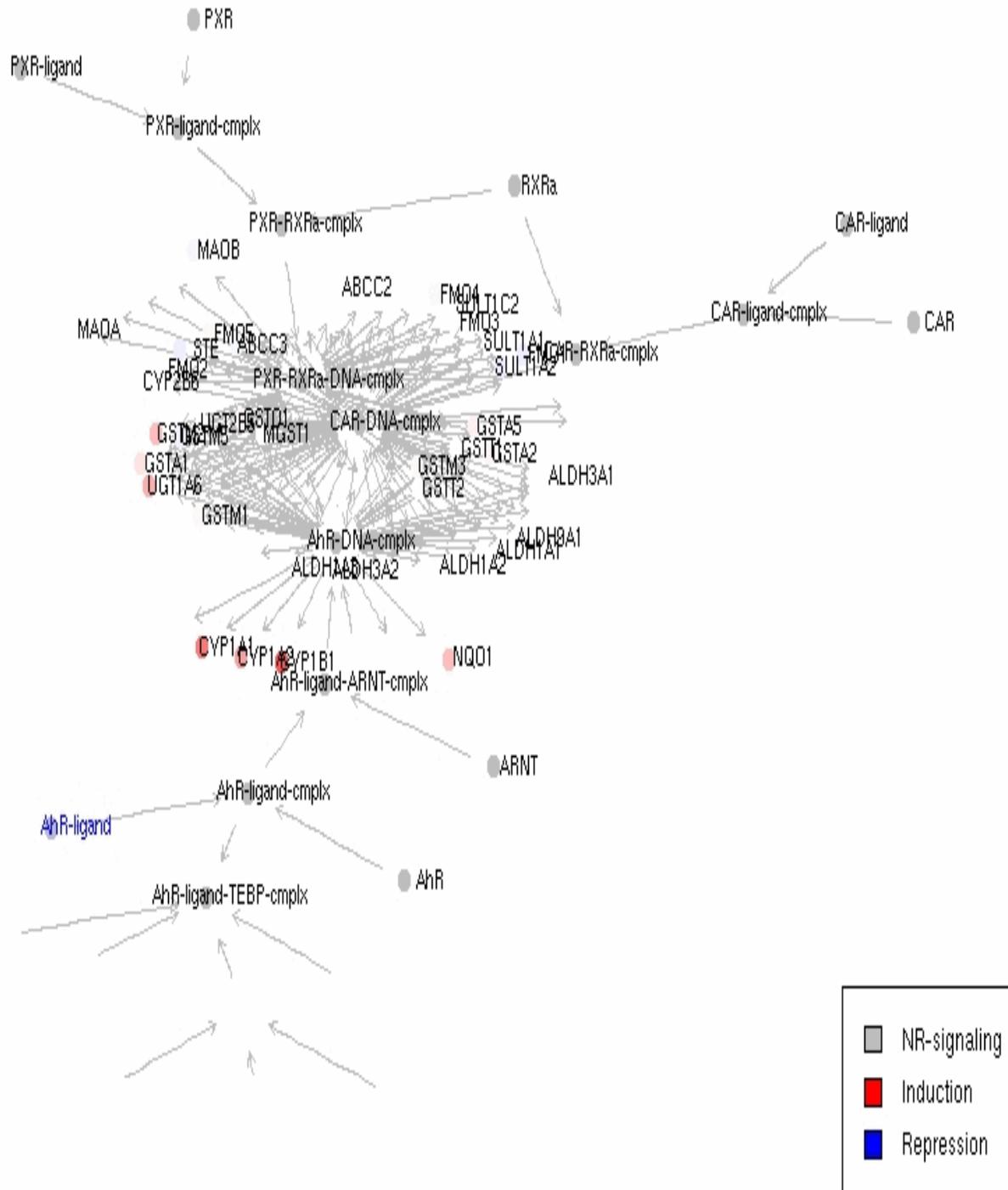


Pregnenolone-carbonitrile (125 mkd) XME Expression



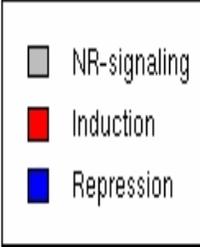
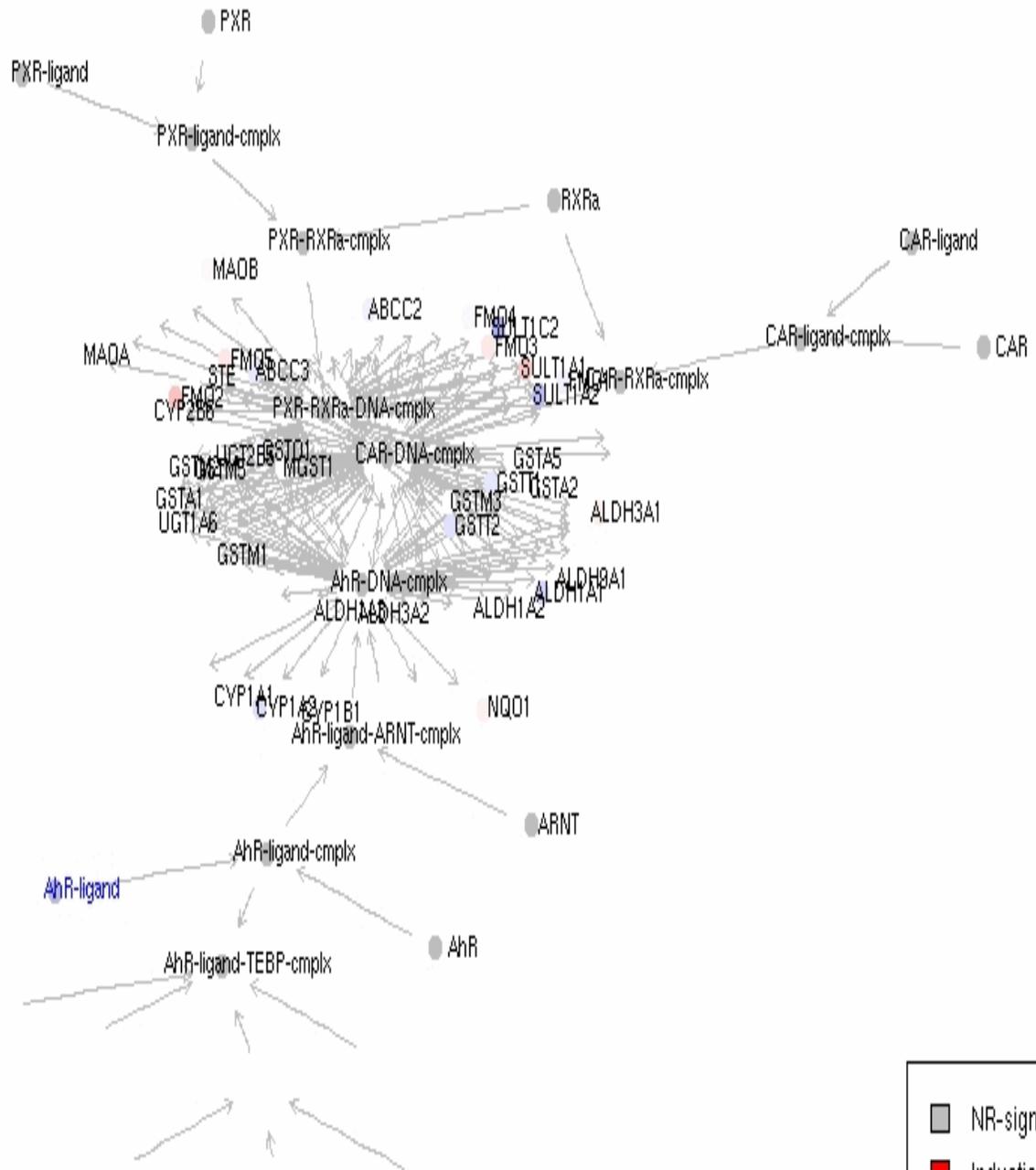


Beta Naphthoflavone (125 mkd) XME Expression



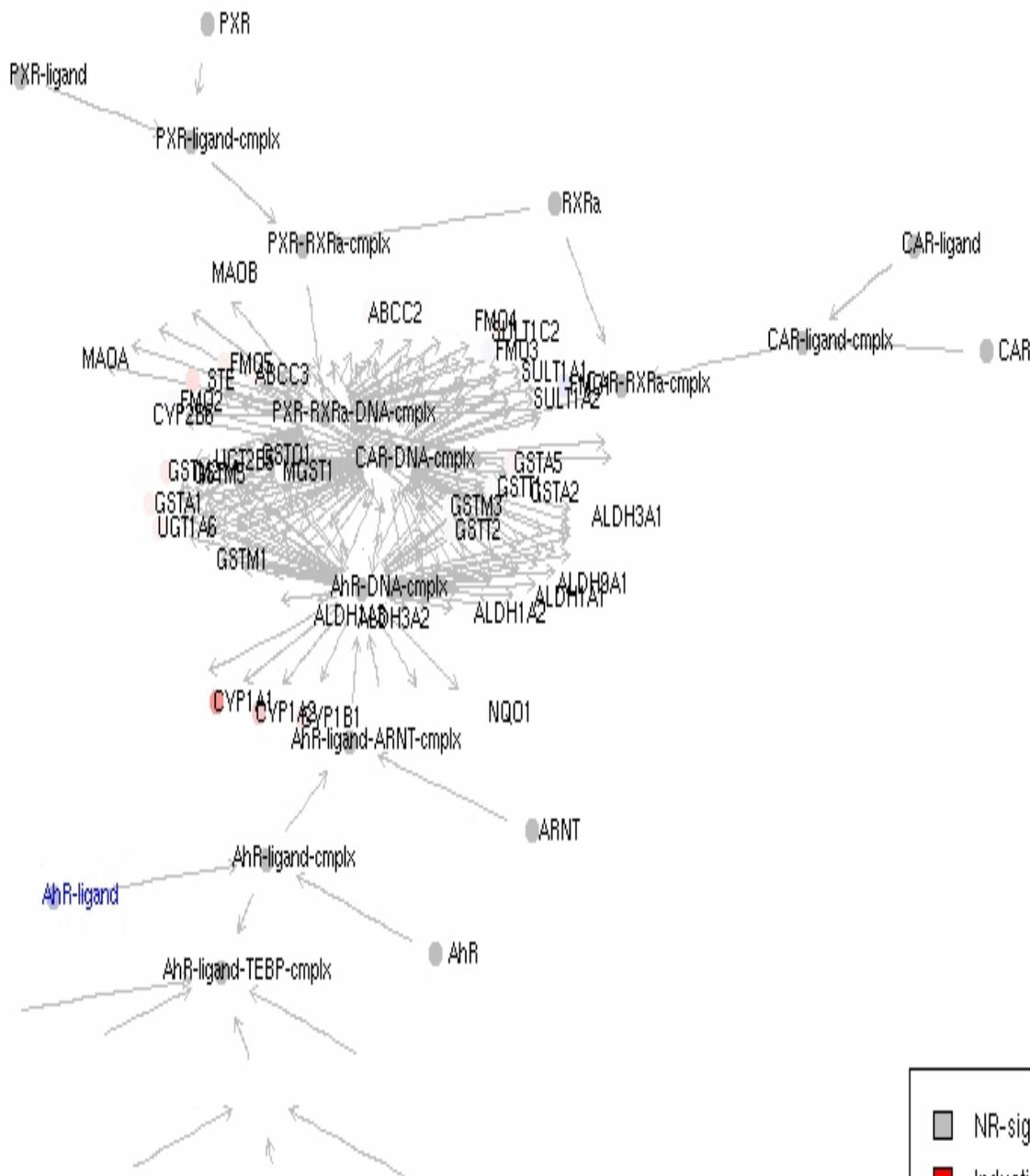


Dexamethasone (15.5 mkd) XME Expression



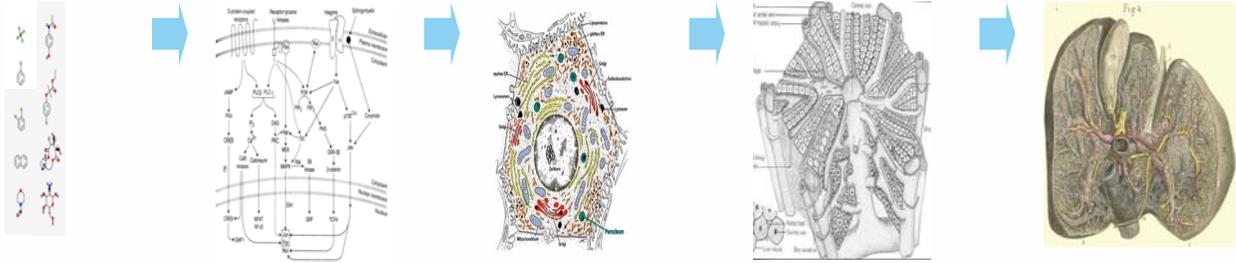


Flutamide (15.6 mkd) XME Expression



- Integrating biological information from disparate sources into a logically coherent system
- Developing network analysis algorithms to aid in identifying molecular pathways perturbed by chemical exposure and modeling dynamics
- Generating large-scale / quantitative data on expression, proteins, metabolites and other endpoints dose/time data with

Virtual Liver Project Plan: Biological Models



Chemical

Molecular
response

Cellular
response

Tissue
response

Organ
response

Year 1

Year 2

Year 3

- Model normal liver homeostatic pathways: NR-signaling, expression, xenobiotic metabolism
- Related to endogenous metabolism

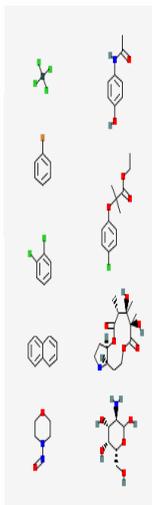
- Model cellular fate: proliferation and cell death
- Relate molecular pathways leading to cell death and cell proliferation

- Model liver normal and pathologic states of liver based on histopathology
- Relate liver pathology model will cell fate

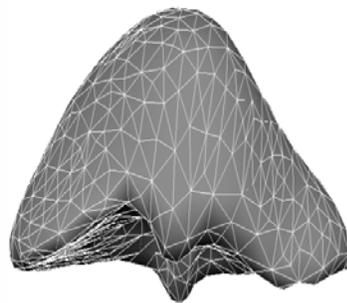
Summary

1. The liver's response to environmental chemicals spans multiple levels of organization – from molecular interactions to alterations in tissue structure.
2. A computational model of the liver will require biologically relevant multi-scale computing
3. The project will initially focus on modeling specific aspects of biology e.g. NR-mediated pathways before expanding to other areas
4. The project will leverage expertise, tools and experimental data within EPA and with external efforts in closely related areas of systems biology

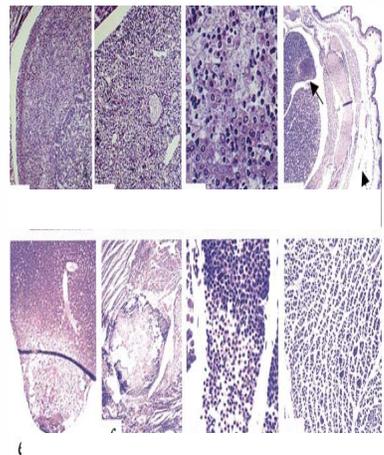
The Virtual Liver: *long-term vision*



Chemicals



Virtual Liver



Predict adverse outcome