European Partnership for
Alternative Approaches to Animal Testing
Brussels – October 1-2, 2019

Computational systems biology/pharmacology approaches:
Translating cellular lesions into quantitative phenotypes

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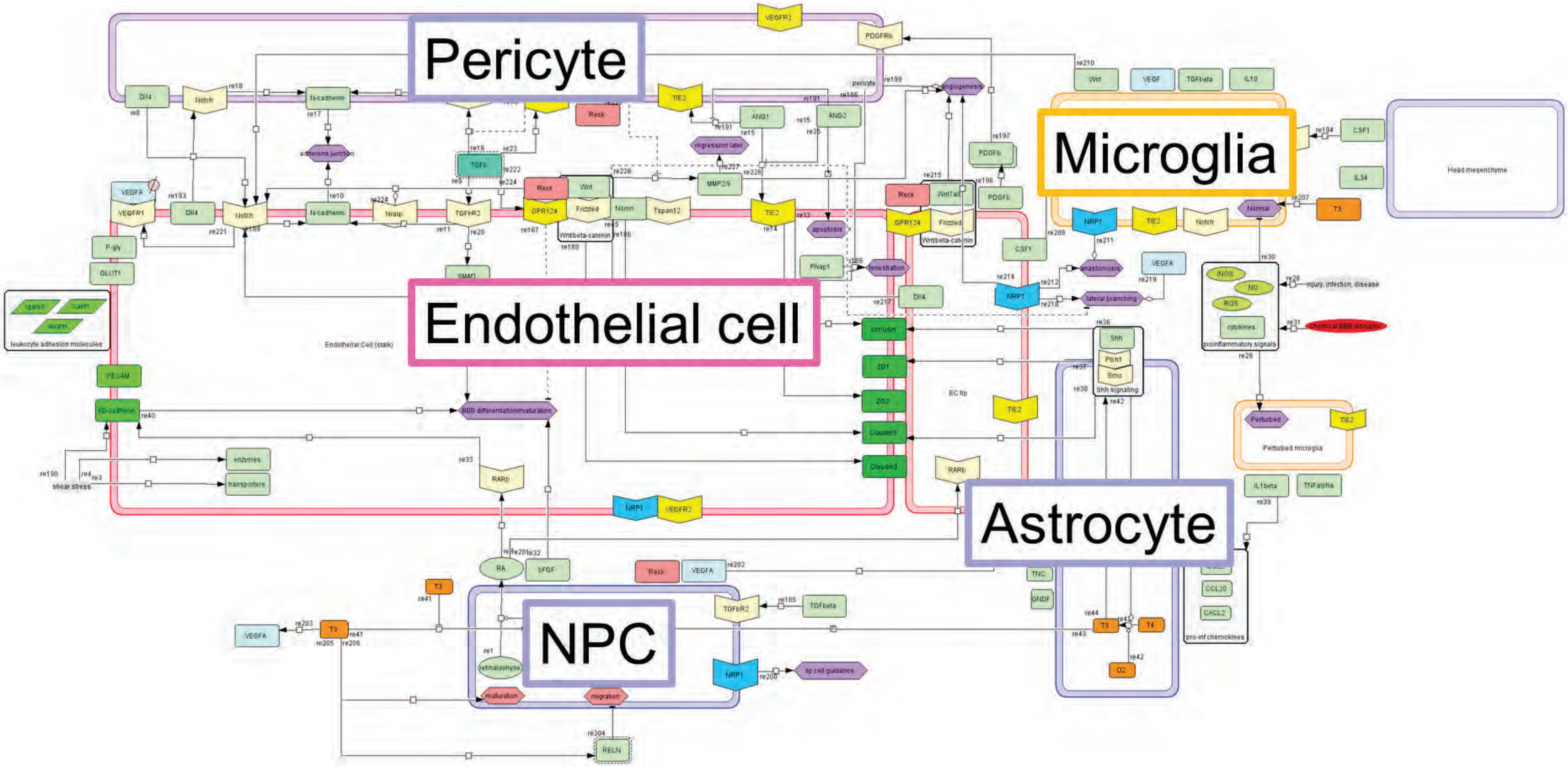
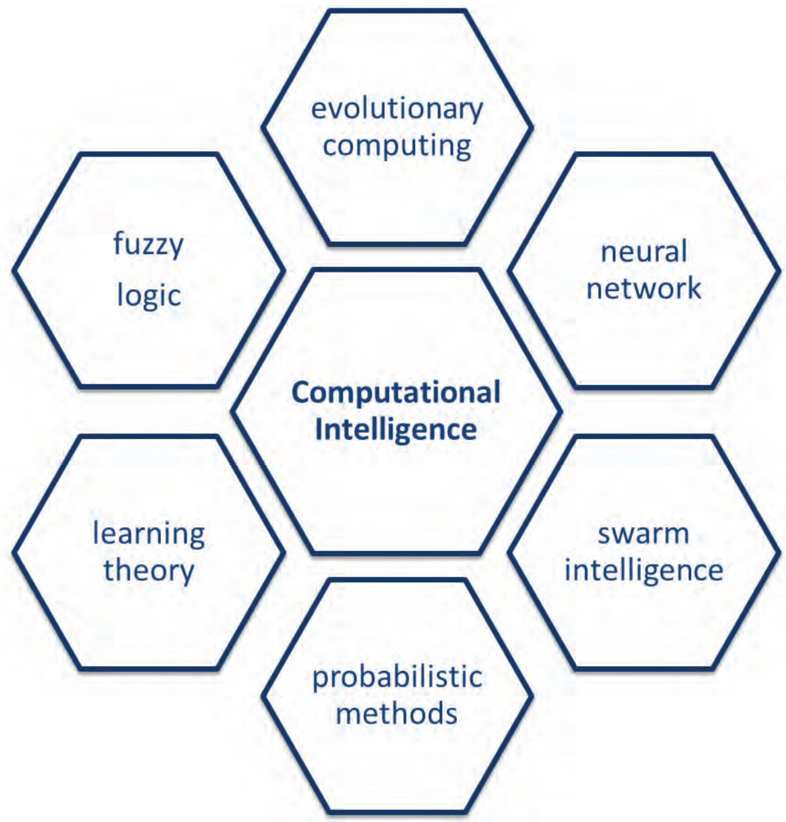


Pericyte
Microglia
Endothelial cell
Astrocyte
NPC
Head mesenchyme
Perturbed microglia
Endothelial Cell (stalk)
EC tip
leukocyte adhesion molecules
proinflammatory signals
pro-inf chemokines
Shh signaling
Wnt/beta-catenin
BBB differentiation/maturation
adherens junction
regression later
angiogenesis
apoptosis
fenestration
anastomosis
lateral branching
tip cell guidance
maturation
migration
shear stress
injury, infection, disease
chemical BBB disruption

Computational Intelligence

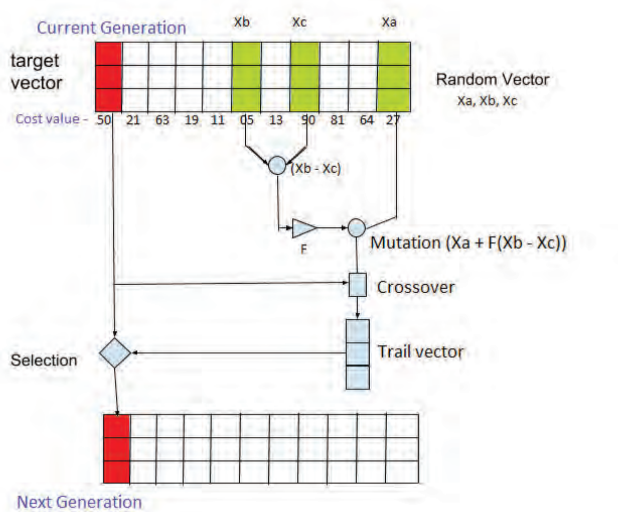
https://www.thescientist.com May, 2019

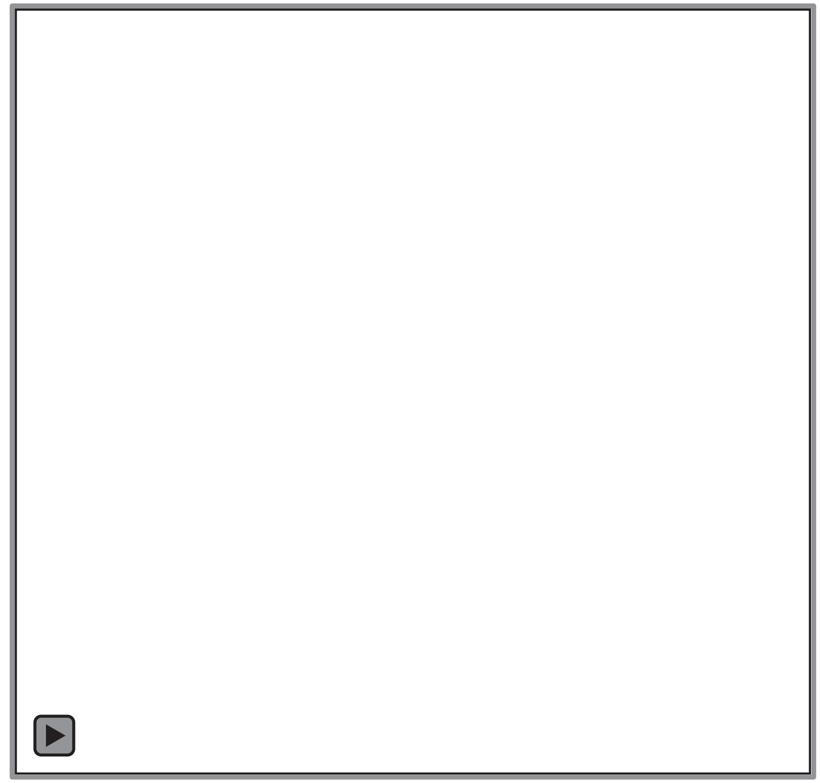


Anatomical homeostasis in a self-regulating ‘Virtual Embryo’

- EA for self-regulation (fitness measure) - simulation executes randomly paired agents (parent cells) that generate daughter cells mutated in their rules.

- You only need to specify the goal of the computation; EA searches rule-space using ‘survival of the fittest’ (good solutions propagate, poor solutions discarded).

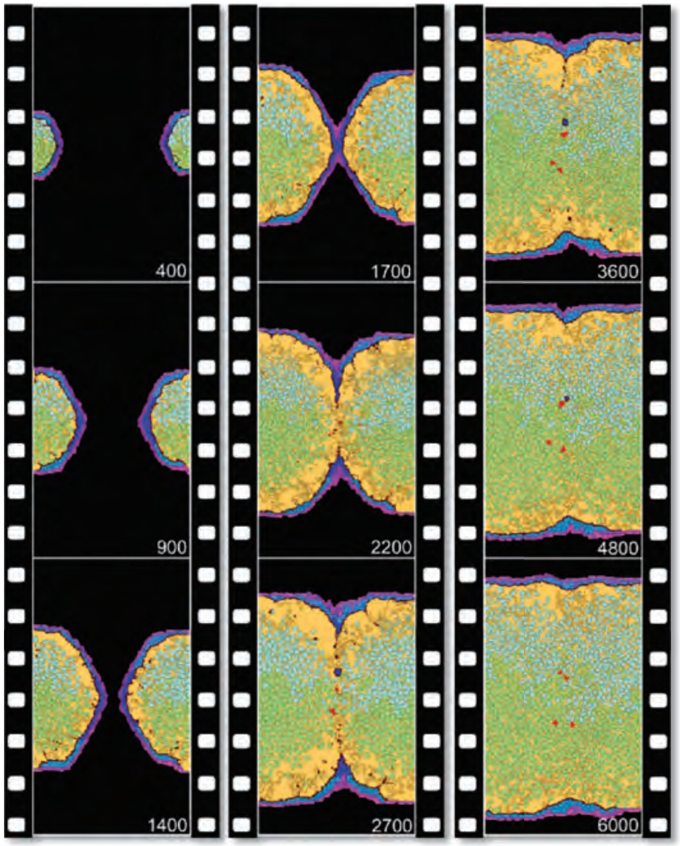




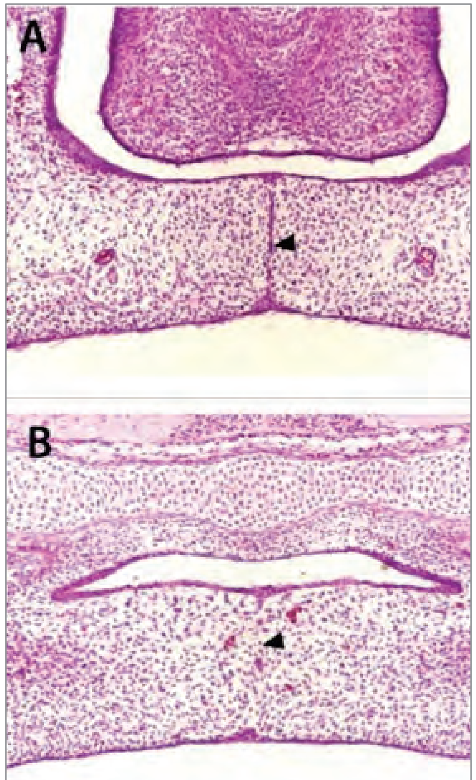
SOURCE: Andersen, Newman and Otter (2006) Am. Assoc. Artif. Intel.

Morphogenetic fusion (palate)

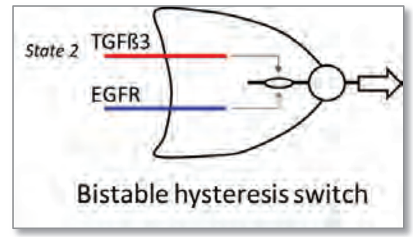
in silico

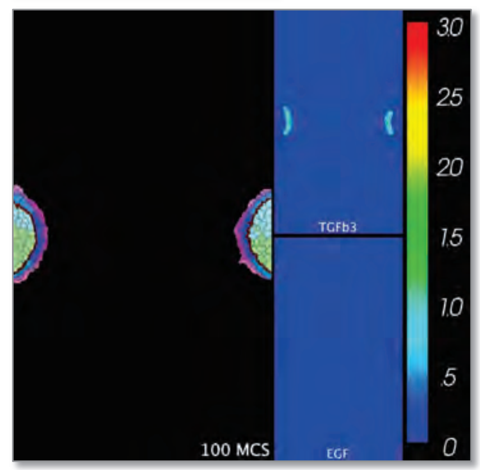


in vivo



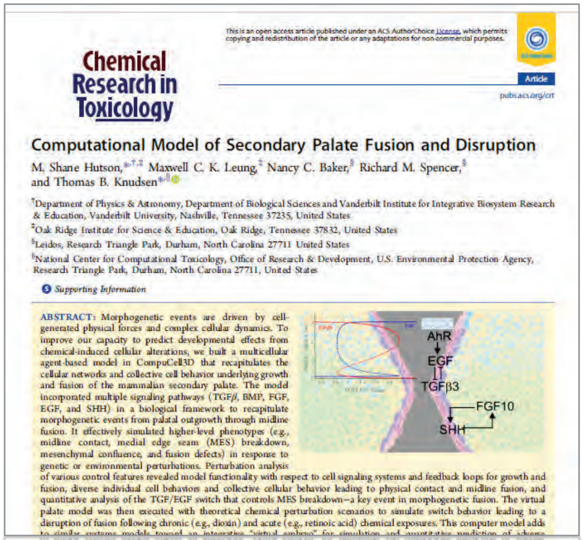
Jin and Ding (2006) Development





SOURCE: Hutson et al. (2017) Chem Res Toxicol

Smart model …



Chemical Research in Toxicology

Article

pubs.acs.org/crt

Computational Model of Secondary Palate Fusion and Disruption

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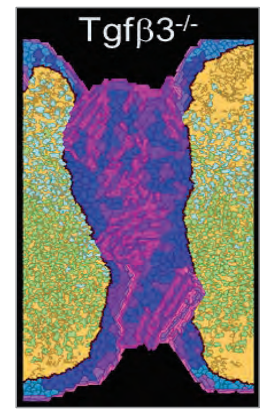
Supporting Information

ABSTRACT: Morphogenetic events are driven by cell-generated physical forces and complex cellular dynamics. To improve our capacity to predict developmental effects from chemical-induced cellular alterations, we built a multicellular agent-based model in CompuCell3D that recapitulates the cellular networks and collective cell behavior underlying growth and fusion of the mammalian secondary palate. The model incorporated multiple signaling pathways (TGFβ, BMP, FGF, EGF, and SHH) in a biological framework to recapitulate morphogenetic events from palatal outgrowth through midline fusion. It effectively simulated higher-level phenotypes (e.g., midline contact, medial edge seam (MES) breakdown, mesenchymal confluence, and fusion defects) in response to genetic or environmental perturbations. Perturbation analysis of various control features revealed model functionality with respect to cell signaling systems and feedback loops for growth and fusion, diverse individual cell behaviors and collective cellular behavior leading to physical contact and midline fusion, and quantitative analysis of the TGF/EGF switch that controls MES breakdown—a key event in morphogenetic fusion. The virtual palate model was then executed with theoretical chemical perturbation scenarios to simulate switch behavior leading to a disruption of fusion following chronic (e.g., dioxin) and acute (e.g., retinoic acid) chemical exposures. This computer model adds

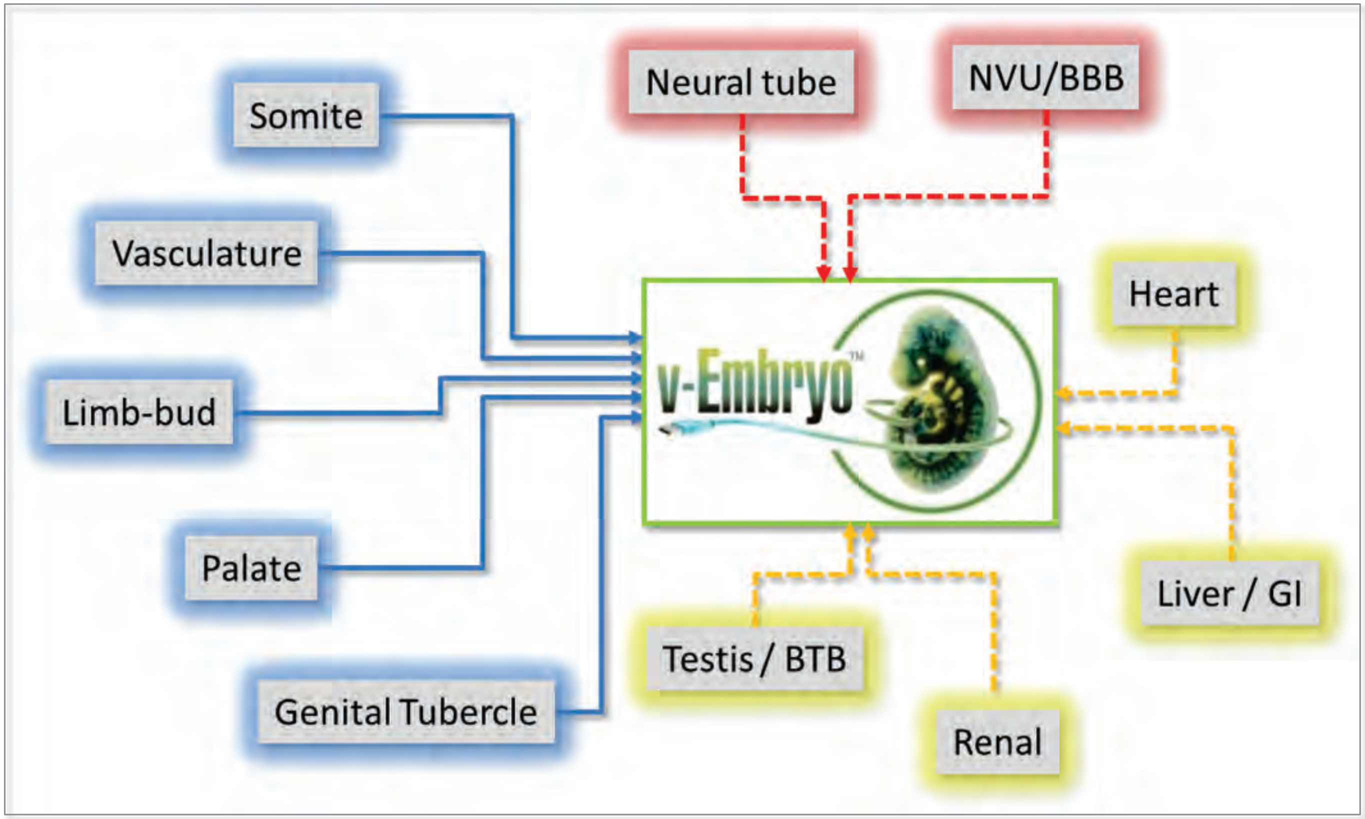
Reviewer Comment: *"Crucial mechanisms occurring during palate fusion, especially opposing palatal shelf adhesion, are not considered in the model. In fact, the main reason why Tgf-b3 KO mice have cleft palate is a failure of opposing MEE adhesion, leading to separation of palatal shelves after their initial contact. Even in those strains in which palatal shelves adhere partially, I have never seen a MES as the one shown in Fig. 5."*

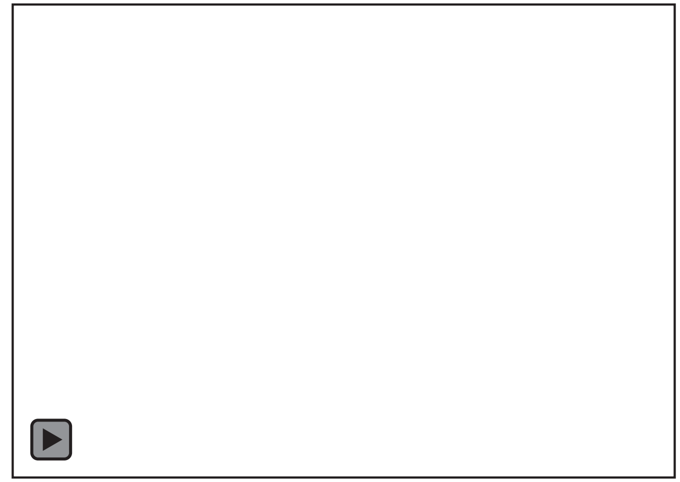
Our Response: TGF-b3 knockout mouse palates transduced with ALK vectors *in vitro. (from Dudas et al. 2004).*



SOURCE: Hutson et al. (2017) Chem Res Toxicol

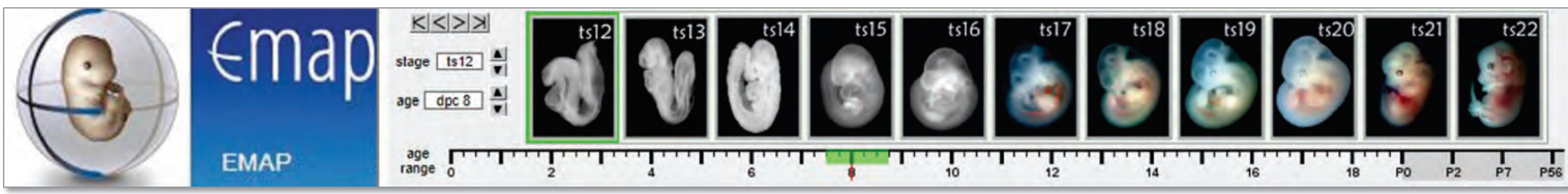
In silico dose-response: *translating ↑EGF/TGFb in vitro profile into a critical effect*





VTLS
- *access to models & simulations*
- *VT-KB (knowledgebase)*
- *Literature mining*
- *tied to ToxCastDB*
- *high-performance computing*

vtls.epa.gov/



https://www.emouseatlas.org/emap/ema/home.php

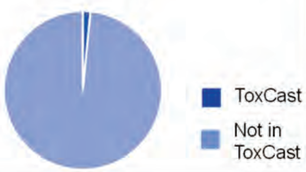
Take Home Messages from Rusty …

Russell
Thomas
Director

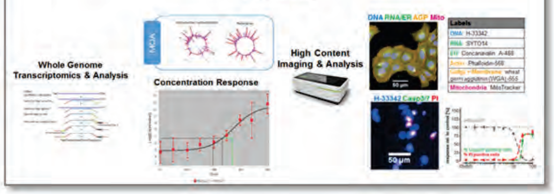
- Multiple opportunities exist for using high-throughput and computational approaches to address challenges in toxicology and risk assessment.
- Using high-throughput approaches will require systematically addressing key technical and data analysis challenges.
- Enabling application of high-throughput data to chemical safety decisions will require delivery and integration using a broad range of IT tools.
- Partnering with regulators on case studies will increase confidence and acceleration application to chemical risk assessment.

Some Existing Limitations in HTS and *In Vitro* Test Systems

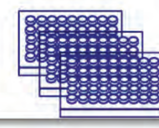
Biological Coverage (Gene Basis)



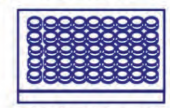
High-Throughput Transcriptional and Phenotypic Profiling



Chemical Coverage and Specific Chemical Types (e.g., VOCs)



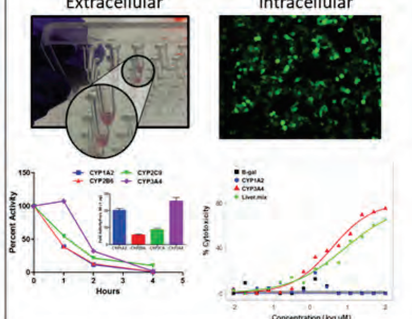
VOC *In Vitro* Exposure System and Water Library



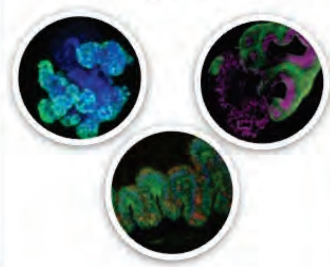
Initial test library of ~70 chemicals

Metabolic Competence

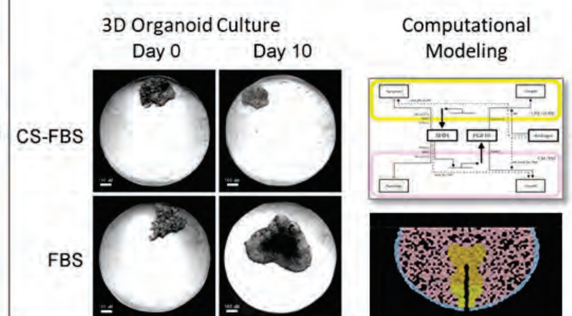
Assay Retrofit for Metabolism



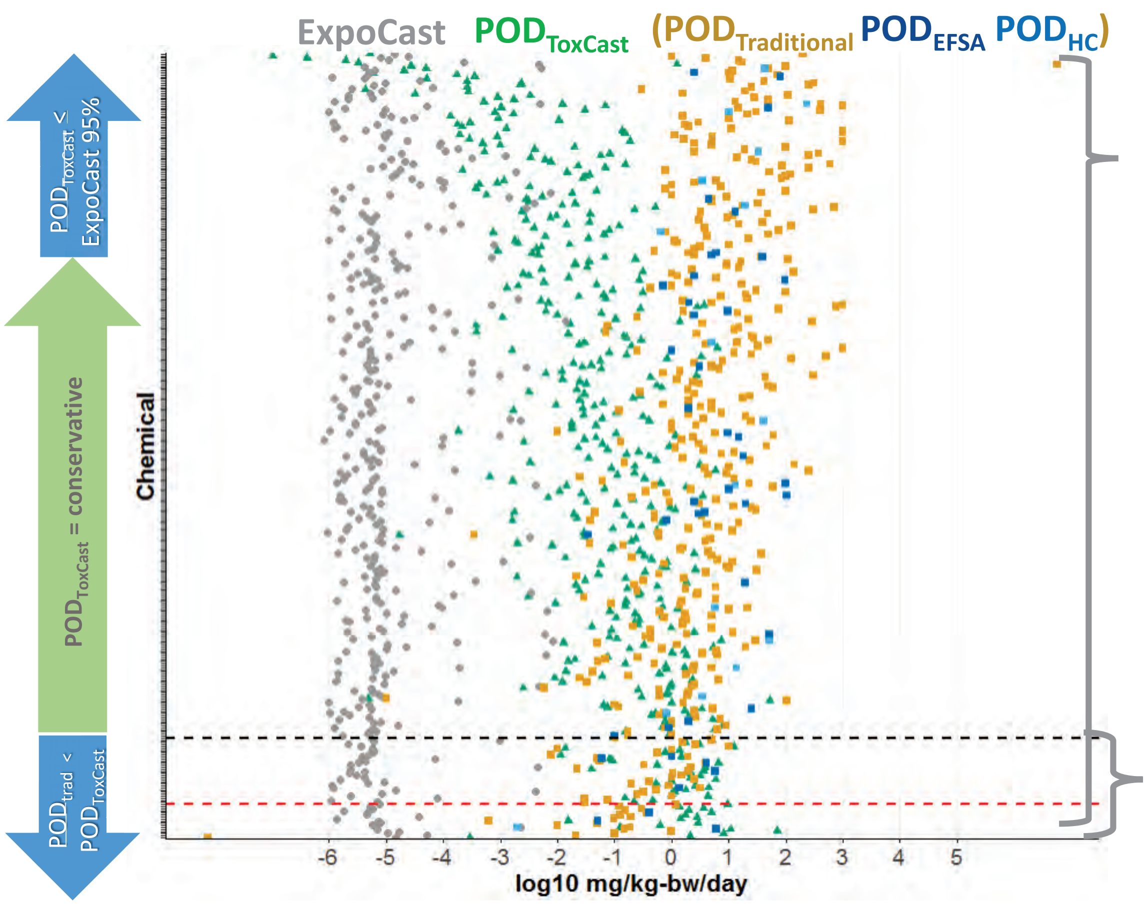
Organ and Tissue Responses



Virtual Tissue Modeling



Bioactivity Provides a Conservative Estimate of a NOAEL/LOAEL



Total =

380 chemicals

httk, ToxCast data, and POD value(s) currently available

For ~91.3% of the chemicals, $POD_{ToxCast}$ was conservative.

(~130-fold with human HTTK

~40-fold with rat HTTK)

Missing an important component of biology?