Virtual Liver: Computational Systems Model of Chemical-Induced Perturbations

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This presentation has been reviewed and approved for presentation but does not necessarily reflect Agency policy.
“...to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals”
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

Molecular response

Cellular response

Tissue response

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

- **Gene-expression**
- **Proteomics**
- **Metabolomics**

**Large-scale profiles**

- Brain
- Blood
- Liver
- Urine

- Histomorphometry

**Xenobiotics** → **Exposure** → **Tissue/Dose/Time** → **omic Data streams & Pathology end-points** → **Measures of “Global” response**
Data Processing and Analysis: Finding The Relevant Biology

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

- Liver
- Cells
- Molecules
- Networks
- Pathways
- Interactions
- Cell fate
- Cellular processes
- Histopathological change
- Morphological change

Organ | Components | Perturbations | Mechanistic Systems Model

- Model of NR-signaling Interactions, pathways and network induced by ligands PPARα, CAR, PXR
- Linkage between molecular networks and higher order cellular processes
- Model cellular processes & fate generated by NR-signaling and Related to Cancer
- Linkage between cell fate and morphological changes
- Morphological & HP changes on the way to cancer related to cell fate
Virtual Liver: Computational Framework for Multiscale Modeling of Chemical-Induced Biological Perturbations

Databases
Literature
Experiments

HepatoCyc → HepatoMap → HepatoSim

Disparate sources of biological information
Knowledgebase of relevant concepts and facts
Model generation through pathway synthesis
Dynamic simulation of models
Chemical-induced Chronic Injury: Possible Mode of Liver Cancer

Environmental Chemicals

Molecular response

Cellular response

Tissue response

Chemicals
- Pesticides: Conazoles, Pyrethroids
- Toxics: DE-71, PCBs, Pthalates, PFAAs

Early response
- NR-sig Gene-regTranscription
  - CAR cis-reg.
  - PXR Trans-reg
  - AhR
  - LXR
  - FXR
  - PPARα
- Xen. Met. Phase I
- Phase II
- Phase III

Cell fate
- Proliferation
- Death
- Apoptosis
- Necrosis

Toxicity Endpoint
- Tumor
- Cancer
Nuclear Receptor Signaling Regulates Xenobiotic Metabolism

NR-mediated XME Induction

Office of Research and Development
National Center for Computational Toxicology
Nuclear Receptor Signaling Regulates Xenobiotic Metabolism

NR-mediated XME Induction

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National Center for Computational Toxicology
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| M30a | M30a | Abcc3 | Abcc2 | Sult1c2 | Sult1a2 | Sult1a1 | Ste | Fmo5 | Fmo4 | Fmo3 | Fmo2 | Fmo1 | Cyp2b6 | Cyp1a1 | Ugt2b5 | Ugt1a6 | Mgst1 | Gstt2 | Gstt1 | Gsto1 | Gstm5 | Gstm3 | Gstm2 | Gstm1 | GSTA5 | Gsta2 | Gsta1 | Nqo1 | Aldh3a1 | Aldh3a2 | Aldh3a1 | Aldh1a3 | Aldh1a2 | Aldh1a1 | Cyp1b1 | Cyp1a2 | Ahr |
|------|------|-------|-------|---------|---------|---------|-----|------|------|------|------|------|--------|--------|--------|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
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**XME induction by NR Activators**
Cyproterone Acetate (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

**Year 1**
- Model normal liver homeostatic pathways: NR-signaling, expression, xenobiotic metabolism
- Related to endogenous metabolism

**Year 2**
- Model cellular fate: proliferation and cell death
- Relate molecular pathways leading to cell death and cell proliferation

**Year 3**
- 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