Development of Virtual Tissue Models

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LTG 1 Poster 12

Science Questions

- How do we measure, model, and predict the key attributes of the MOA that could impact risk assessment?
- How do we get better and more detailed understanding of MOA at various scales and reduce the associated uncertainty in a shorter time frame than traditional methods have allowed?
- How can biological networks be modeled from 'omics data to infer or predict cell behavior and tissue injury?
- How do we incorporate in vitro data into future toxicity testing in a way that will support risk assessment?

Why Virtual Tissues ?

Tissues are the physiologically relevant level for understanding chemical-induced toxicity. Virtual Tissues (v-Tissues) are a novel computational paradigm for modeling cellular systems, and for simulating their dynamic behavior to generate histomorphological outcomes. The application of v-Tissues to risk assessment requires a computable description of the tissue and data on the cellular responses and related molecular events for the relevant toxicity MOA(s).

Virtual Tissue Goal

The goal of the virtual tissue models is to develop predicitve models of chemical induced toxicity. These models will initially use existing biologically-based dose response (BBDR) models. These models will be adapted to incorporate descriptions of the genetic and cellular networks underlying the normal biology of the system.

It is envisioned that as these models are developed they will provide an organizing principle of experimental design, data collection and analyses. In addition, these models will provide a platform for species extrapolation. As the models become more refined, they will rely more heavily on data from human tissues and less on information from experimental animals.

Methods/Approach

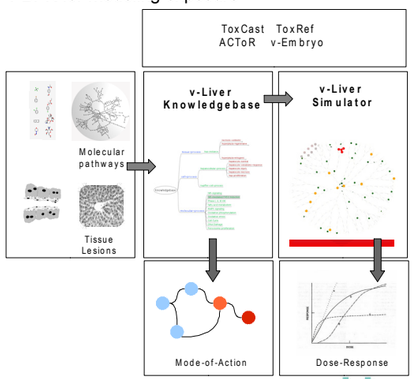
v-Liver

What is the v-Liver?
The v-Liver is a cross-ORD/EPA project aimed at developing risk assessment tools for simulating chronic liver injury across chemicals, doses and species. The v-Liver system will enable:
- Computational analysis of MOA(s) leading to adverse hepatic outcomes across chemicals, species, genders and populations
- Simulation of MOA across doses to assess hepatic lesion development in humans

Why the Liver?
The liver is the most frequent source of critical effects from environmental chemicals– understanding their human relevance at low doses will impact risk assessment

Short-Term Goals
- Focus on biologically-based models of hepatocarcinogenesis mediated by nuclear receptor activators in ToxCast for proof of concept (PoC).
- *v-Liver Knowledgebase:* Organize MOA information about PoC chemicals in computable form as molecular and cellular events.
- *v-Liver Tissue Simulator:* Simulate the dynamics of molecular and cellular processes in the hepatic lobule leading to histological changes.
- Evaluate simulations of dose-dependent lesions for PoC chemicals using *in vitro* data from ToxCast.

Long-Term Goals
- Extend the Knowledgebase to analyze chronic liver injury MOA for new chemicals, genomic variation, genders and life stages
- Extend the v-Liver Simulator to whole liver and integrate with PBPK for modeling exposure



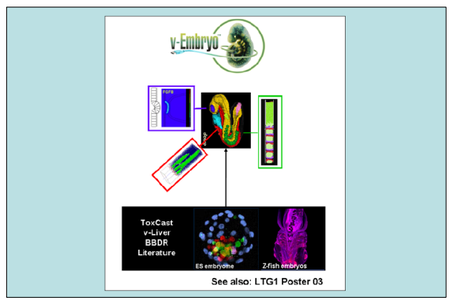
v-Embryo

What is the v-Embryo?
An interdisciplinary research and technology pipeline for the computational analysis of developmental toxicity to:
- **simulate** key signaling pathways, interlocking genetic networks and cellular dynamics in developing tissues;
- **model** how embryonic cells react to chemical exposure individually and collectively as a complex system;
- **analyze** emergent behaviors and canalizing influences following stimulus / injury / perturbation; and
- **understand** how this complexity contributes to the differential susceptibility of developing tissues across dose, stage and time

Why the Embryo?
Embryogenesis entails a precise order of tissue development in time and space. Minor perturbations from prenatal exposure can have life-long consequences at the personal and societal level.

Short-Term Goals
- Build knowledgebase (VT-KB) and front end simulation engine (VT-SE) for developmental processes and toxicities
- Construct cell-based computational models for prototype morphogenetic processes and embryonic modules
- Tune the models to enable emergent organization and self-regulation during network-level stimuli/injury/mutation
- Predict abnormal developmental trajectories and cellular modes of action that result from chemical perturbations

Long-term goals
- Grow VT-KB and VT-SE with relevant information and parameters for developmental processes and toxicities
- Expand prototype computational models to broader stages, embryonic modules, and species
- Merge individual models to support integrative analysis of developmental toxicity *in toto*



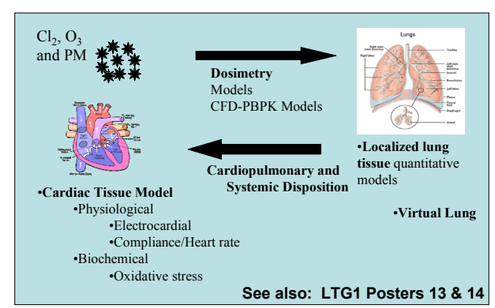
v-CardioPulmonary

What is the v-CardioPulmonary?
A computational systems model that can be used to organize experimental and epidemiological data used to predict organ toxicities due to air pollutant exposure. The project will start with parallel BBDR modelling projects to describe reactive gases (chlorine, Cl_2 and ozone, O_3) and particulate matter. Each individual project will be designed to facilitate integration of the results in a second phase where a virtual system will be built from the individual BBDR models/data. This virtual system should then be capable of modelling cumulative effects from criteria and toxic air pollutants.

Why the Cardio Pulmonary System?
Exposure to air pollutants, notably reactive gases and PM, is associated with increased risk for asthma and cardiovascular and pulmonary morbidity and mortality. Due to the broad based exposure these effects have significant economic and personal costs.

Short-Term Goals
- Build hybrid computational fluid dynamic (CFD) – physiologically-based pharmacokinetic (PBPK) Models of airflow and tissue dosimetry of reactive gases (Cl_2 and O_3) in rodent and human respiratory tract.
- Extend existing multi-path particle dosimetry (MPPD) model with PBPK description of respiratory tract tissue reactions.
- Extend respiratory tract tissue description with cell types and interactions to represent physiological and biochemical endpoints
- Develop an initial tissue-level cardiac component to describe
  1. Cardiopulmonary and systemic distribution
  2. Tissue-level reactions of the cardiac system representing structure, cell types, and interactions to represent physiological and biochemical endpoints

Long-term goals
1. Assess the models with epidemiological studies
2. Expand the respiratory tract and cardiac tissue descriptions with applicable molecular interaction networks and cell state modules for multi-scale simulation of injury.



Impact and Outcomes

- This research effort will integrate the broad range of biological, toxicological, and epidemiological information used in risk assessments for these tissues.
- This research effort will integrate computational modeling and data generation to support the development of quantitative models for use in risk assessment.
- Qualitative and quantitative analyses of HTP screening data from ToxCast and other programs will be used for mode of action determination and development of quantitative models.

Future Key Products

- New toxicity pathway assays for Tox21 chemical screening and prioritization (short term)
- Data to support the use of toxicity pathway data in risk assessment via weight of evidence (mid term)
- Quantitative models linking toxicity pathway data to adverse outcomes in humans (long term)
- Data to support the use of resulting quantitative models in risk assessment (long term)

Researchers Involved

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