United States Environmental Protection Agency

v-Liver™ The Virtual Liver Project: Simulating Hepatic Lesions

v-Tissues 2009, April 21-22, 2009

This work was reviewed by EPA and approved for publication but does not necessarily reflect official agency policy.

Office of Research and Development
National Center for Computational Toxicology

Background

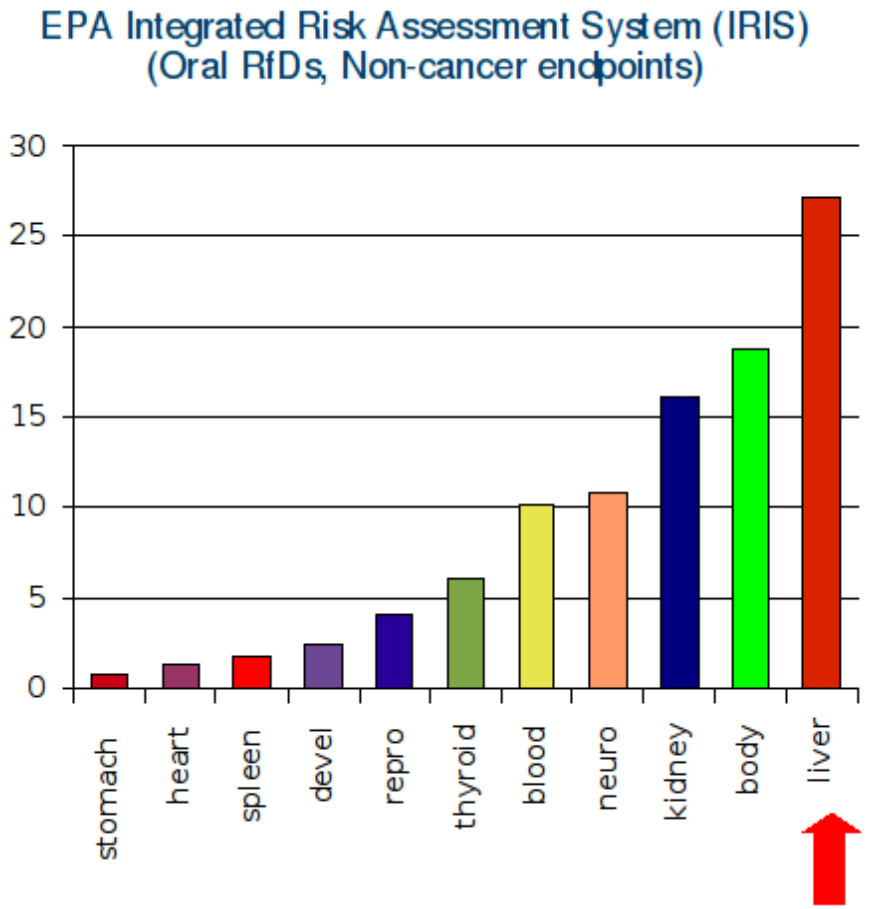
- ~10,000 HPV chemicals - little/no biological data !
- Animal testing infeasible / uncertain value
- 2007 NRC - Toxicity Testing 21st Century
- 2008 EPA - Strategic Plan for Evaluating Chemical Toxicity

→ Develop ***in vitro-in silico*** proof of concept

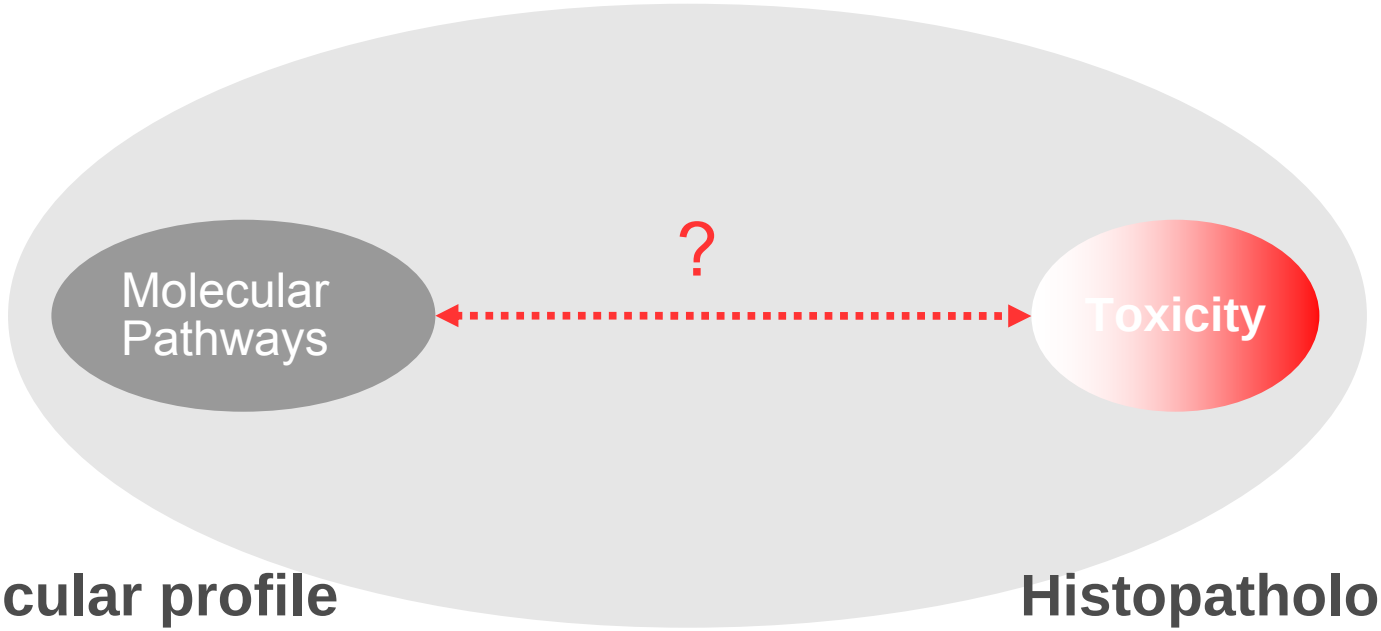
→ Evaluate using environmental chemicals

Why Liver?

- **Primary** organ for environmental chemical **detoxification**
- **Most frequent** site of **adverse effects** (IRIS & ToxRefDB) in rodents – **relevant** to EPA
- **Human relevance** still uncertain
- **Large** amount of **available molecular** and **tissue** data
- **Unmet Need:** Extrapolation across doses, chemicals, species, populations



How to Predict Liver Toxicity ?



Phenotypic anchoring valuable for prioritization

Difficult to elucidate mode-of-action / dose-response

Toxicity: Cell Alteration

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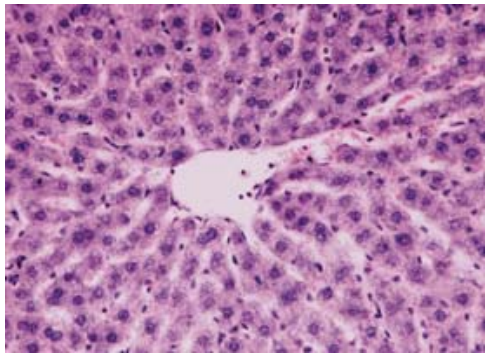
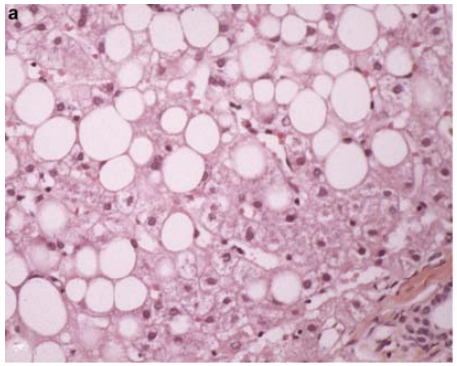
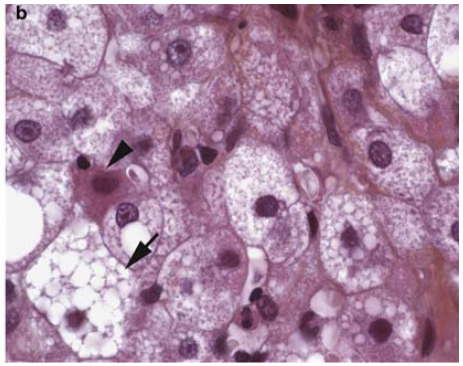
Swelling



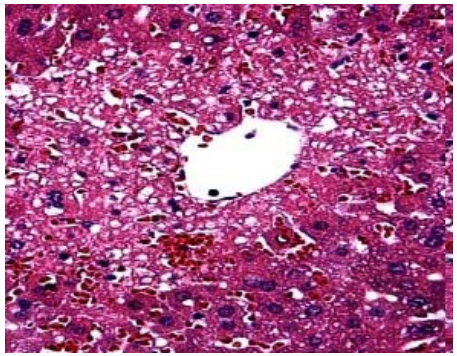
Steatosis, Macroves.



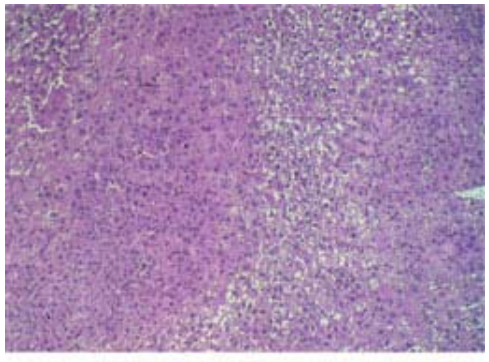
Steatosis, Microves.



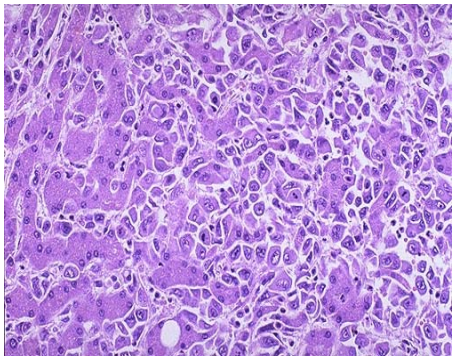
Necrosis



Hyperplasia

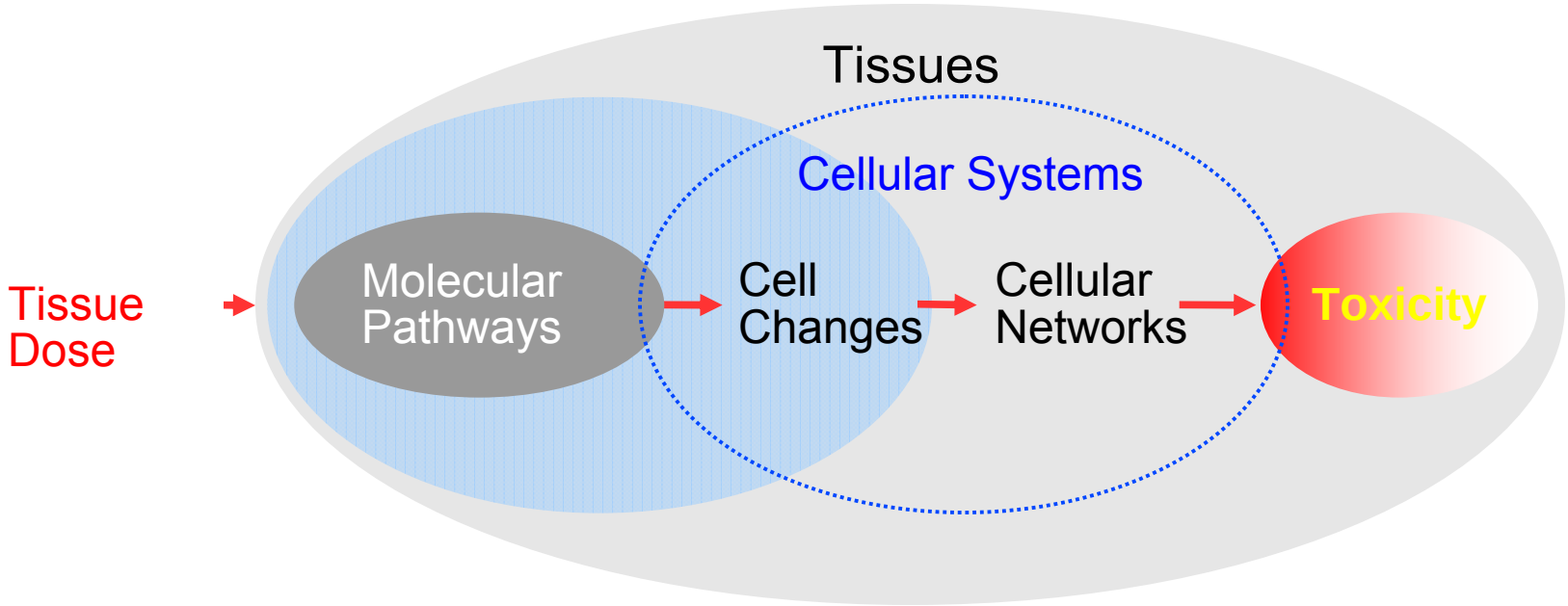


Carcinoma



Fallsehr, *et. al.* World J Gastroenterol 2005 March 7;11(9):1303-1306
Jean-Paul Duong Van Huyen, *et. al. Modern Pathology (2006) 19, 1277–1288.0*
Uskoković-Marković, *et. al. J Pharm Pharmaceut Sci 10(3):340-349, 2007*
library.med.utah.edu/WebPath

Toxicity: Cross-Scale Phenomena



Tissue lesions propagated by dynamic cellular networks

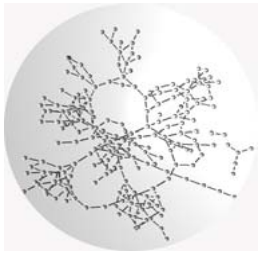
Cell changes are caused by molecular pathways

Use a cell-oriented view to deal with complexity ...

"Cells .. are the unit of function" - Sydney Brenner, 2006

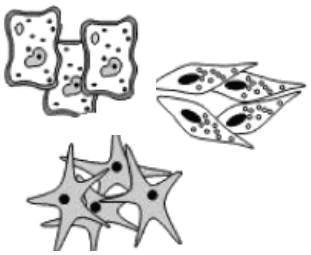
Virtual Liver: v-Liver™

Agent-Based Cellular Systems Model

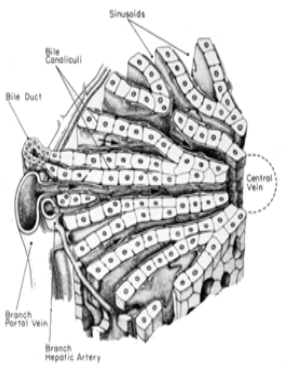


Tissues

Key events in cell response



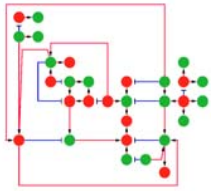
Cell Signaling



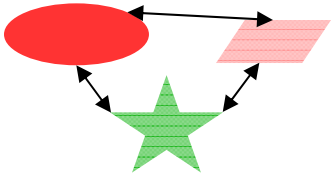
Blood Flow

Virtual Tissues

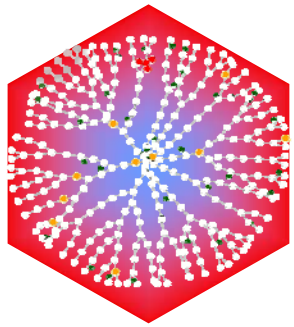
Molecular Logic
Cell Changes



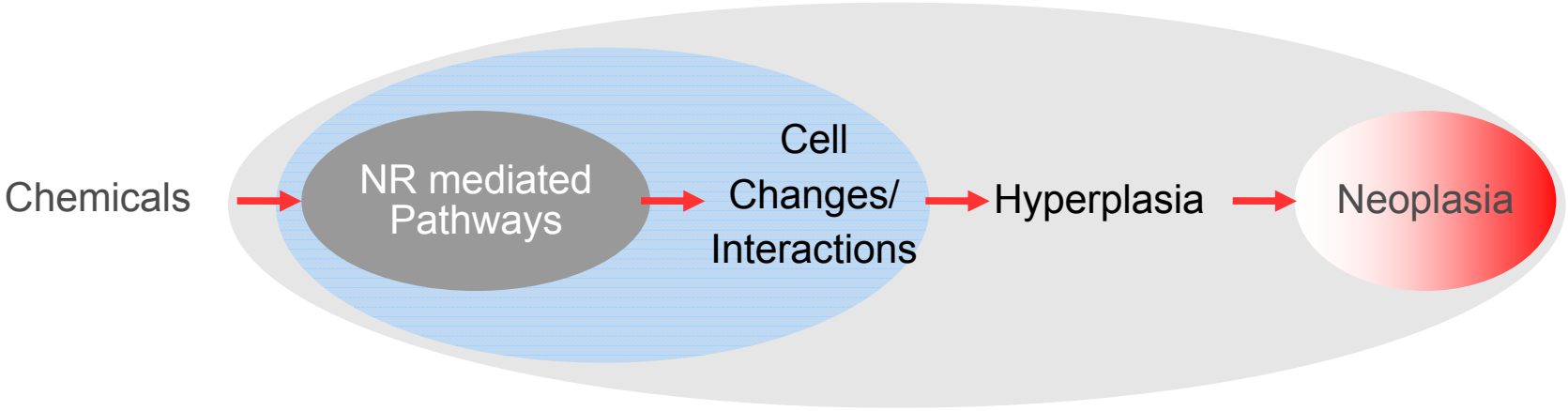
Cell Interactions



Spatial Cellular System



v-Liver™: Proof of Concept



Goal: Simulate dose-dependent events in nuclear receptor-mediated proliferative lesion formation

Modes-of-Action: Regenerative proliferation, Mitogen, DNA Damage

Approach: Cross-scale Cellular Systems Model

v-Liver: Proof of Concept

A) Select environmental chemicals from ToxCast Phase I

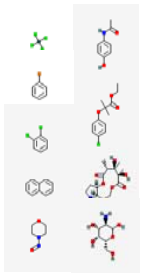
B) Integrate knowledge on key cellular events in hepatocarcinogenesis

C) Develop tissue simulation platform: key cell interactions and cell state changes

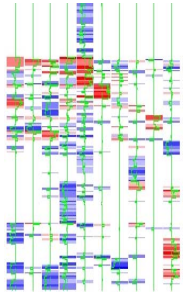
D) Evaluate using PoC chemicals

v-Liver™ Architecture

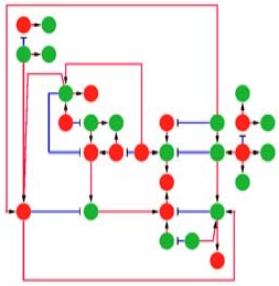
Assays	v-Liver Knowledgebase	v-Liver Simulator	Outcomes



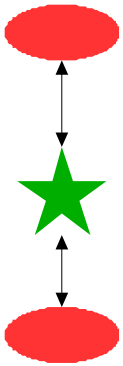
Env. Chems



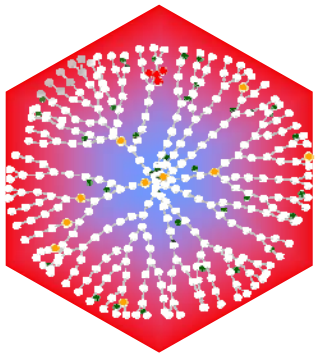
ToxCast HTS, HCS *ex vivo*



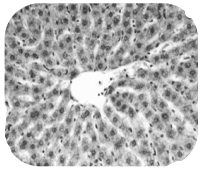
Molecular Events

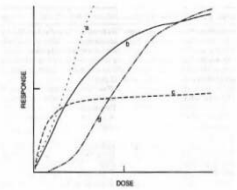


Cell-Cell Events



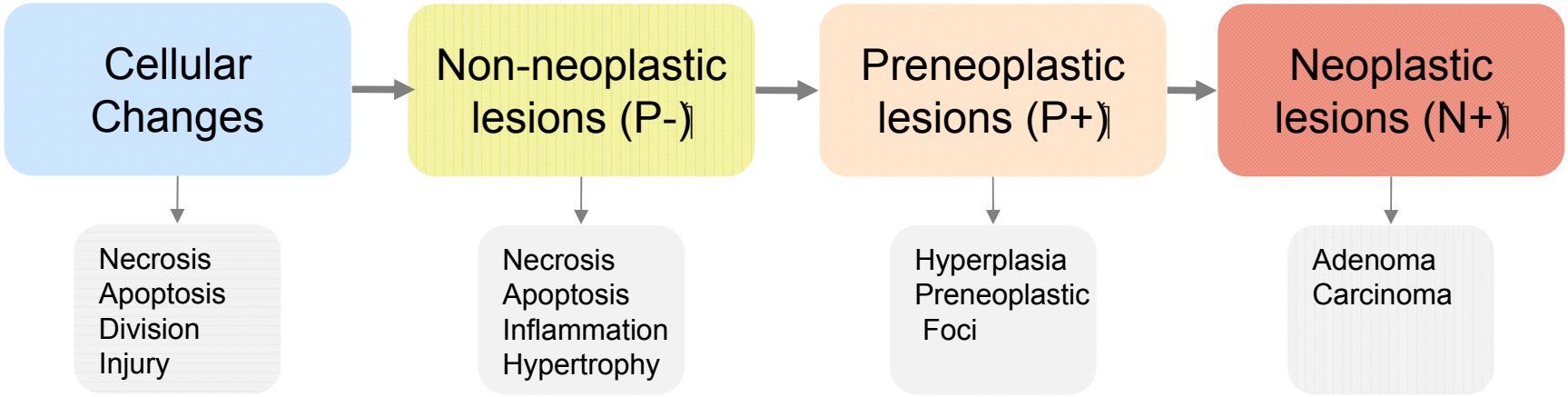
Cell Sys. & Blood Flow





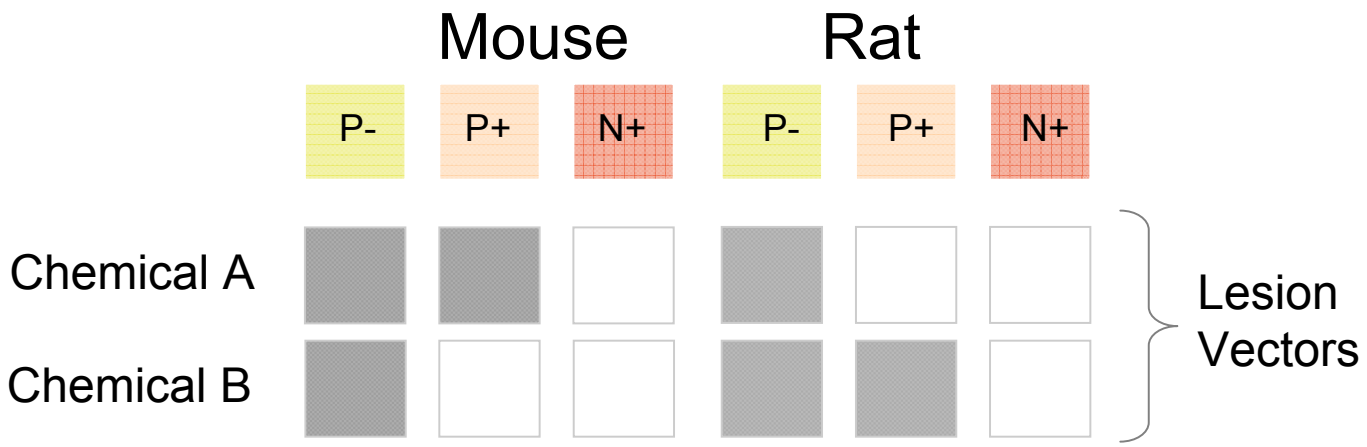
Cellular & Tissue Effects

Chronic Toxicity: Cancer



- Multiple molecular and cellular pathways
- Incomplete information about mechanisms
- Carcinogenesis us chemical & dose dependent

Data on Lesion Progression



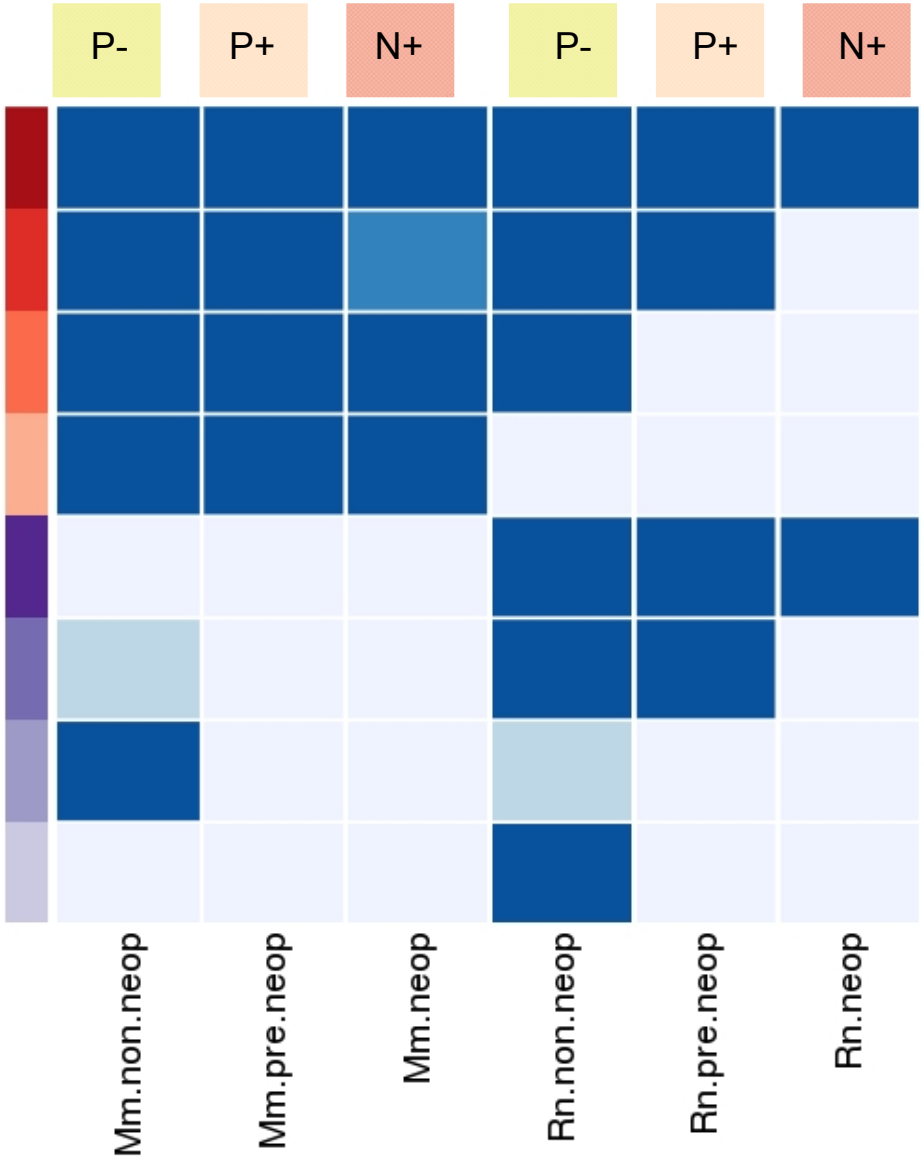
- Lesion progression can be species-dependent
- Summarize chemical-induced tissue effects across rat and mouse

Cancer Lesion Progression

ToxRefDB:
220 Chemicals

Rodent
testing studies

Detailed
histopathology

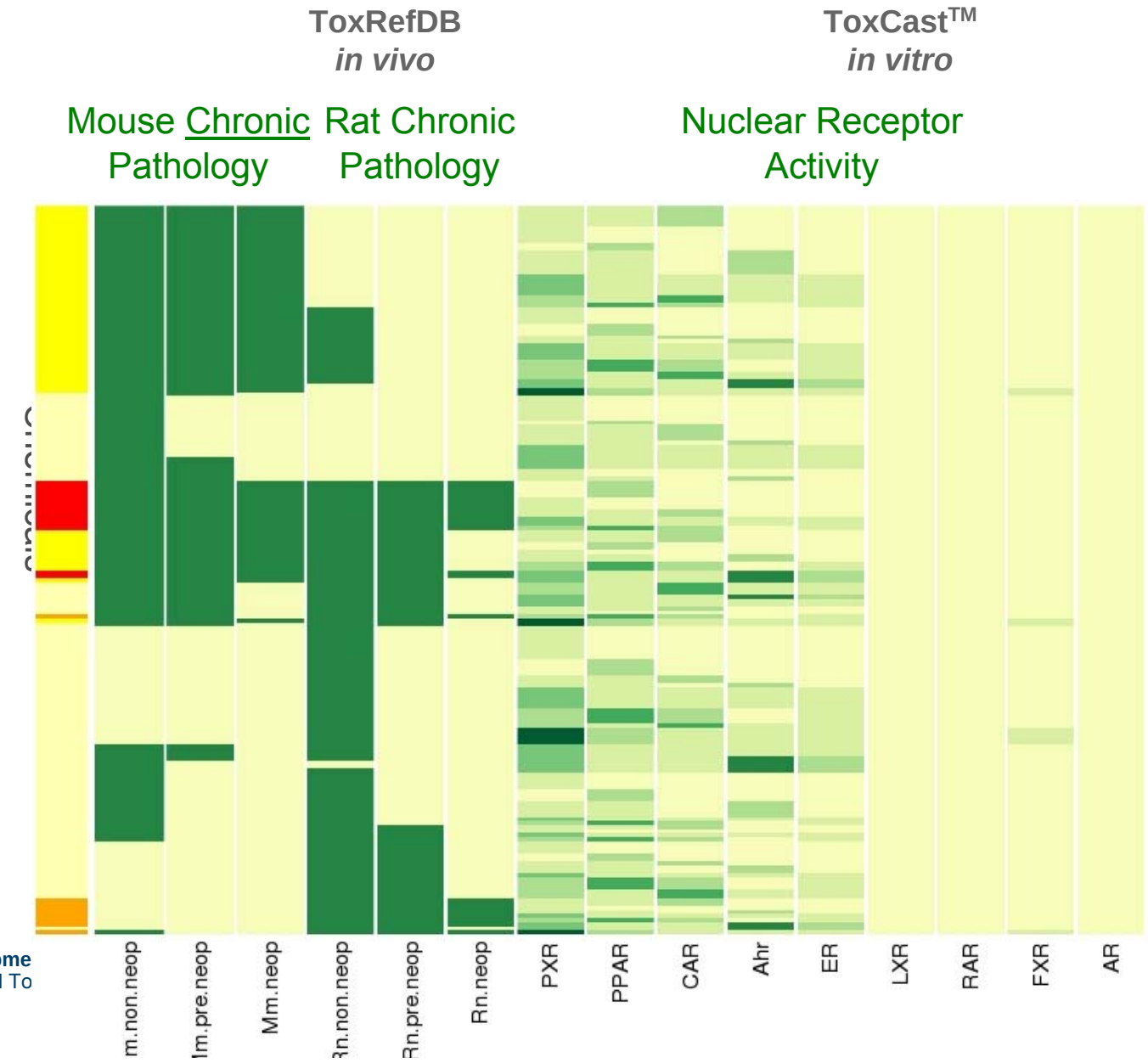


Rodent Cancer & NRs

ToxCast:
309 Chemicals
600 Assays
Chronic Pathology

20 PoC Chemicals
Nuclear receptor +
Chronic pathology +/-

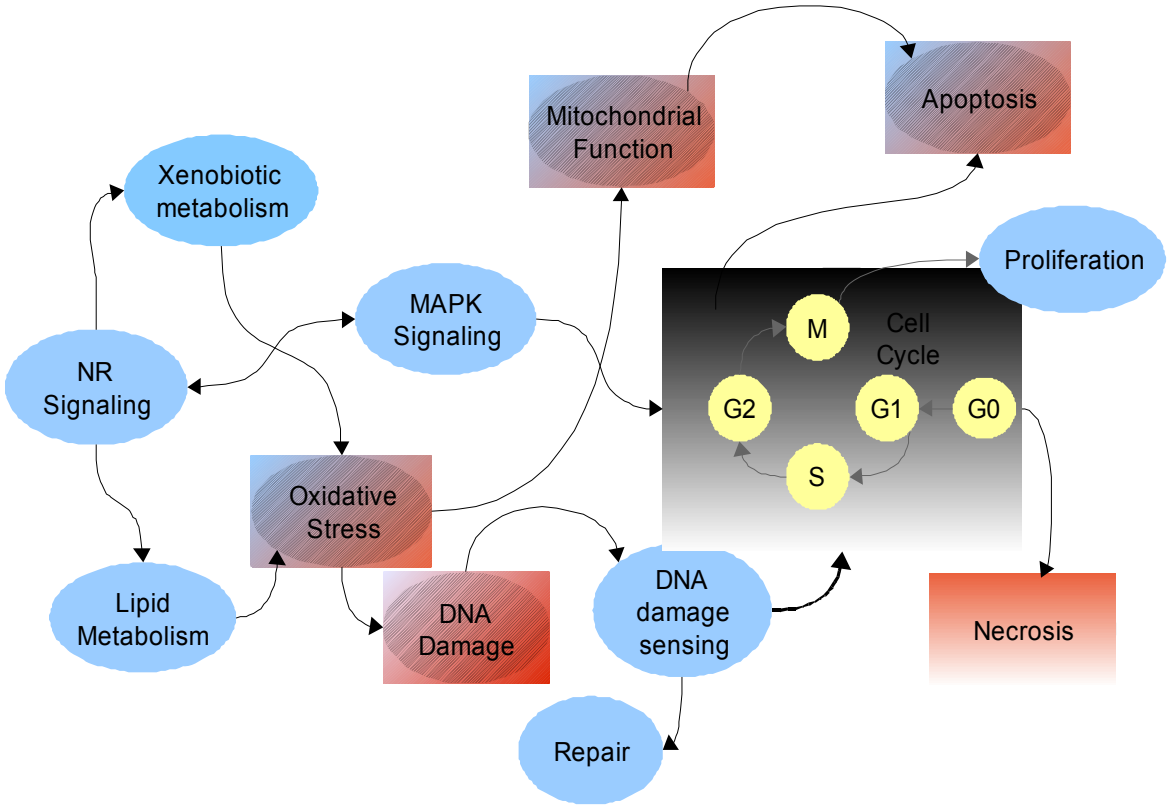
Conazoles
Pyrethroids
Phthalates
Perfluorinated



Cellular Pathways: *Macrostates*

Mine literature, DBs and prior data:

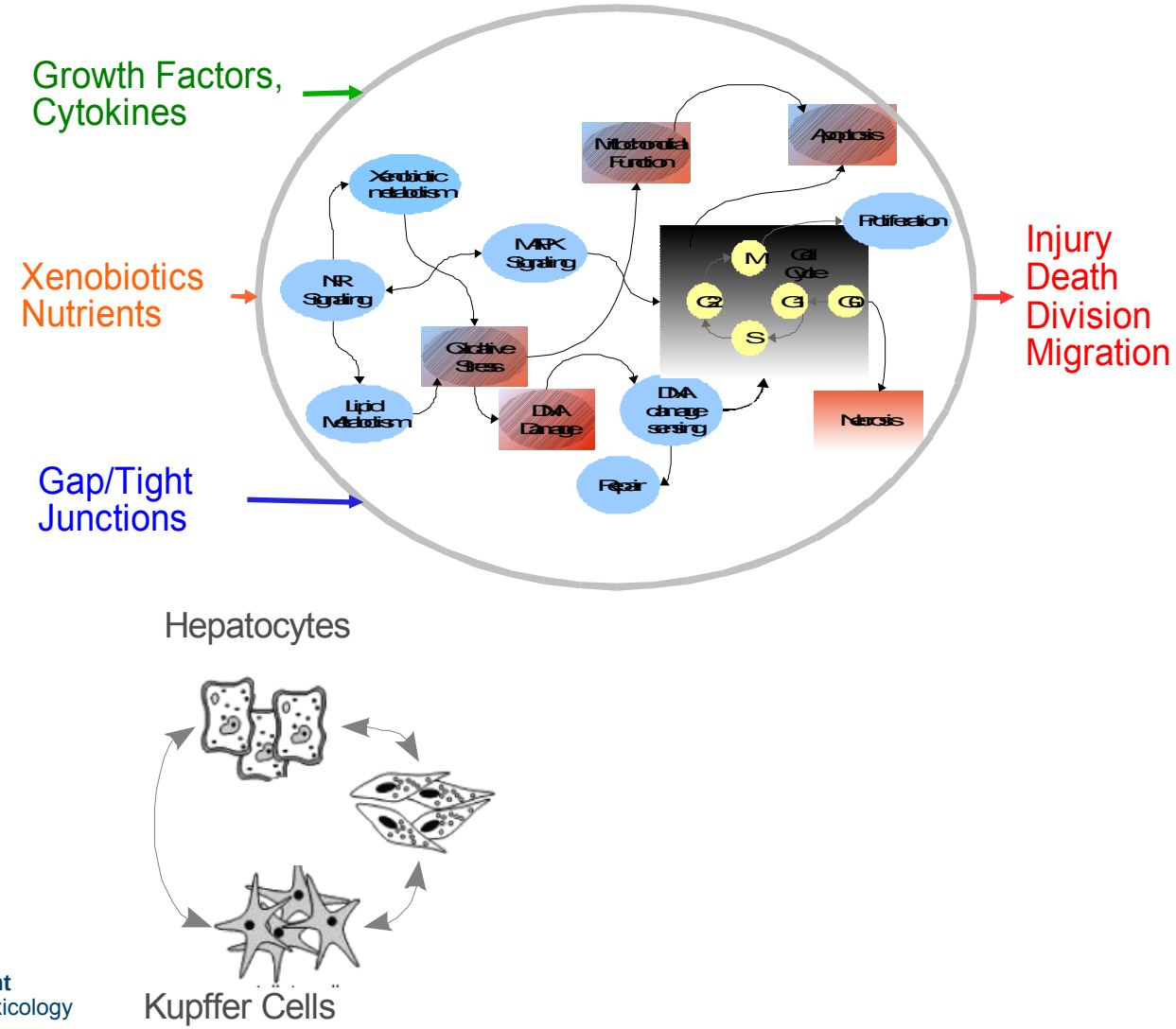
Cellular pathways involved in death, division, initiation & promotion

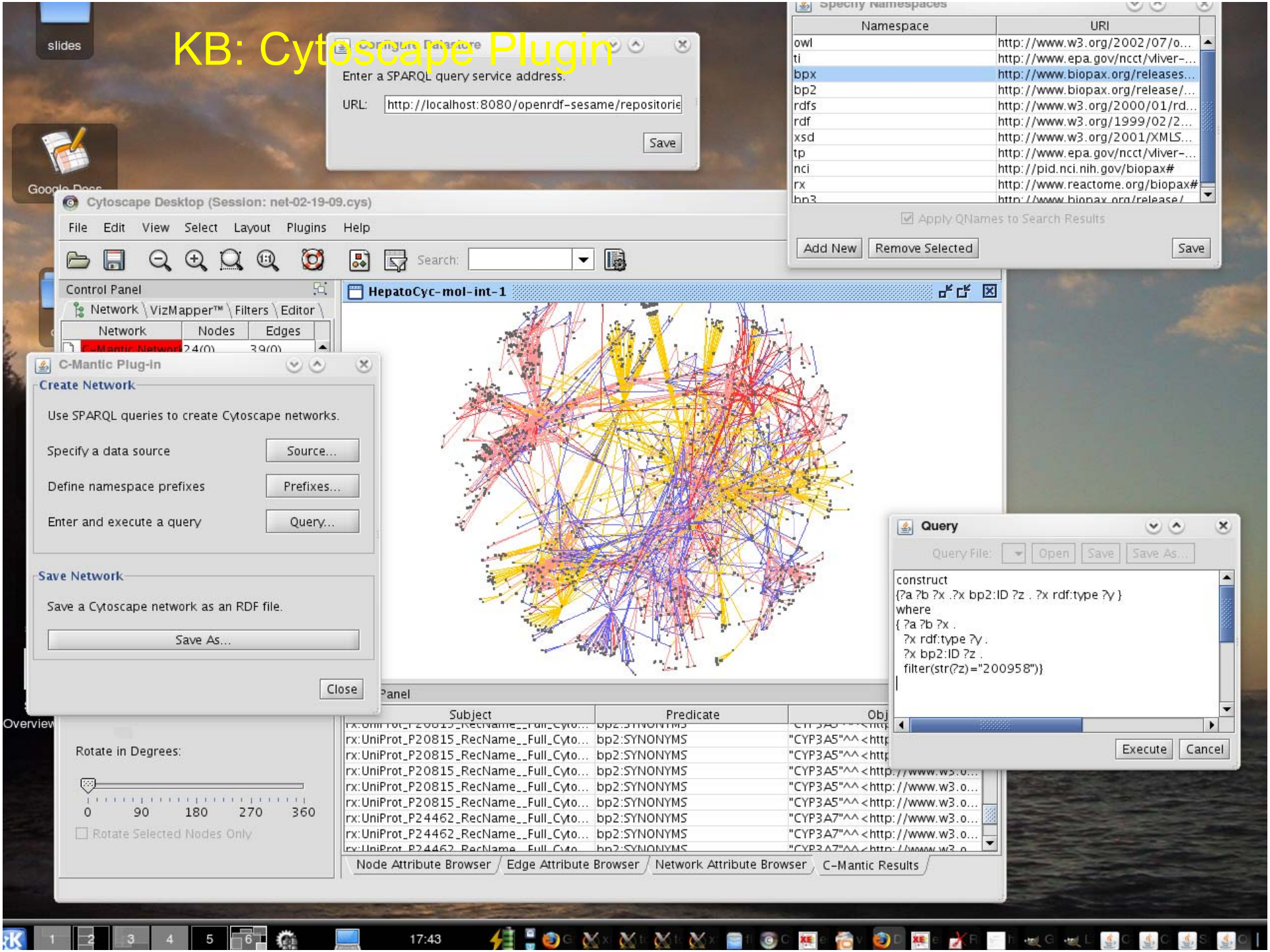


Cellular Interactions

Mine literature, DBs and prior data

Cells & interactions involved in cancer progression




KB: Cytoscape Plugin
slides
Enter a SPARQL query service address:
URL:
http://localhost:8080/openrdf-sesame/repositorie
Save
Specify Namespaces
Namespace
URI
owl
http://www.w3.org/2002/07/o...
ti
http://www.epa.gov/ncct/vliver-...
bpx
http://www.biopax.org/releases...
bp2
http://www.biopax.org/release/...
rdfs
http://www.w3.org/2000/01/rd...
rdf
http://www.w3.org/1999/02/2...
xsd
http://www.w3.org/2001/XMLS...
tp
http://www.epa.gov/ncct/vliver-...
nci
http://pid.nci.nih.gov/biopax#
rx
http://www.reactome.org/biopax#
Apply QNames to Search Results
Add New
Remove Selected
Save
Cytoscape Desktop (Session: net-02-19-09.cys)
File
Edit
View
Select
Layout
Plugins
Help
Search:
Control Panel
Network
VizMapper™
Filters
Editor
Network
Nodes
Edges
HepatoCyc-mol-int-1
C-Mantic Plug-in
Create Network
Use SPARQL queries to create Cytoscape networks.
Specify a data source
Source...
Define namespace prefixes
Prefixes...
Enter and execute a query
Query...
Save Network
Save a Cytoscape network as an RDF file.
Save As...
Close
Query
Query File:
Open
Save
Save As...
construct
{?a ?b ?x .?x bp2:ID ?z . ?x rdf:type ?y }
where
{ ?a ?b ?x .
?x rdf:type ?y .
?x bp2:ID ?z .
filter(str(?z)="200958")}
Execute
Cancel
Rotate in Degrees:
0
90
180
270
360
Rotate Selected Nodes Only
Subject
Predicate
rx:UniProt_P20815_RecName__Full_Cyto...
bp2:SYNONYMS
"CYP3A5"^^<http://www.w3.o...
rx:UniProt_P24462_RecName__Full_Cyto...
"CYP3A7"^^<http://www.w3.o...
Node Attribute Browser
Edge Attribute Browser
Network Attribute Browser
C-Mantic Results
17:43

Virtual Hepatic Lobule

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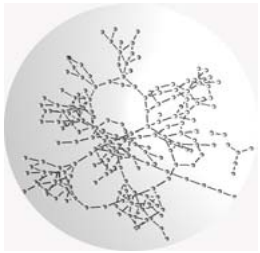


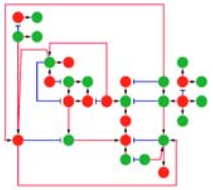
Knowledgebase

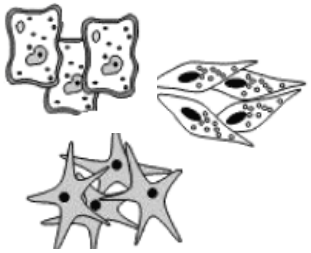
Key events in cell response

In vitro data

Tissue Simulator

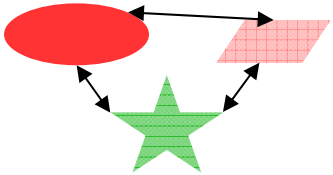
Molecular Logic
Agent Decisions

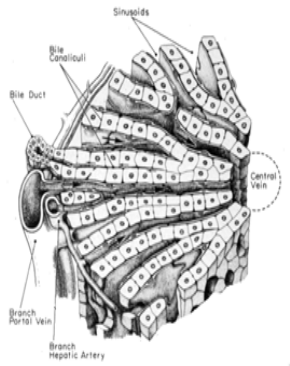




Cell Signaling

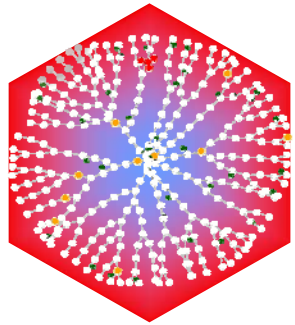
Agent Communication



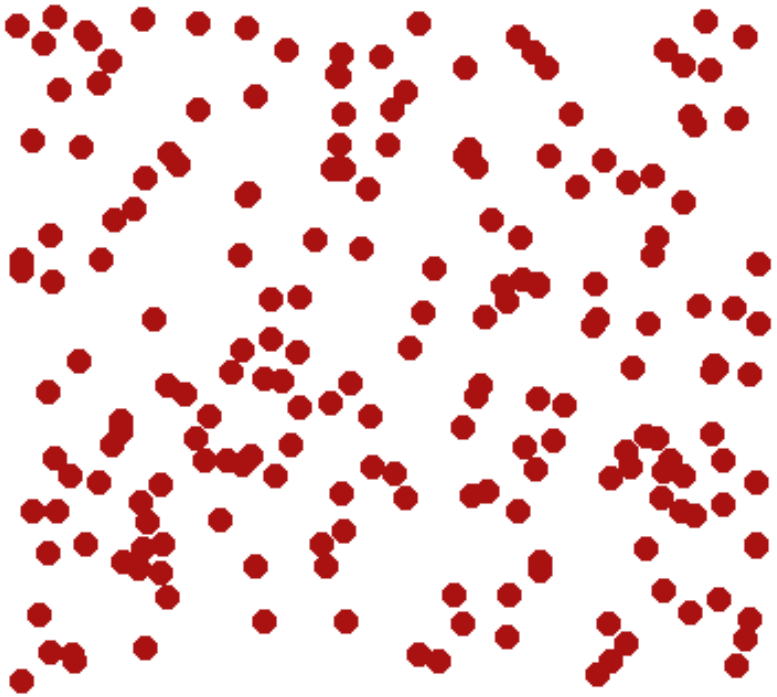


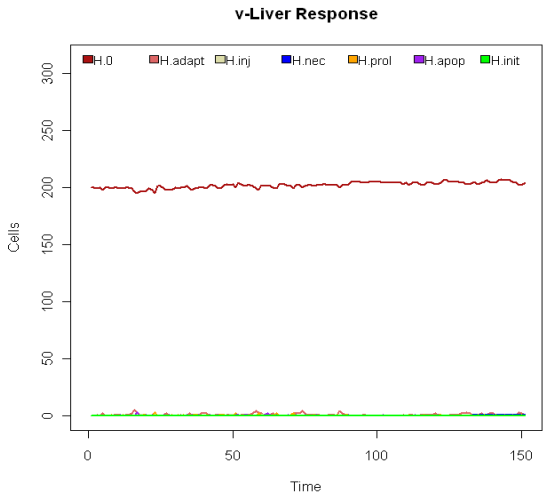
Blood Flow

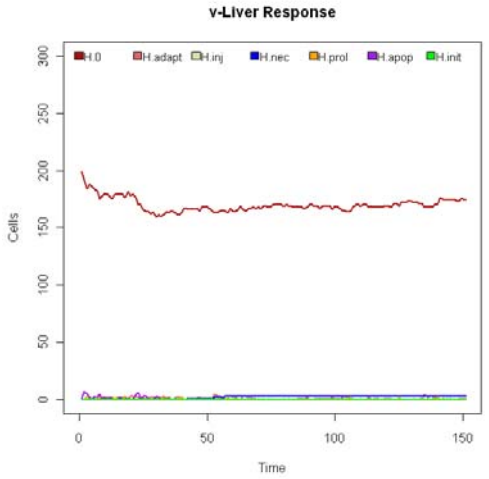
Multi-Agent System



Simulate *in vitro* Hepatocytes







Normal/Quiscent

Stressed/Adaptive

Stressed/Injured

Necrotic

Proliferative

Apoptotic

Simulating Chemical Effects

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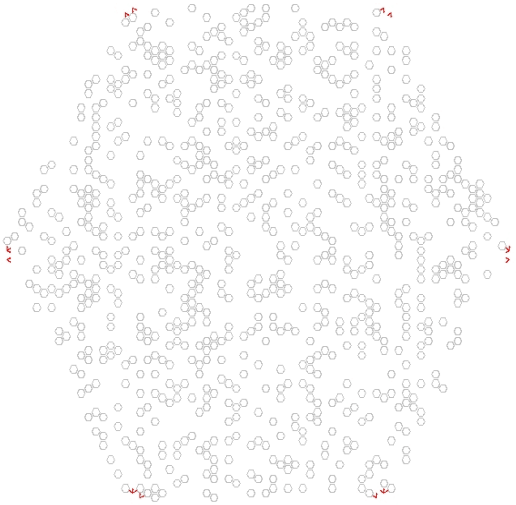
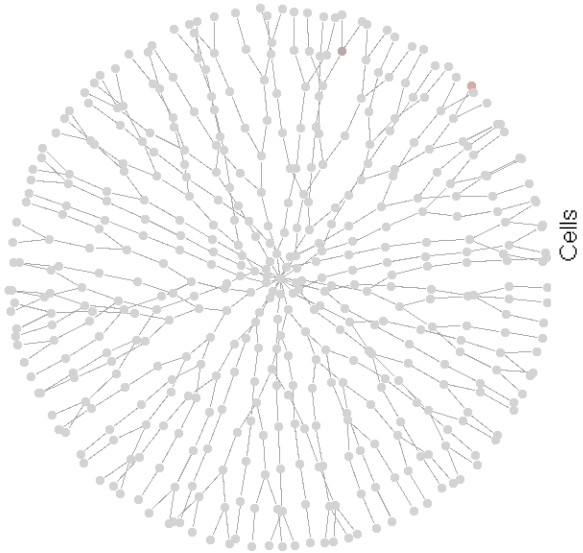
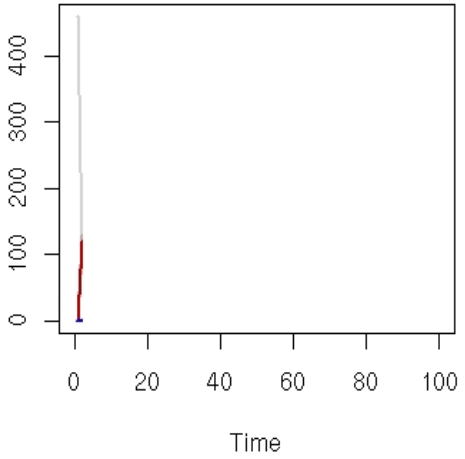
Microdosimetry

“Virtual Tissue”

Simulated Outcome







Multi-agent system: spatial distribution of agents with tight junctions

Dynamics of multi-agent system: temporal changes in cell death/ proliferation

Challenges

- Dealing with incomplete knowledge
- Using *in vitro* data in an *in vivo* context
- Dealing with time across molecular and cellular scales
- Evaluating *in vivo* predictions – how do we calibrate and evaluate tissue models ?

Multi-disciplinary Team: Cross-EPA/ORD & External

John Wambaugh
Jason Pirone
Mike DeVito
Nicholas Luke
Rory Conolly
Thomas Knudsen
David Dix
Matt Martin
Keith Houck
Richard Judson
David Reif
Woody Setzer
Amar Singh
Lockheed Martin