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Computational Toxicology and Prenatal Development

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CompTox Community of Practice
August 25, 2011

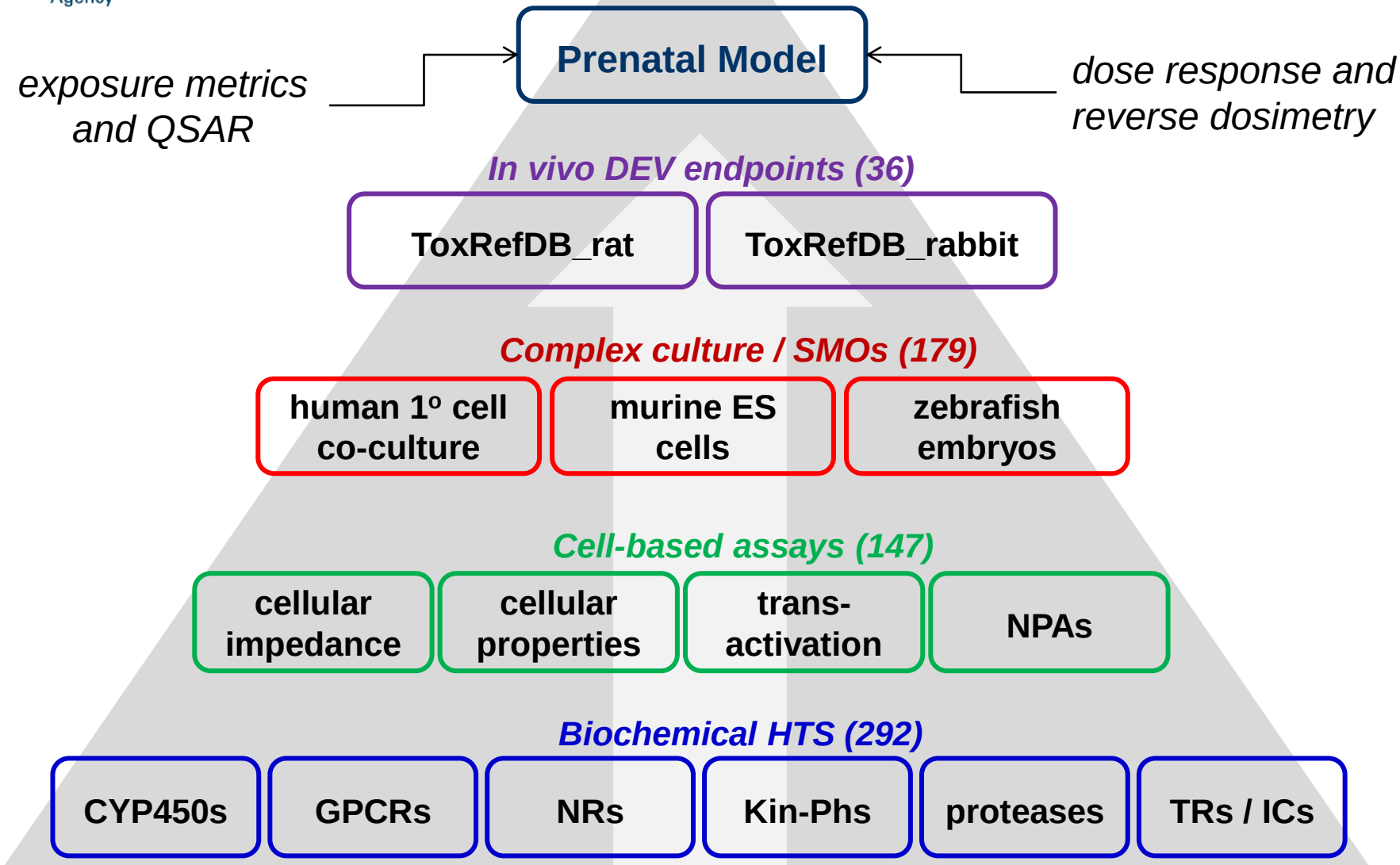
Embryogenesis:
orchestration of cellular complexity

EMBRYONIC CELL BEHAVIORS	CONSEQUENCES OF DISRUPTION
cell growth & death	incorrect cell number
differentiation & function	missing cell types
cell motility & adhesion	disorganization
clocks & organizers	chaos and ataxia
genetic signals & responses	dysregulation
ECM synthesis & remodeling	loss of mechanical properties

Systems models

- **ToxCast/Tox21:** HTS paradigm enables data-driven chemical prioritization and the capacity for predictive toxicology
- **Need:** computational models that reconstruct the dynamics and mechanics of diverse tissues and complex *in vivo* systems
- **Cell networks:** predicting cell-level behavior is complex enough without the emergent potential of a multicellular system
- **Goal:** develop and use cell agent-based models to help inform prioritization, evaluate mechanisms, and predict toxicity

ToxCast DevTox model



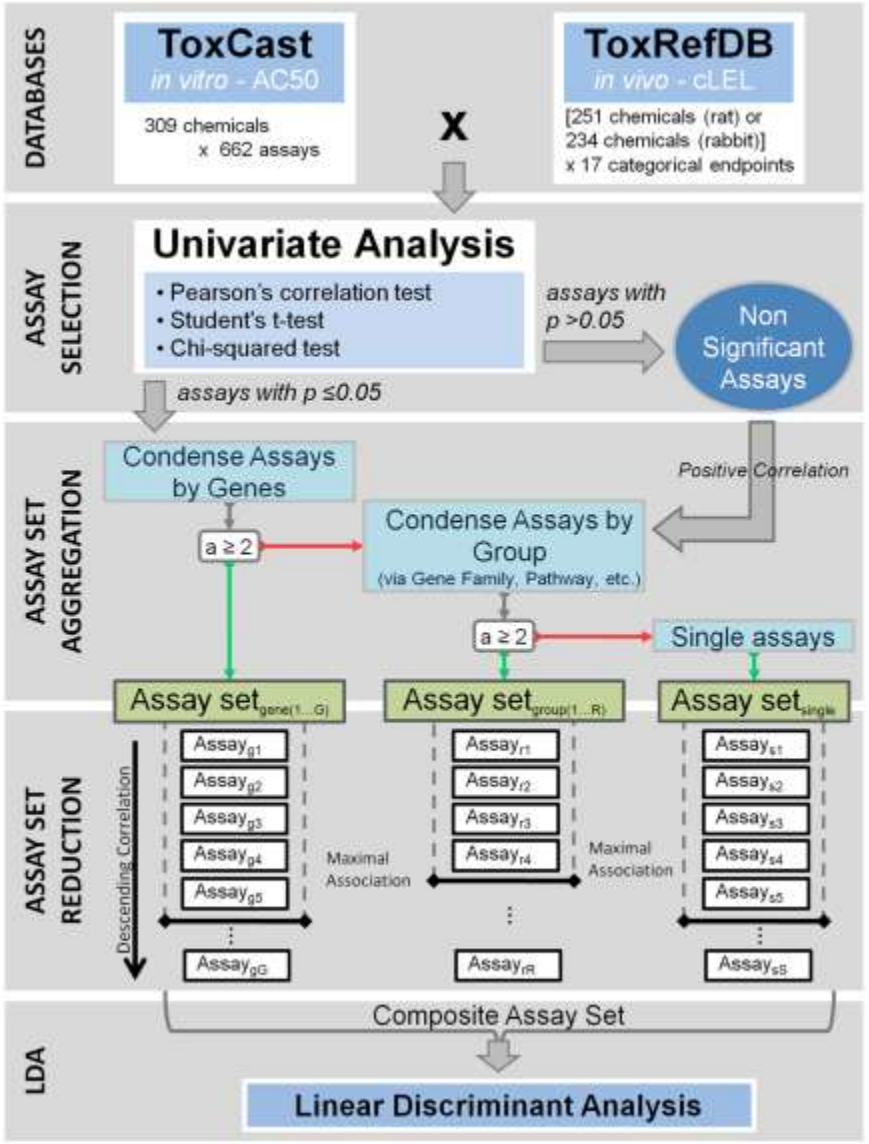
Prenatal models

- general idea to mine signatures of DevTox from ToxCast/Tox21 data
  - find significant univariate features (single assay feature to DEV endpoint)
  - build multivariate signatures (multiple features to DEV endpoint)
  - map features to known pathways, processes, phenotypes

- predictive DevTox models completed with ToxCast Phase-I data

rat-rabbit prenatal ToxRefDB: Sipes et al. 2011, Toxicol Sci (in press)
mESC differentiation: Chandler et al. 2011, PLoS One 6(6): e18540
angiogenesis: Kleinstreuer et al. 2011, Env Hlth Persp (in press)
zebrafish development: Padilla et al. (submitted)
zebrafish concordance: Sipes et al. 2011, Birth Defects Res C (in press)

- ToxCastDB: AC50s for 309 Phase-I chemicals for 662 *in vitro* features
- ToxRefDB: 17 endpoints in pregnant rats (251) and rabbits (234)
- assays aggregated and reduced by genes/pathways/processes
- linear model assessment with five-fold cross-validation on 80/20 split



SOURCE: Sipes et al. 2011 Toxicol Sci (in press)

Global prenatal model

Model predicts DevTox in rats with >70% BA

Model predicts predict DevTox in rabbits with >70% BA

Train BA: 0.71 ± 0.01
Test BA: 0.70 ± 0.09

Train BA: 0.75 ± 0.02
Test BA: 0.71 ± 0.03

Rat Feature	Individual Assay	Weight	p-value
RAR	ATG_RARa_TRANS ATG_RARb_TRANS NVS_NR_hRAR_Antagonist	0.58	8.37E-02
GPCR	NVS_GPCR_hPY2 NVS_GPCR_hOpiate_mu NVS_GPCR_hORL1 NVS_GPCR_hM1	0.55	8.08E-03
TGFβ	ATG_TGFb_CIS BSK_BE3C_TGFb1_down	0.38	6.34E-03
MT	CLM_MicrotubuleCSK_Destabilizer_24hr	0.30	1.74E-02
SENS_CYP	CLZD_CYP1A1_48 CLZD_CYP2B6_48	0.26	5.19E-03
AP1	ATG_AP_1_CIS	0.24	1.70E-01
SLCO1B1	CLZD_SLCO1B1_48	0.11	1.29E-02
CYP	NVS_ADME_rCYP2A2 NVS_ADME_rCYP2B1	0.06	3.22E-03
HLA-DR	BSK_BE3C_hLADR_up	-0.38	2.13E-02
PXR	ATG_PXR_TRANS NCGC_PXR_Agonist_human	-0.24	2.06E-01
IL8	BSK_LPS_IL8_down BSK_SAg_IL8_down	-0.23	1.36E-01
PGE2	BSK_LPS_PGE2_down	-0.18	4.25E-02

Similar features between models

(positive predictors)

(negative predictors)

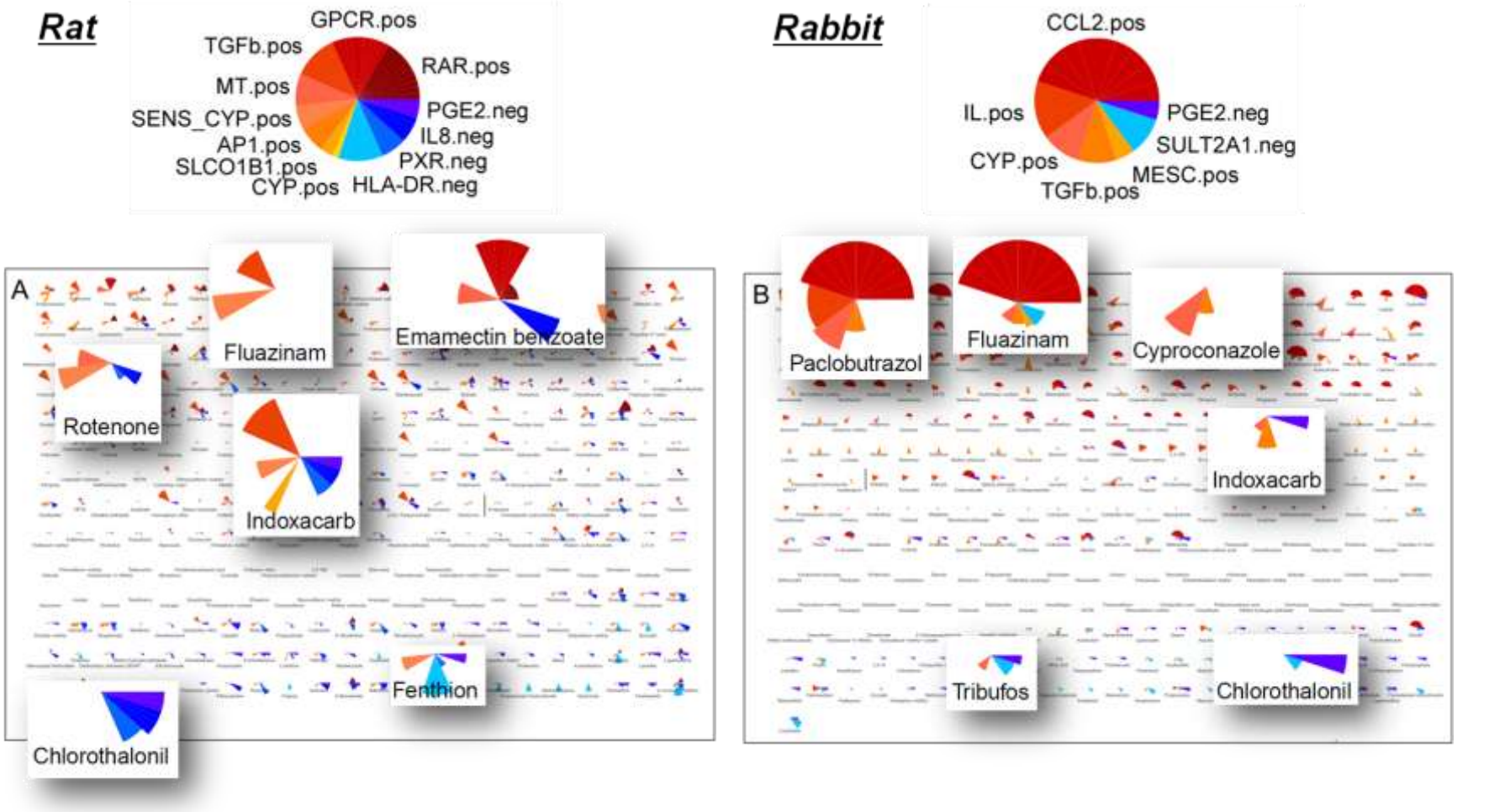
Rabbit Feature	Individual Assay	Weight	p-value
CCL2	BSK_3C_MCP1_up BSK_SM3C_MCP1_up BSK_SAg_MCP1_up BSK_LPS_MCP1_up BSK_KF3CT_MCP1_up	1.15	1.5E-06
IL	BSK_BE3C_IL1a_up BSK_LPS_IL1a_up BSK_LPS_IL8_up	0.39	3.9E-03
CYP	CLZD_CYP1A1_24 NVS_ADME_rCYP2A2	0.24	4.6E-03
TGFβ	BSK_BE3C_TGFb1_up BSK_BE3C_TGFb1_down	0.28	1.0E-01
MESC	MESC_CellCount_AC50_Down MESC_MHC_AC50_Down	0.13	8.6E-02
SULT2A1	CLZD_SULT2A1_6	-0.26	4.1E-04
PGE2	BSK_LPS_PGE2_down	-0.15	2.4E-02

Positive predictors

Negative predictors

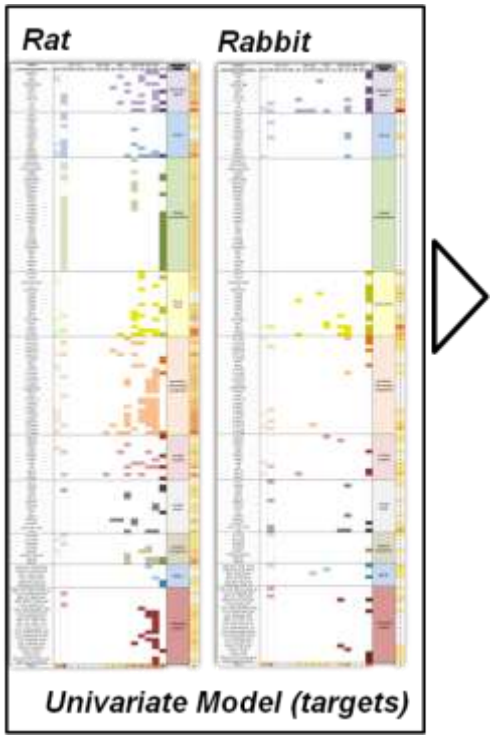
SOURCE: Sipes et al. 2011 Toxicol Sci (in press)

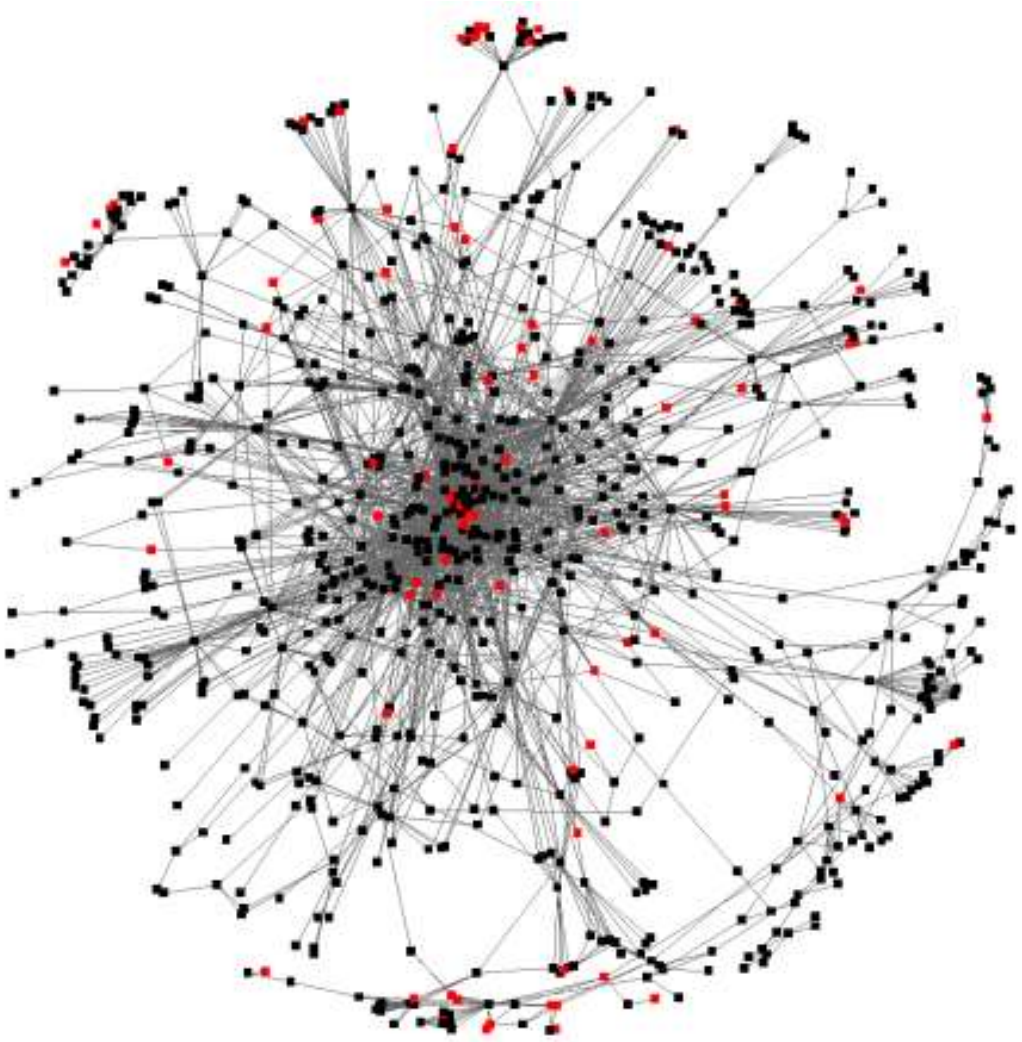
Prioritization



Features mapped by GO-process

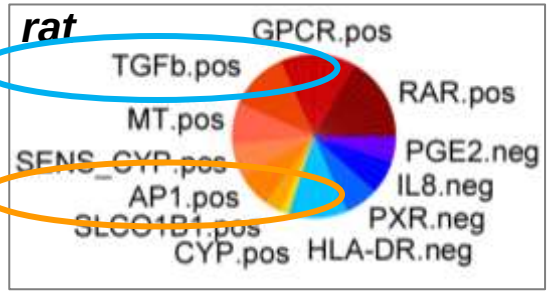
univariate DevTox features
multivariate DevTox features

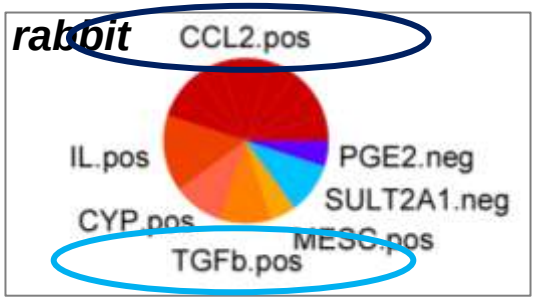




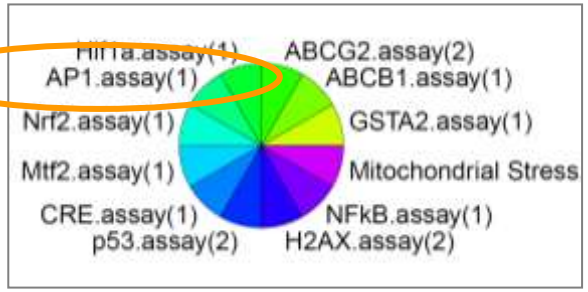
HTS detected pathway

ToxRefDB_prenatal

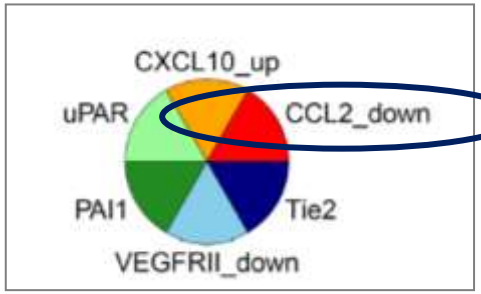




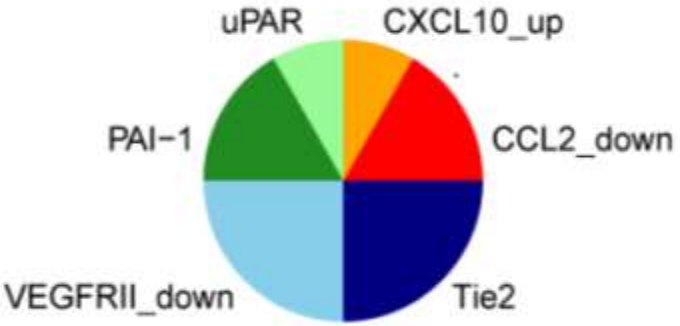
mESC growth & differentiation

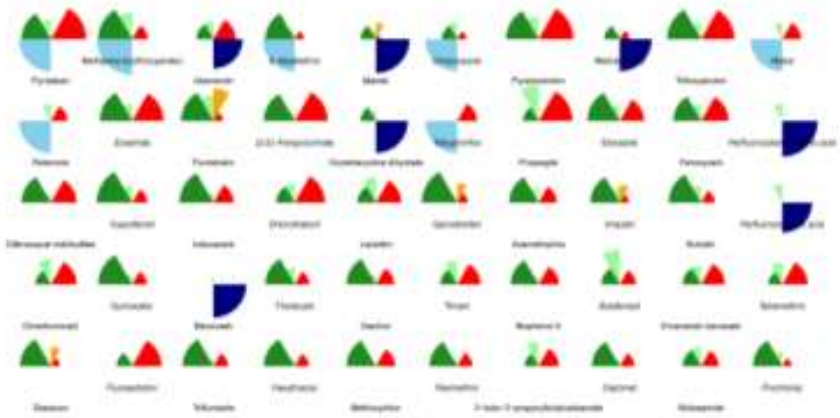


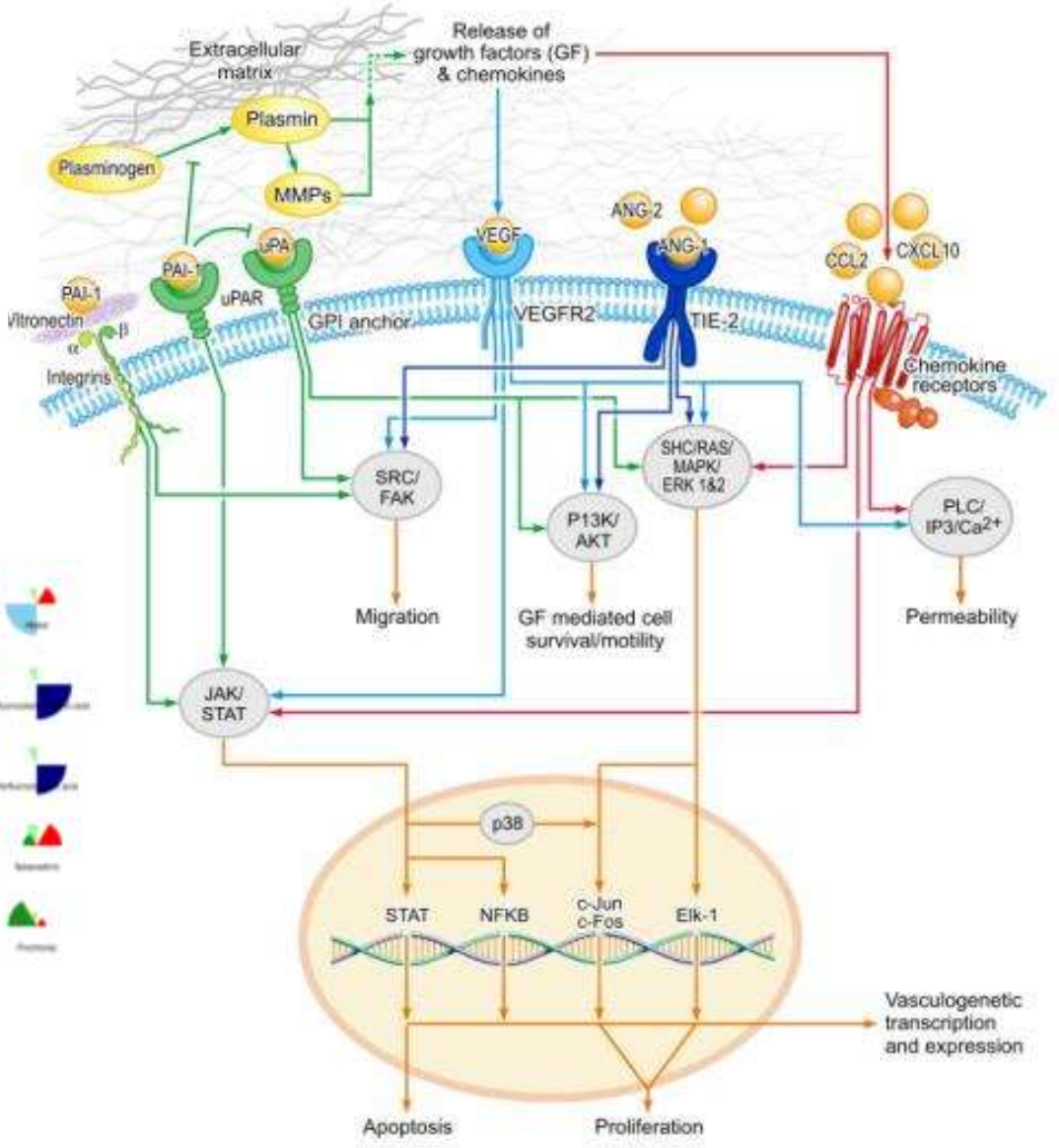
angiogenesis



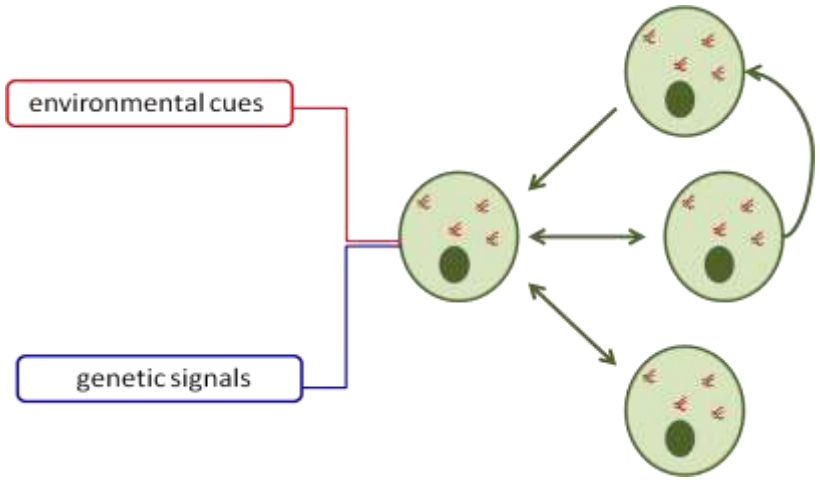
Angiogenesis & Vascular disruption

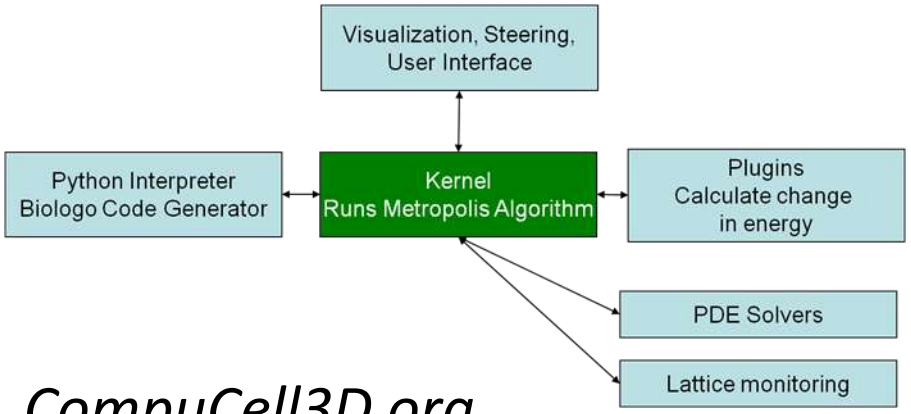




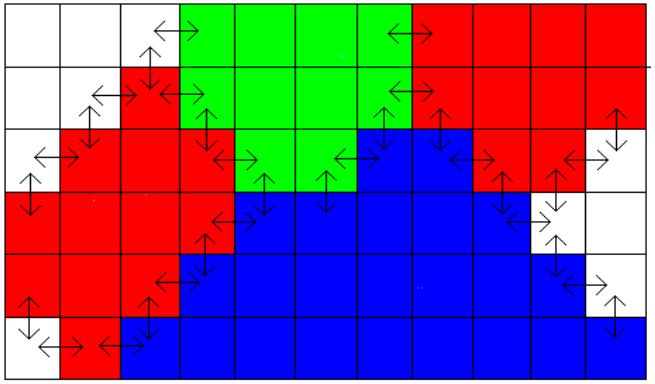


Cell-agent-based models





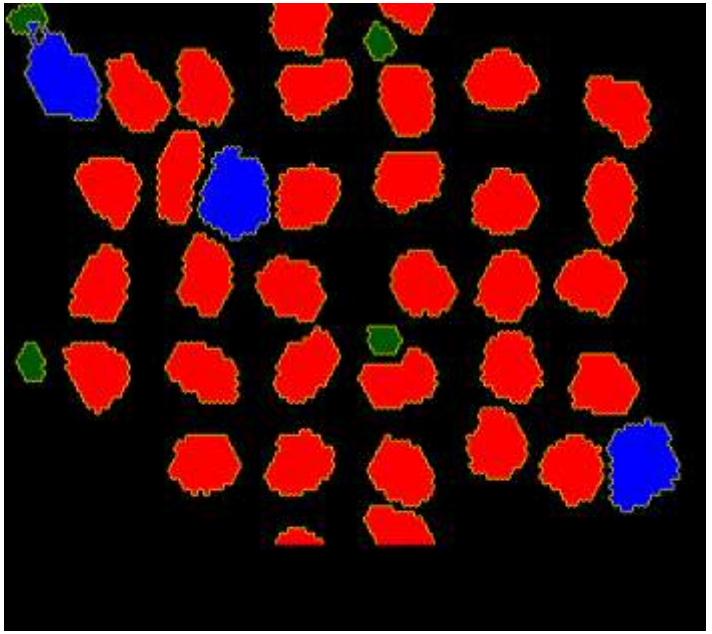
CompuCell3D.org



- stochastic cellular behaviors
- specified cellular activities
- PDE solvers for biochemical gradients
- toolbox of morphogenetic processes
- executes collective cell behavior
- enables emergent properties

Simple CC3D model

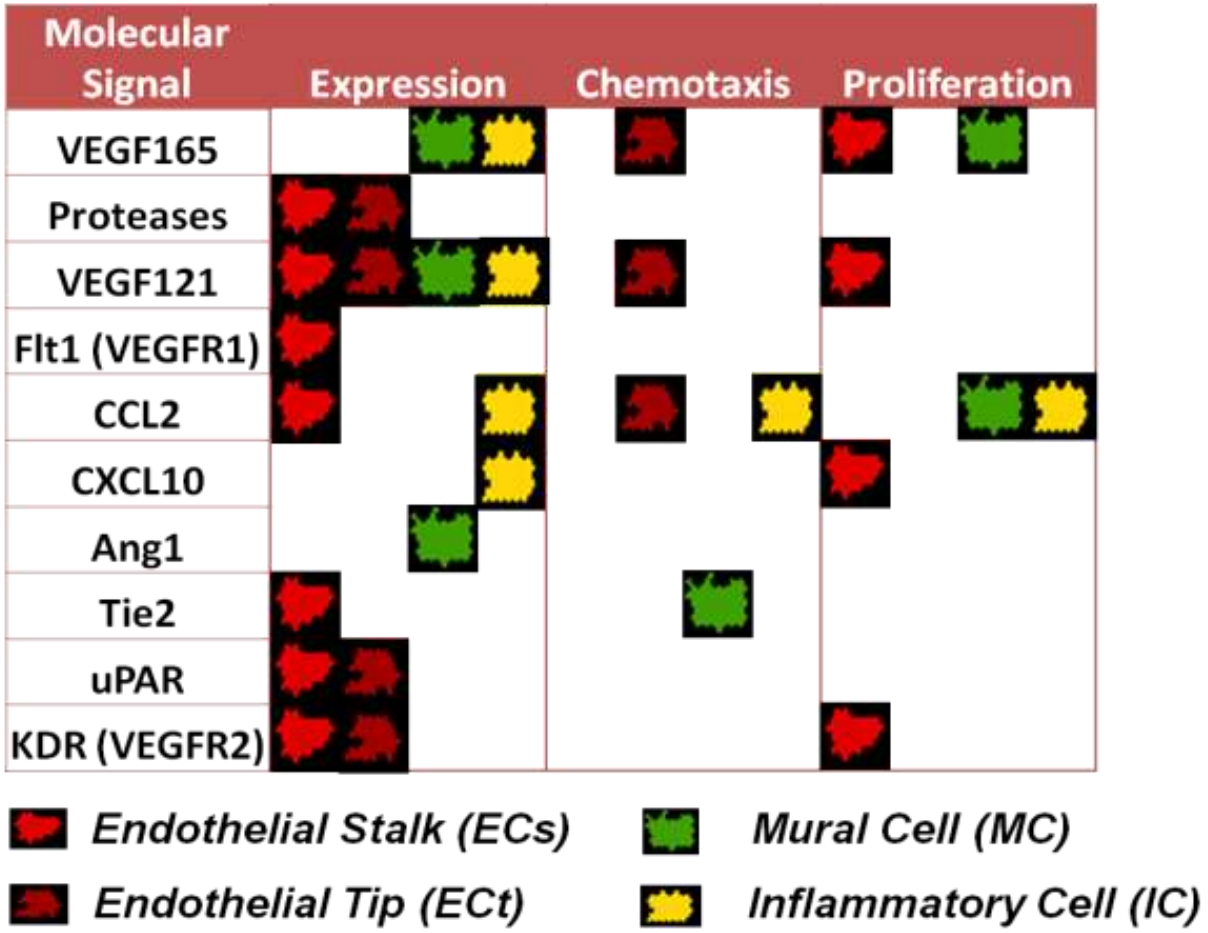
macrophage navigating RBCs toward a microbial pathogen



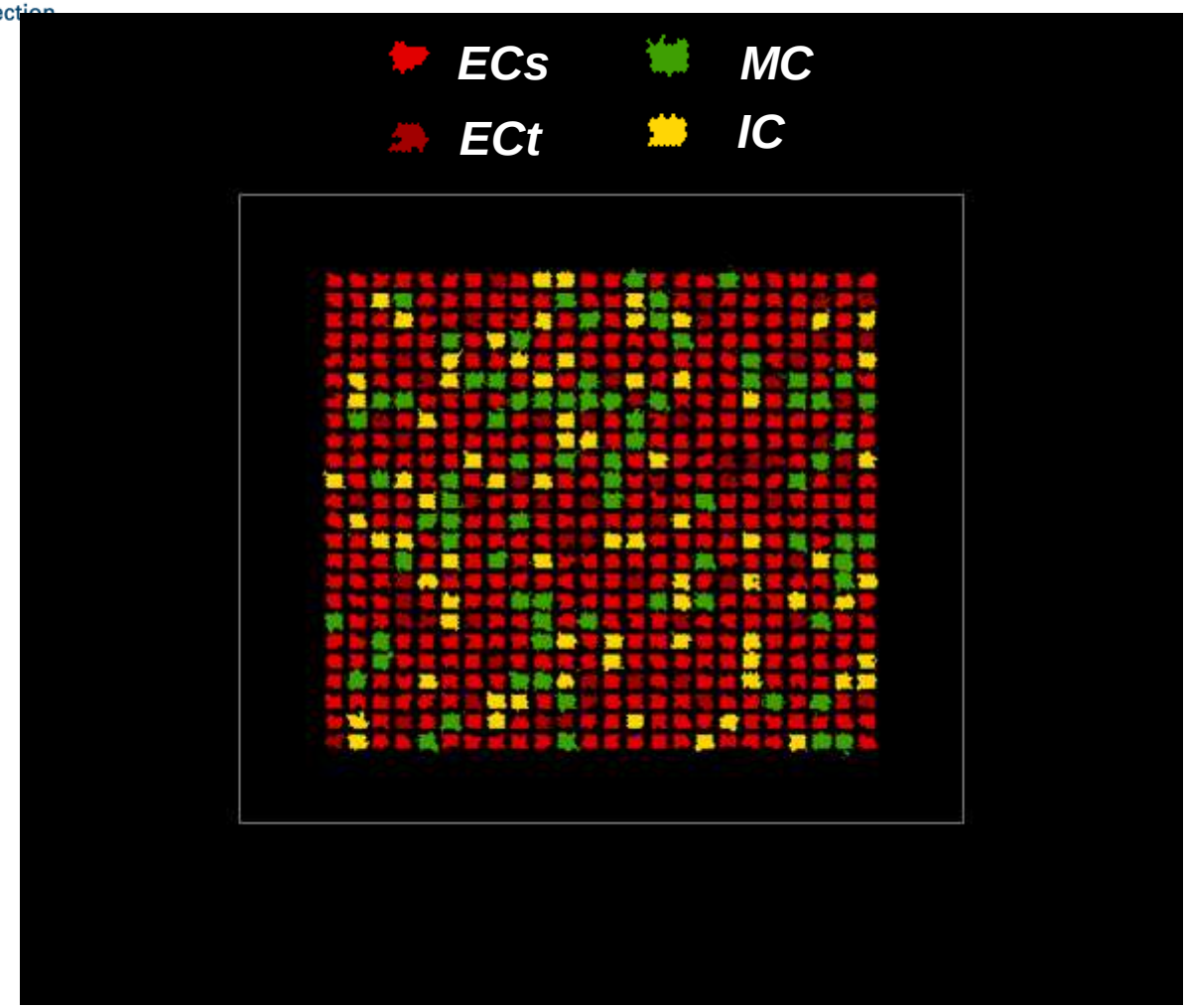
simple CompuCell3D model

SOURCE: M Rountree, NCCT

Angiogenesis is more complex



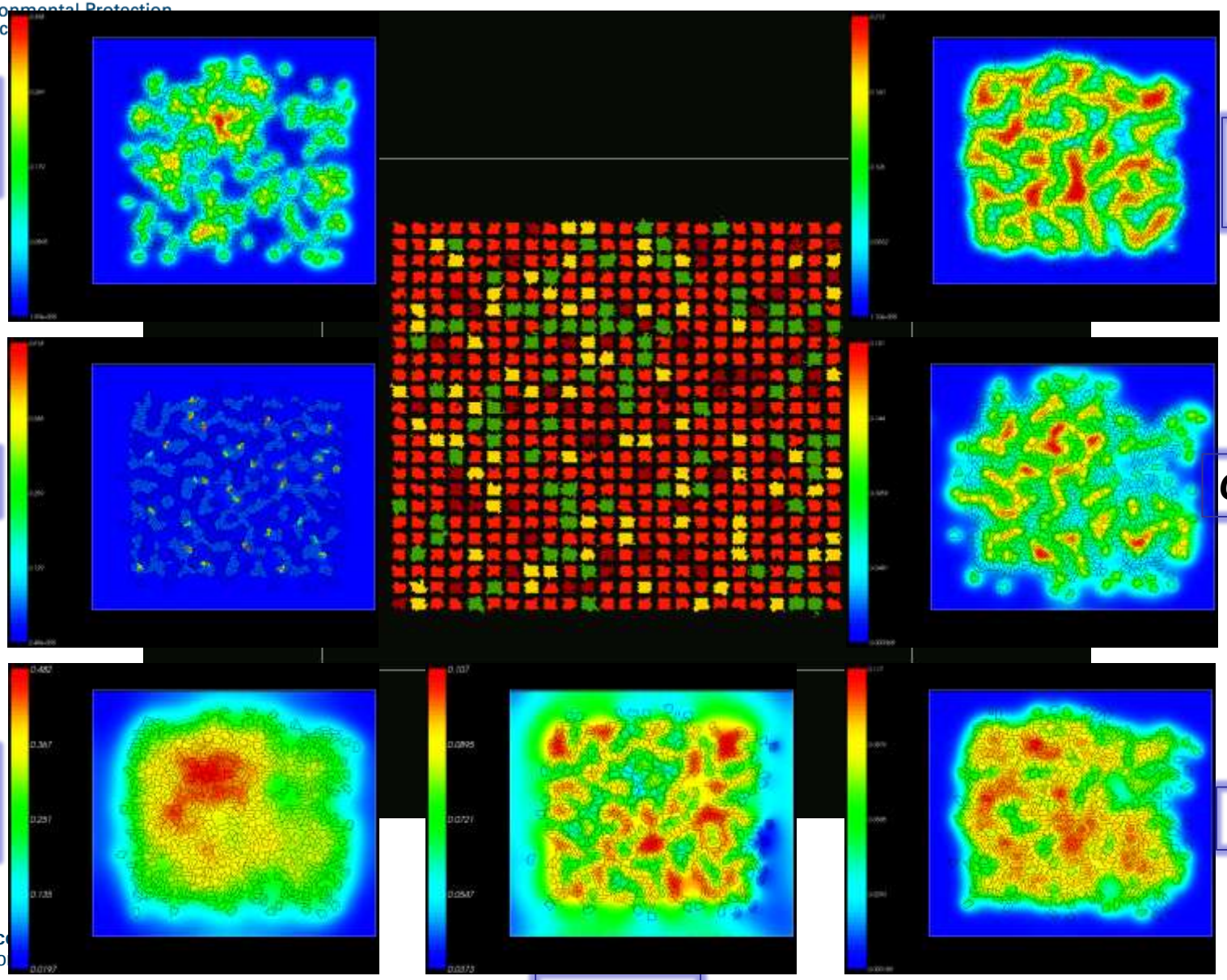
Angiogenetic field at time=0



SOURCE: Kleinstreuer et al. (in preparation)

Virtual angiogenesis

United States Environmental Protection Agenc



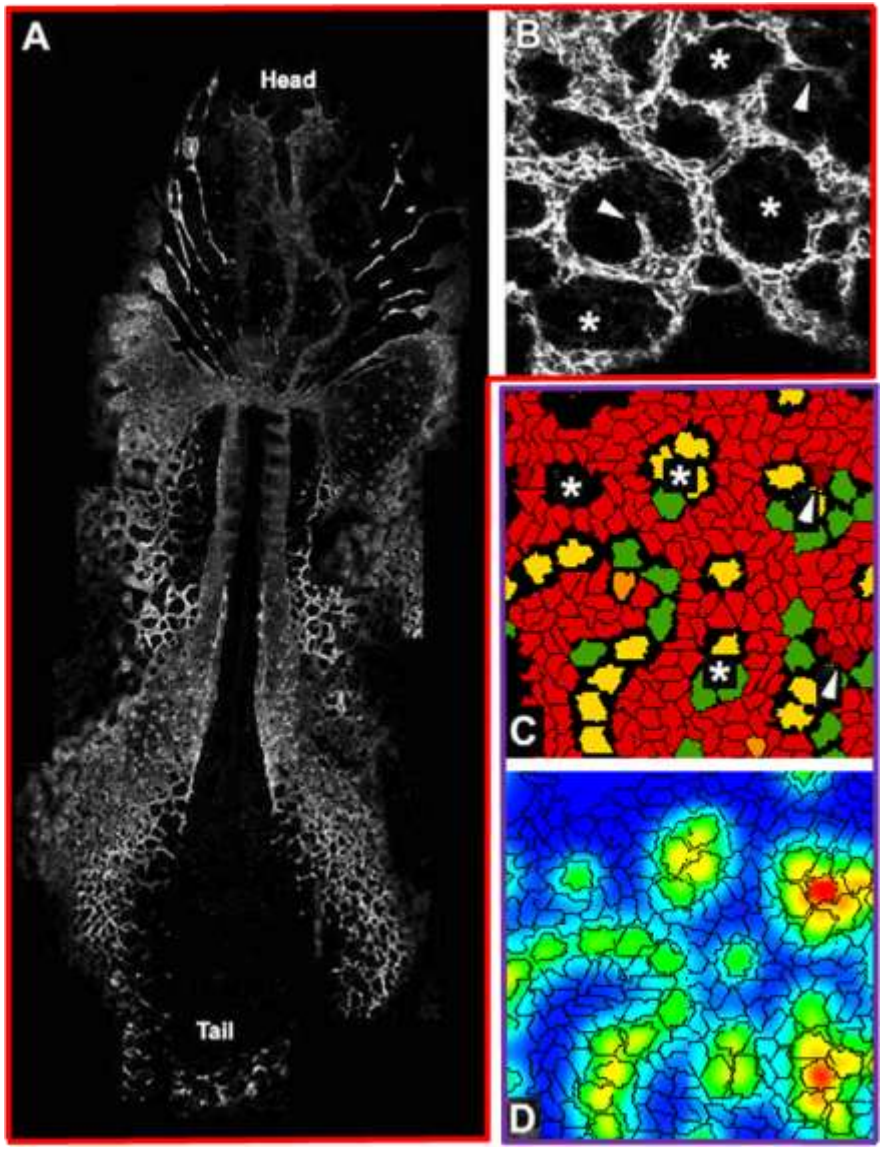
Normal phenotype

United States Environmental Protection Agency

Vascular tree, 2-day quail embryo (A,B)
[Herrero and Kohn (2009) M³AS]

CC3D Simulation Results (C,D)

- ***Endothelial Stalk***
- ***Endothelial Tip***
- ***Mural Cell***
- ***Inflammatory Cell***



In situ

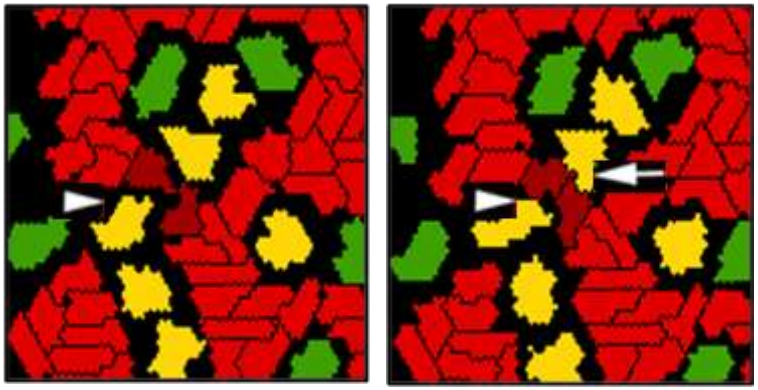
In silico

VEGF gradient

Emergence

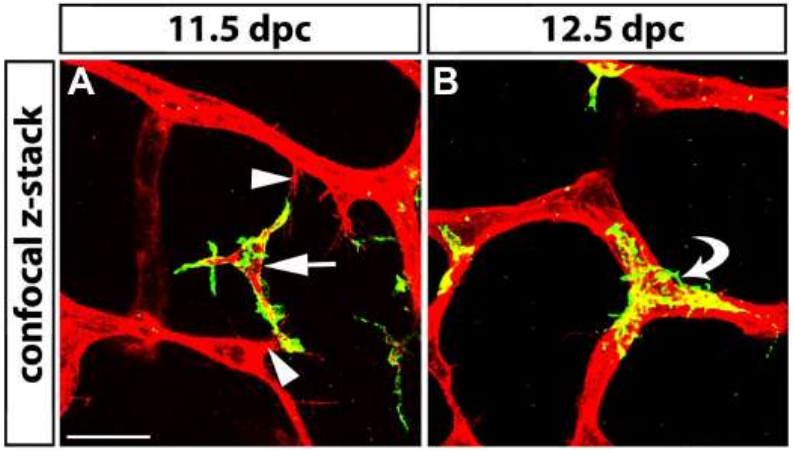
Time →

- ***Endothelial Stalk***
- ***Endothelial Tip***
- ***Mural Cell***
- ***Inflammatory Cell***



In silico

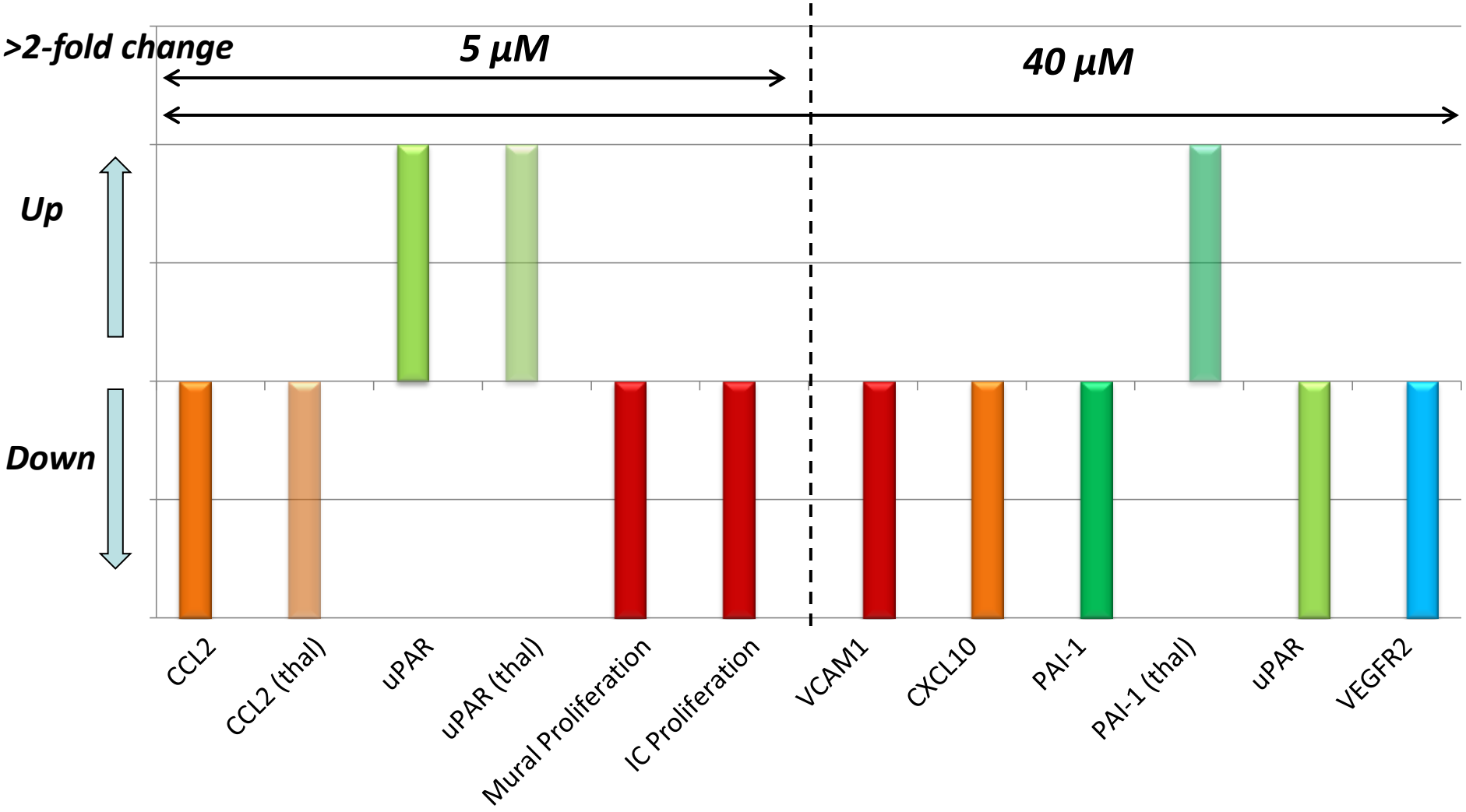
Emergence (bridging)



In vitro

[Fentin et al. (2010) Blood]

TEST CASE: Thalidomide and 5HPP-33



TEST CASE: Thalidomide and 5HPP-33

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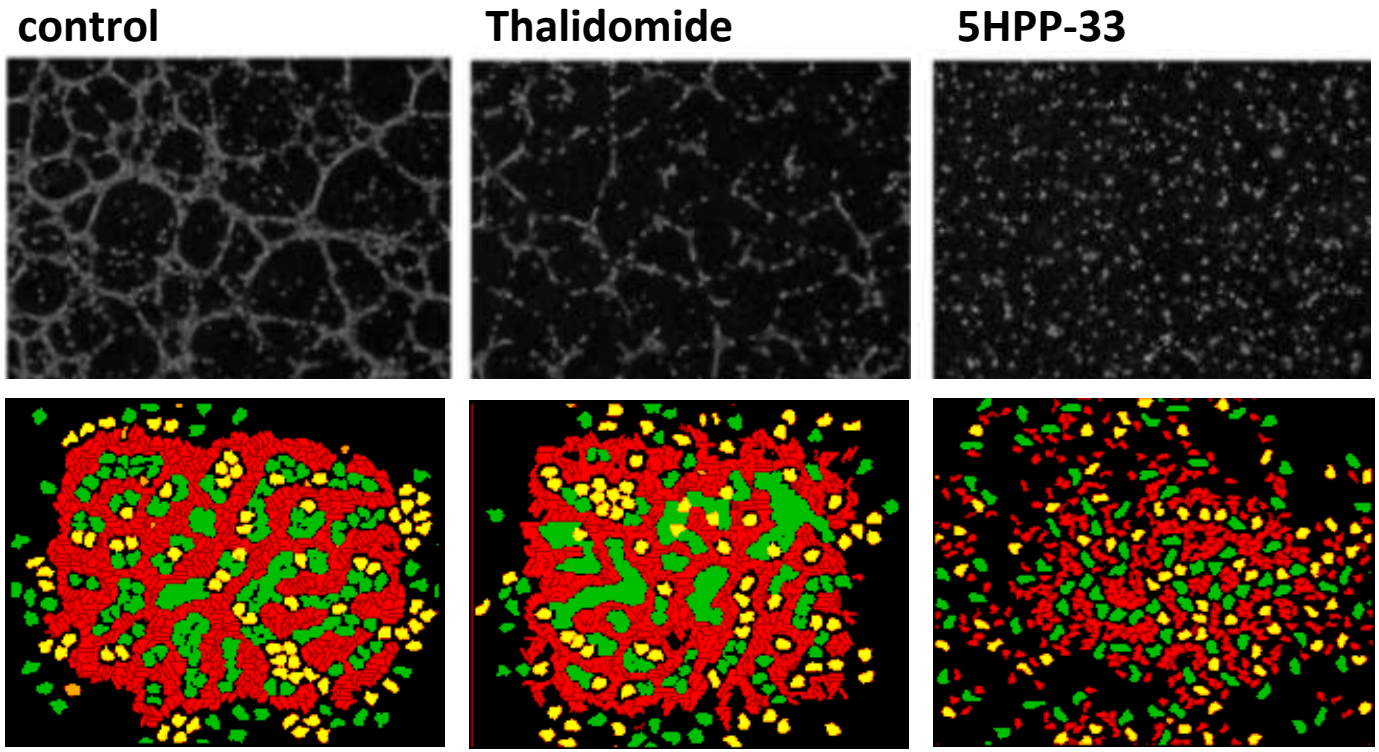
In vitro

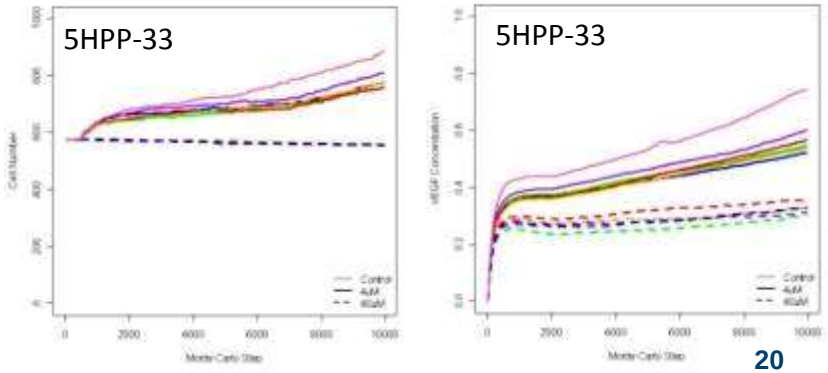
SOURCE: Noguchi et al. 2005, Bioorg Med Chem Lett. 15 :5509-13. (experimental, 100 uM)

In silico

SOURCE: Kleinstreuer et al. 2011, in preparation (ToxCastDB, 40 uM)

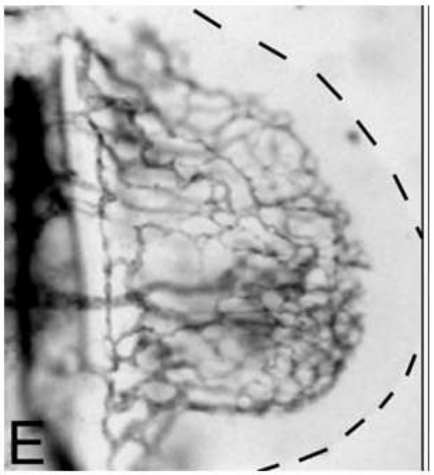


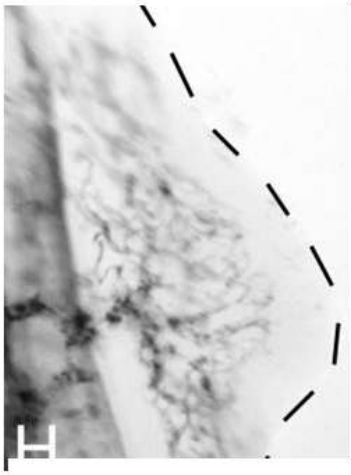
quantitative prediction emergent from ToxCast HTS data input (AC50s)

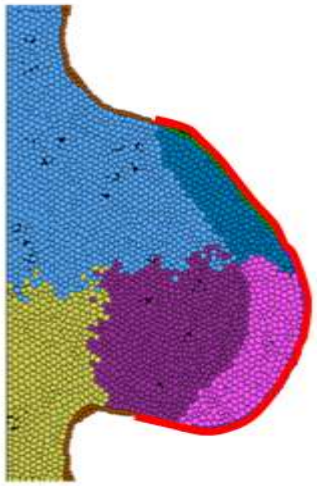


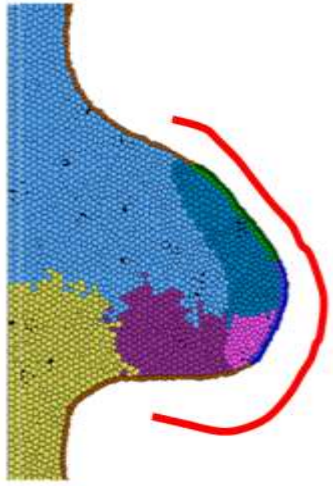
Integration (in progress)

Chick limb ***+CPS49*** ***Virtual limb*** ***PCD in AER***









Thalidomide induces limb defects by preventing angiogenic outgrowth during early limb formation

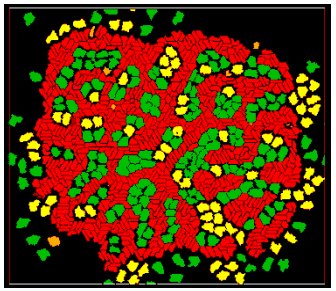
Christina Therapontos[a,b], Lynda Erskine[b], Erin R. Gardner[c], William D. Figg[d], and Neil Vargesson[a,b,1]

Therapontos et al. PNAS 106: 8573-8578, 2009

Rountree et al., 2011
(in preparation)

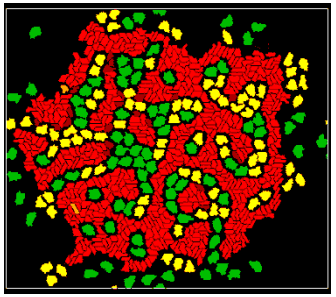
Application to ToxCast

endothelial connectivity (plexus), in-degree (branching), vessel uniformity (width), sprouting

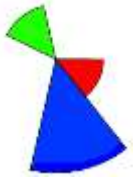


control

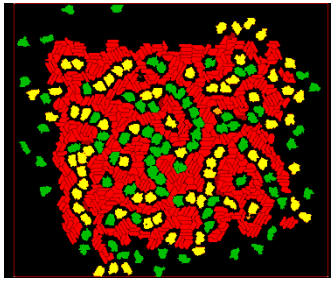
weakened mural adhesion to nascent vessels; altered endothelial growth and spreading behavior, lack of sprouting due to Flt1 inhibition



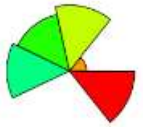
TxC-P



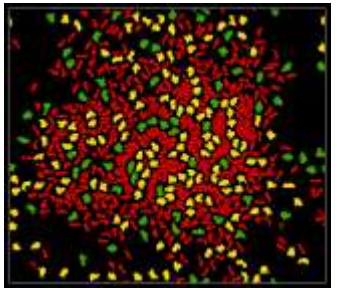
endothelial hyperplasia with decreased cell migration and polarization possibly due to increased uPAR – enhances ECM locking



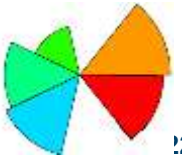
TxC-T



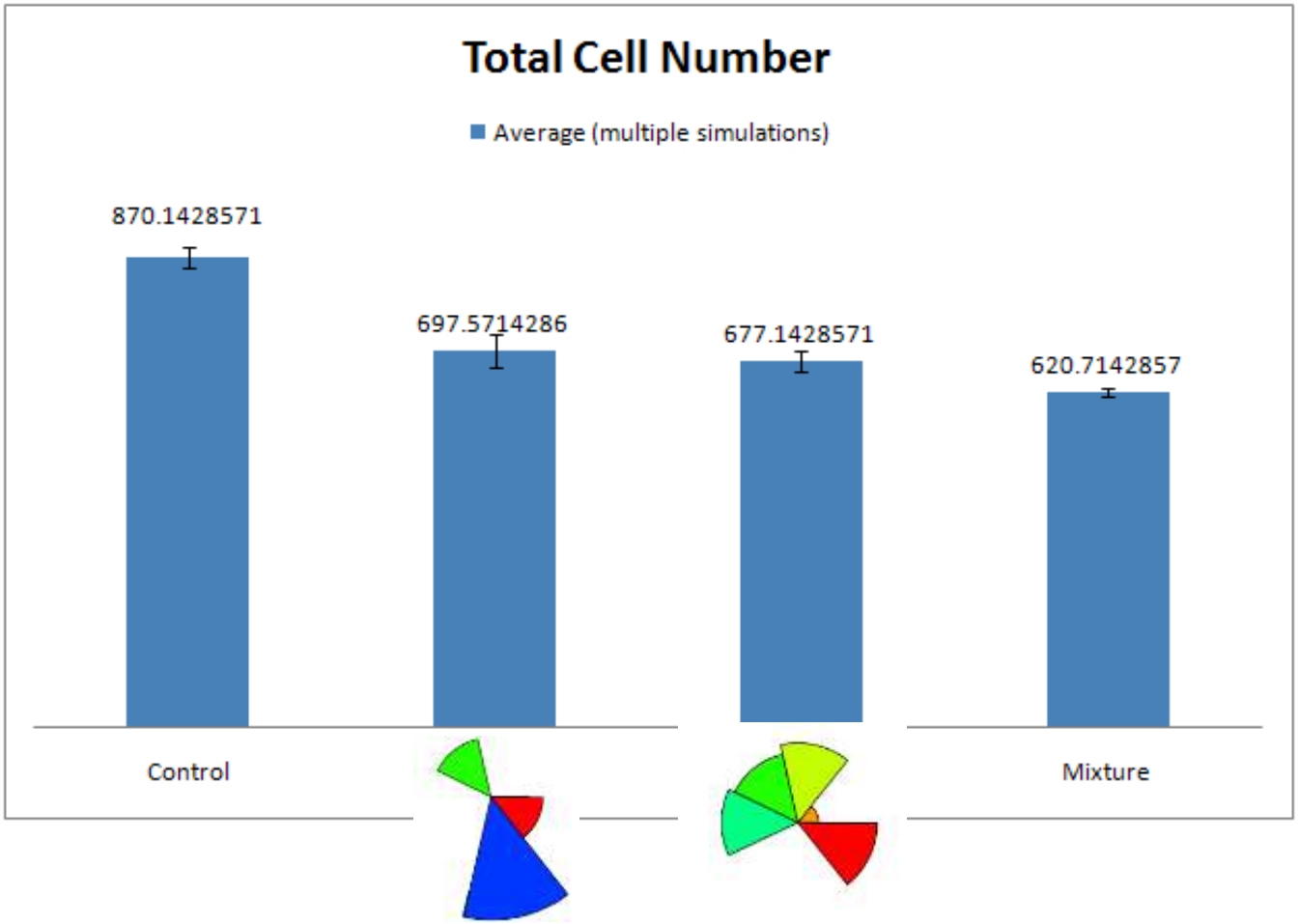
little to no vessel formation



TxC-Y



Virtual mixture



Summary

- **Goal:** applying HTS data, *in silico* tools, and models to look globally at developmental processes and toxicities in a new way
- **Approach:** predictive and mechanistic models that dynamically integrate data with relevant information about embryonic systems
- **Virtuomics:** run 'what-if' scenarios to predict adverse outcomes from different perturbations (chemicals, concentrations, mixtures)
- **Benefit:** scientifically-based predictions on how development might be affected across a range of complex factors

http://www.epa.gov/ncct/v-Embryo/

Acknowledgements

http://www.epa.gov/ncct/