11TH WORLD CONGRESS ON ALTERNATIVES AND ANIMAL USE IN THE LIFE SCIENCES

Computational Synthesis and Integration for Systems Toxicology in the Animal-free Zone
S109, Wednesday, September 1

3Rs in transition From development to application
VIRTUAL CONGRESS - AUGUST 2021

Computational Intelligence: Opening DART's 'Black Box' with Agent-Based Models

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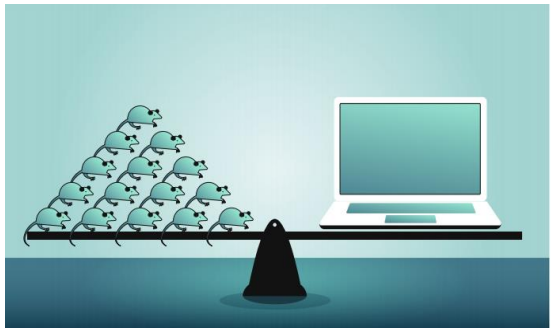
DISCLAIMER: The views expressed are those of the presenters and do not reflect Agency policy.

Context: *cell-based and in silico models for predictive toxicology*

- The technologies we use and biological questions we ask have become increasingly dependent on data science and computational approaches.

- An explosion of complex data from high-throughput screening (HTS) assays enable profiling large chemical libraries for molecular and cellular determinants of bioactivity.

- To operationalize these *in vitro* data for toxicological evaluation in the animal-free zone, mechanistic models need to drive biomolecular lesion propagation into higher levels of biological organization.



Kling (2019) Nature Lab Animal

Can the computer replace lab animal testing?

- mapping the chemical world: structural alerts based on expert read-across.
- opening the 'black box': performance-based models from *in vitro* profiling.
- a step further: **c**omputer (*in silico*) models that predict consequences.

Opportunities and Challenges for predictive DART

- De-scaling a mammalian embryo into simpler HTS assays for *in vitro* evaluation brings the challenge of re-composing the full complexity of anatomical development for predictive DART.
- Machine learning of HTS data streams (eg, ToxCast) can bring quantitative understanding to pathways against which *in vitro* data and *in vivo* outcomes may be qualified [Zurlinden et al., 2020].
- Computational embryology can bring knowledge of the system to predict 'critical phenomena' that emerge spontaneously or mechanistically following different pregnancy exposure scenarios.

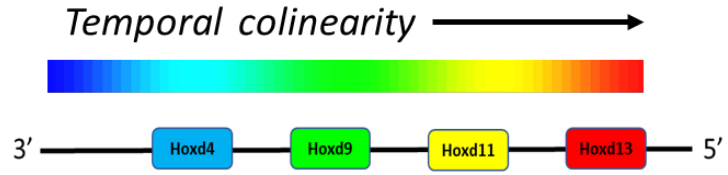
Hypothesis: mechanistic formulation with computational embryology can 'open the black box' of predictive DART in a 3R's-compliant manner ...

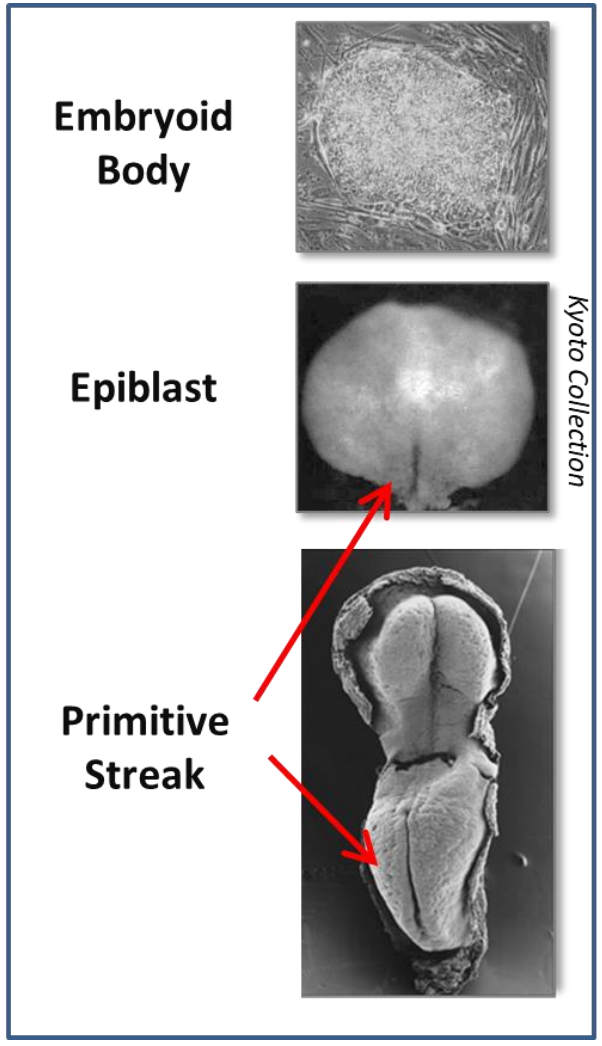
Cellular Agent-Based Models (ABMs):

- Nature-inspired *agents* (cells) and *rules* (behaviors) are set into motion as a self-organizing virtual system, using an open-source modeling environment (**CompuCell3d.org**).
- Soft-computing uses 'fuzzy logic' to simulate forces or properties governing cell activity where rules are inexact or knowledge incomplete (**computational intelligence**).
- Can change course in response to a particular situation or stimulus, such as genetic errors or biomolecular lesions fed to the dynamic model from real world data (**cybermorphs**).
- Probabilistic rendering of where, when and how a particular condition might lead to an adverse developmental outcome (**dosimetry / temporality**).

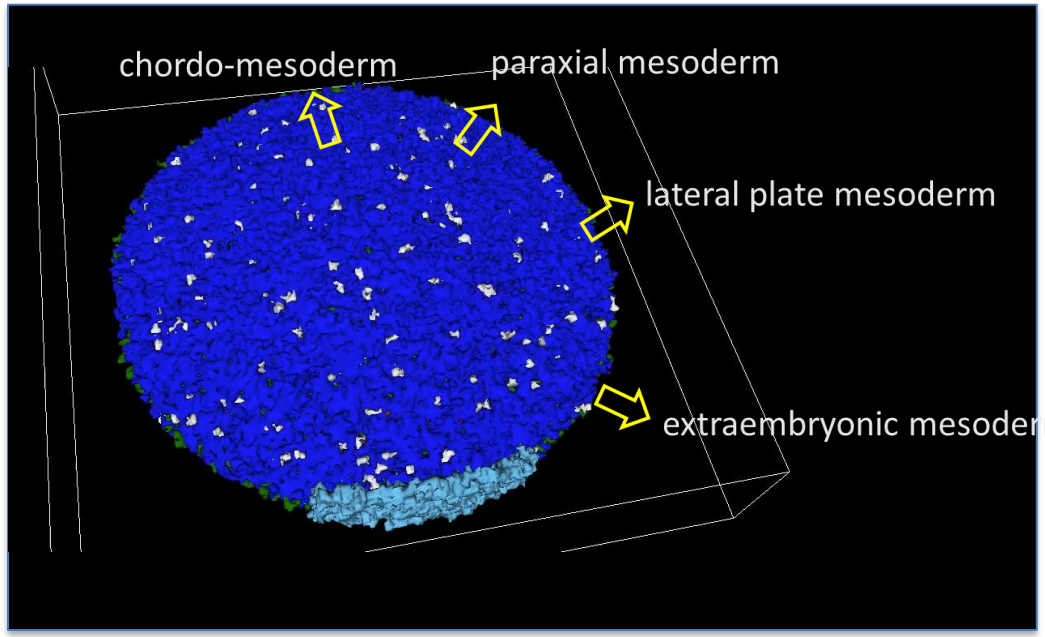
Embryologically-inspired ABMs can be edited with biomolecular data, and altered trajectories then computed as emergent features.

Patterning: *computable emergence of regional mesoderm*





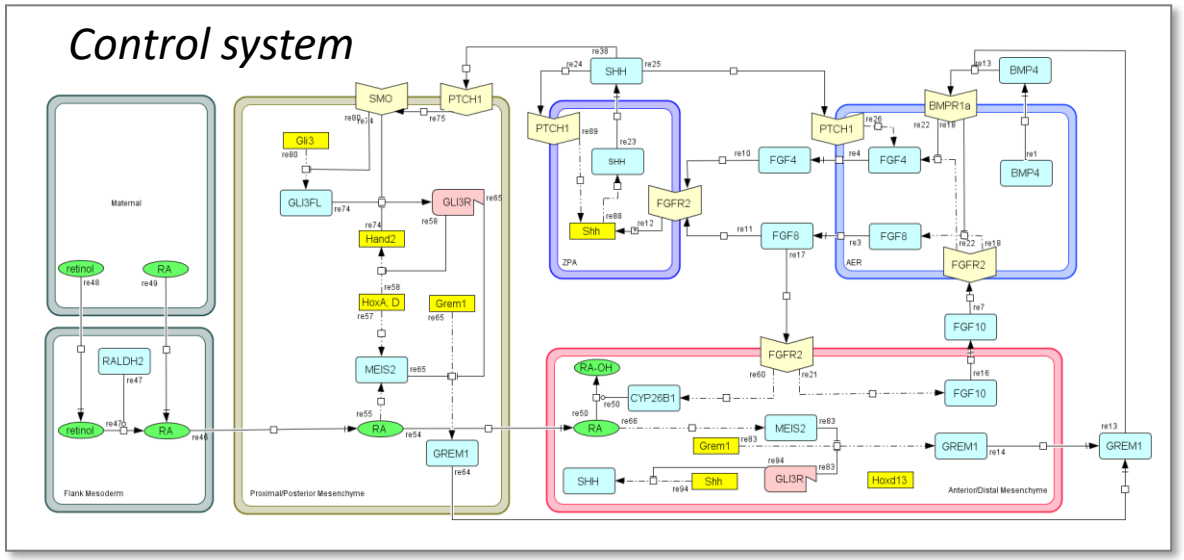
- Cultured hPSCs most closely represent the 'epiblast' of an early embryo during gastrulation (3rd week human), the hallmark of which is the primitive streak (PS).
- Cell migration through the PS is an early determinant of mesodermal fate locking homeobox patterns in '*decoding the genomic blueprint of the fetal body plan*'.

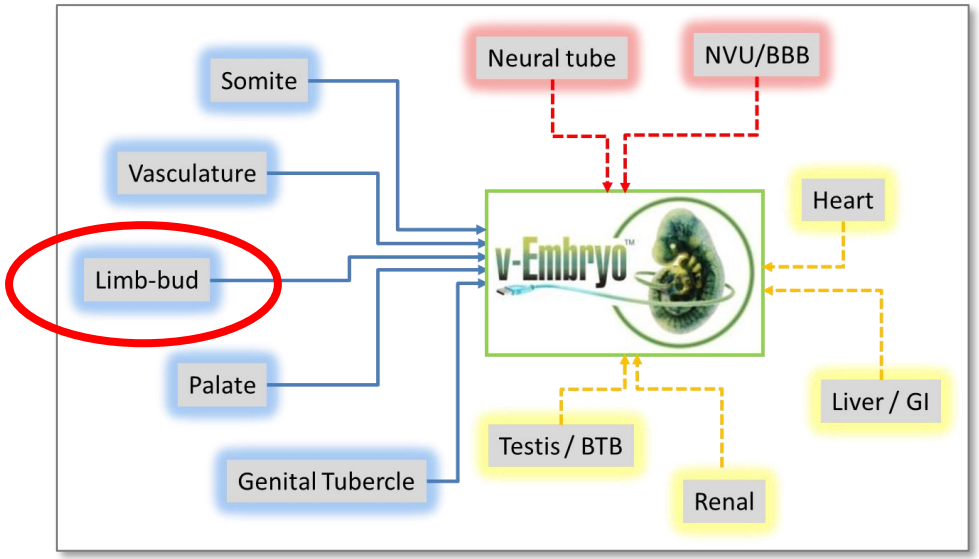


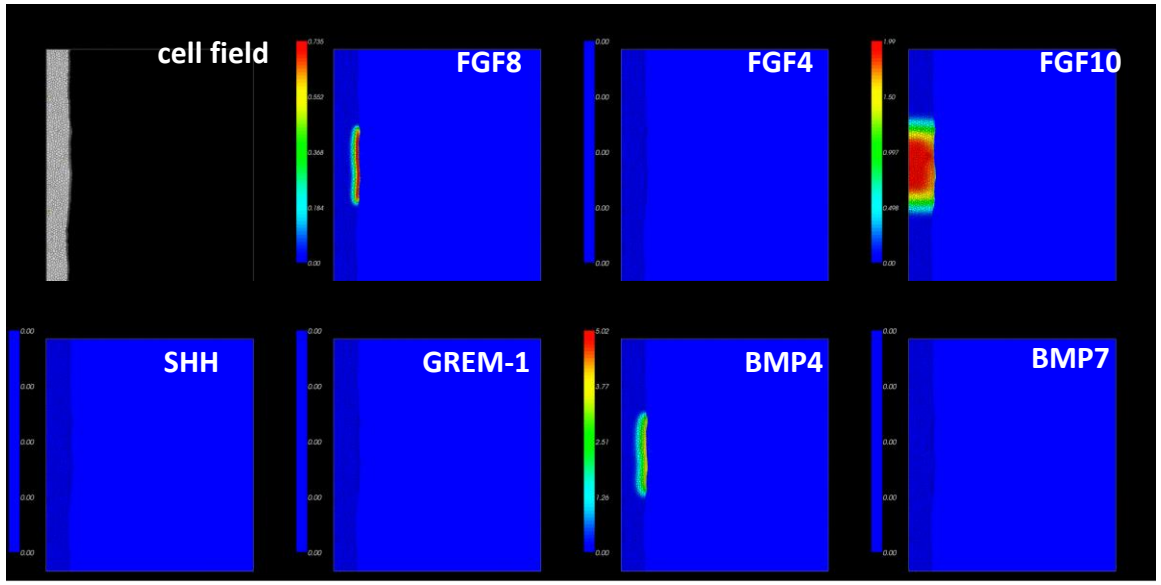
R Spencer (EMVL) - CompuCell3D.org model

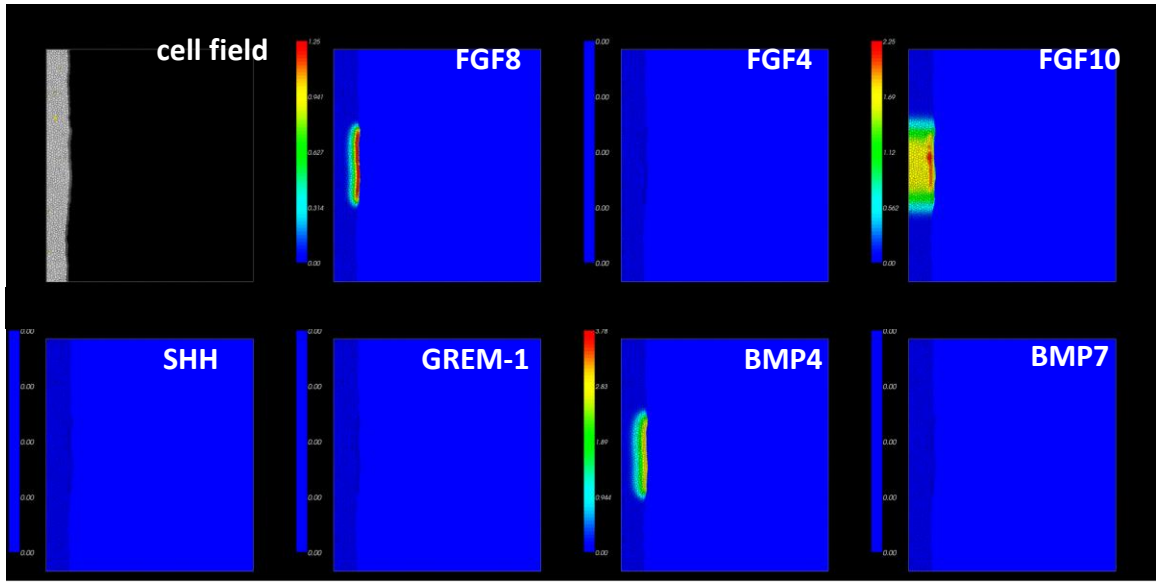
- Input parameters: dynamic signals (eg, FGF2), autonomous HOX clock.
- Stochastic determinants: cell position, timing of migration through PS.
- Emergent property: computable cell numbers for anatomical destiny.
- Editable features: kinematics of signaling, rate of HOX clock.

Putting an AOP in motion: *loss of SHH signaling impairs limb-bud outgrowth*





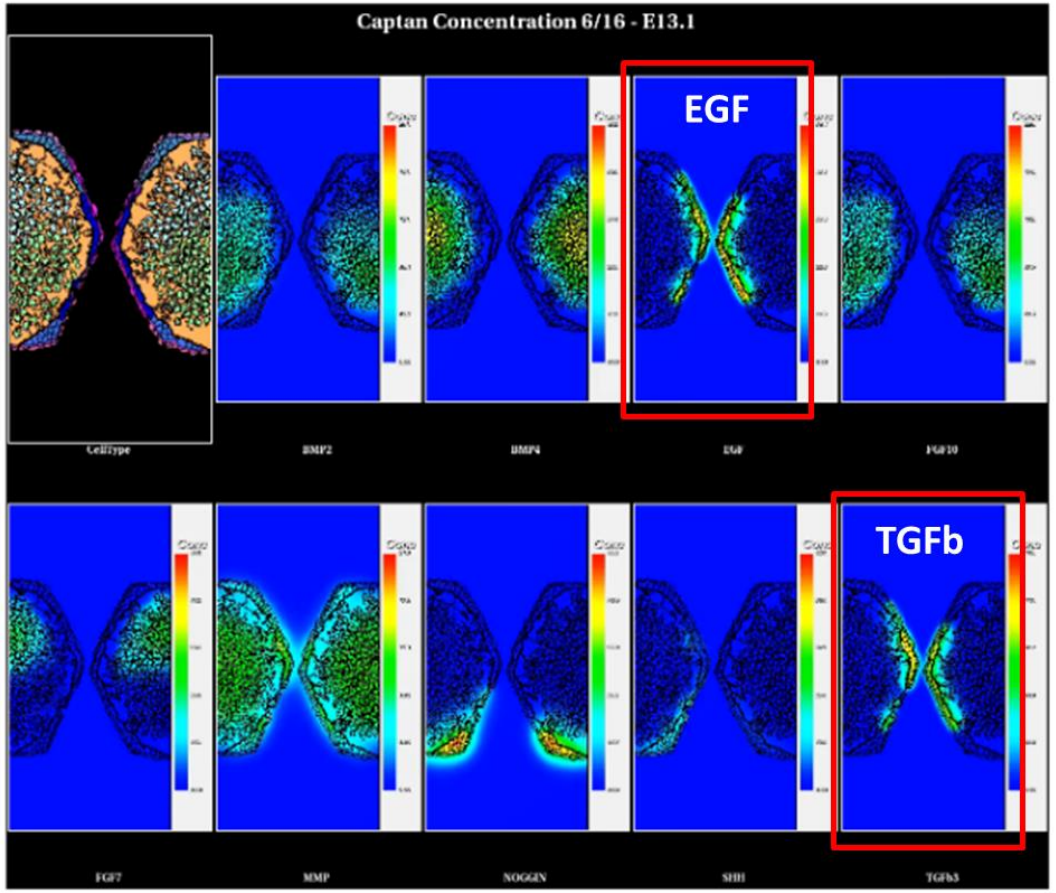




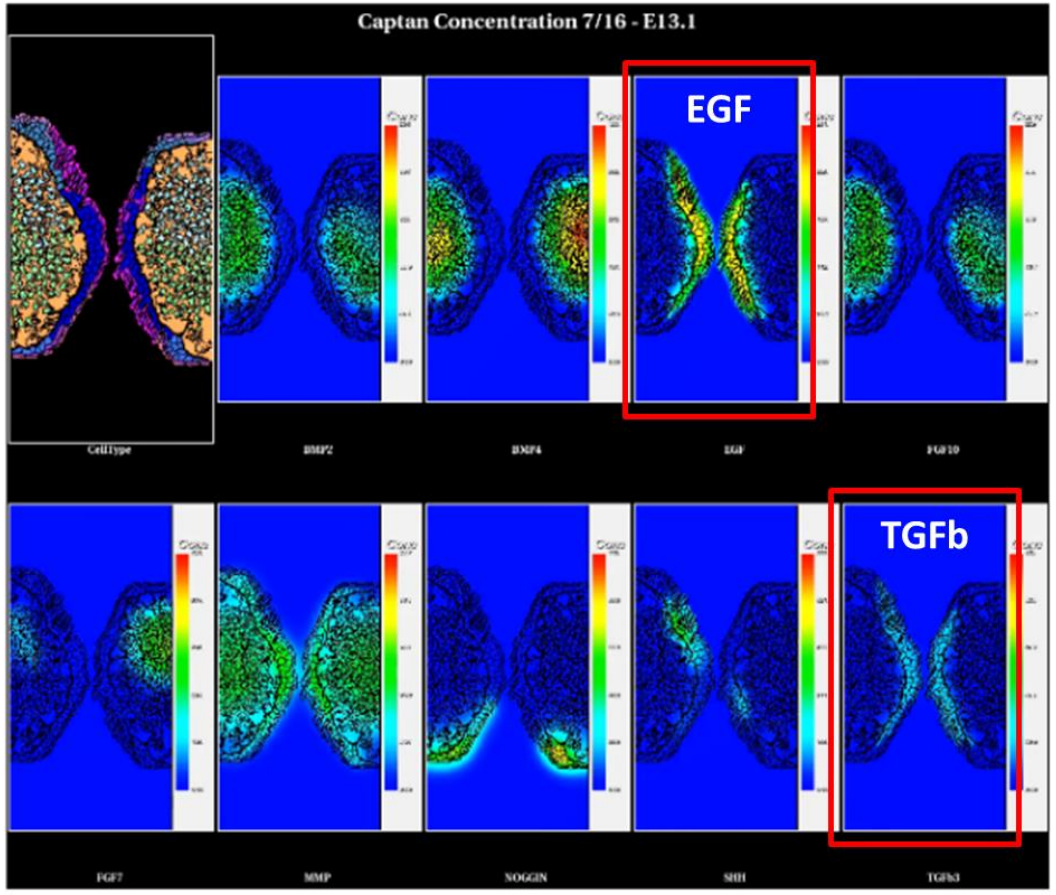
EPA/ORD/CCTE control system built with CellDesigner and simulated with CompuCell3D.org

Toxicodynamics *in silico*: *cell signaling (kinematics) and consequences (dosimetry)*

pre-critical dose

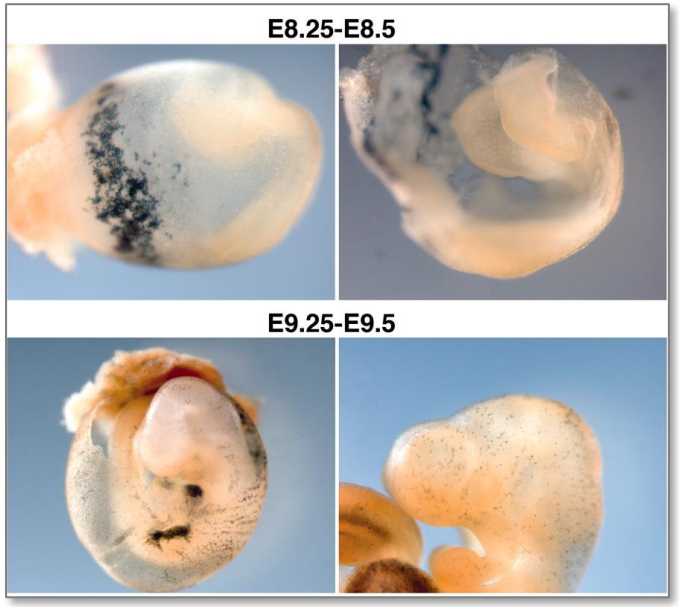


post-critical dose

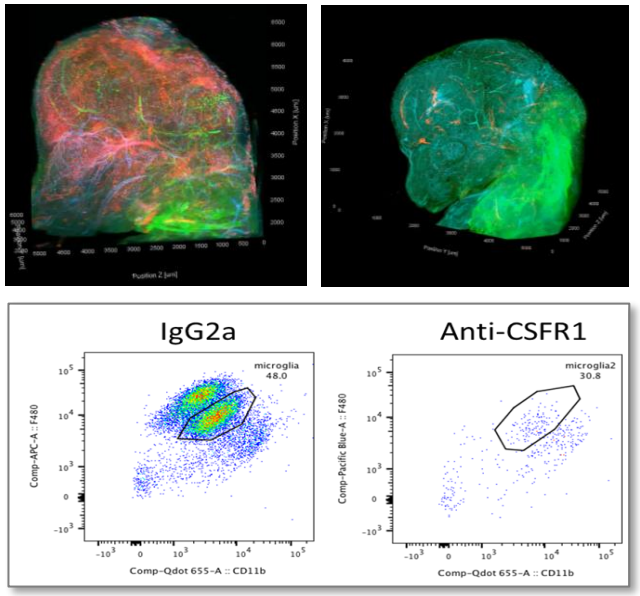


Hutson et al. (2017)

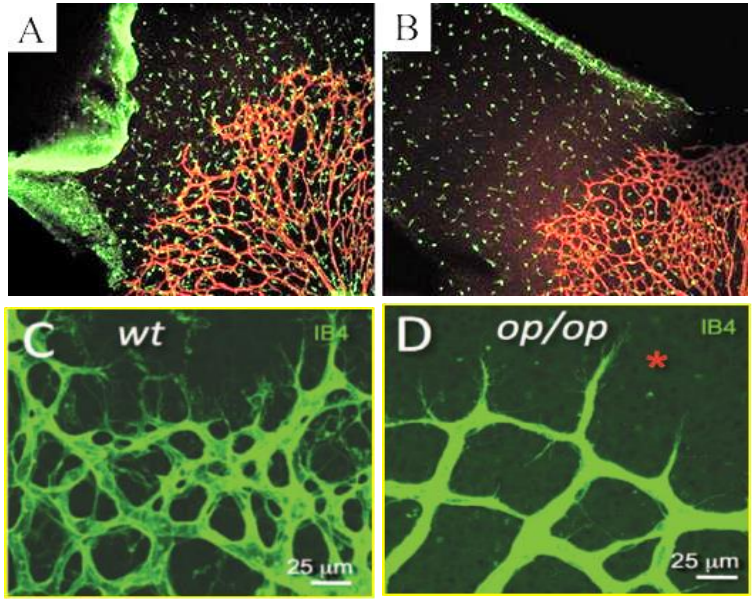
Hypothesis-based testing: *microglia and brain angiogenesis*



Microglia colonize the early neuroepithelium (mouse)
Ginhoux et al. (2010) Science



Microglial deficiency impairs microvascular development
A Silvan, F Ginhoux (WIP)

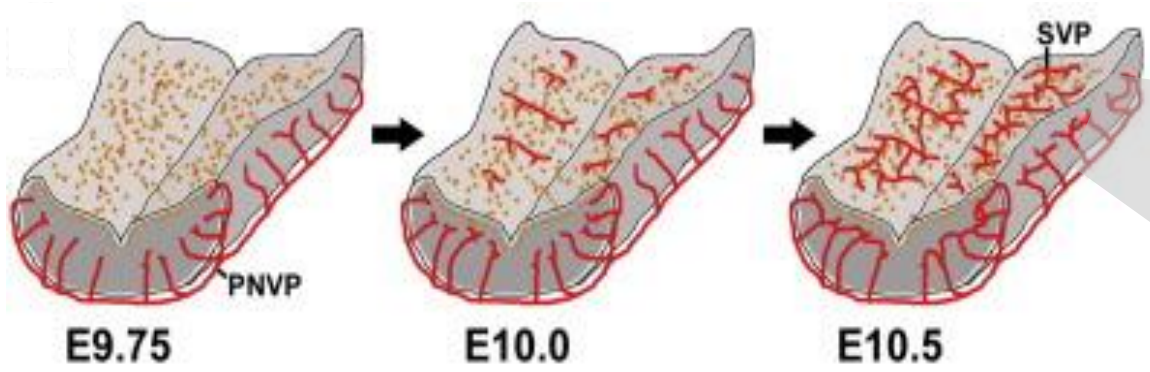


Microglia promote retinal angiogenesis
(A,B) Unoki et al. (2010) IOVS
(C,D) Rymo et al. (2011) PLoS one

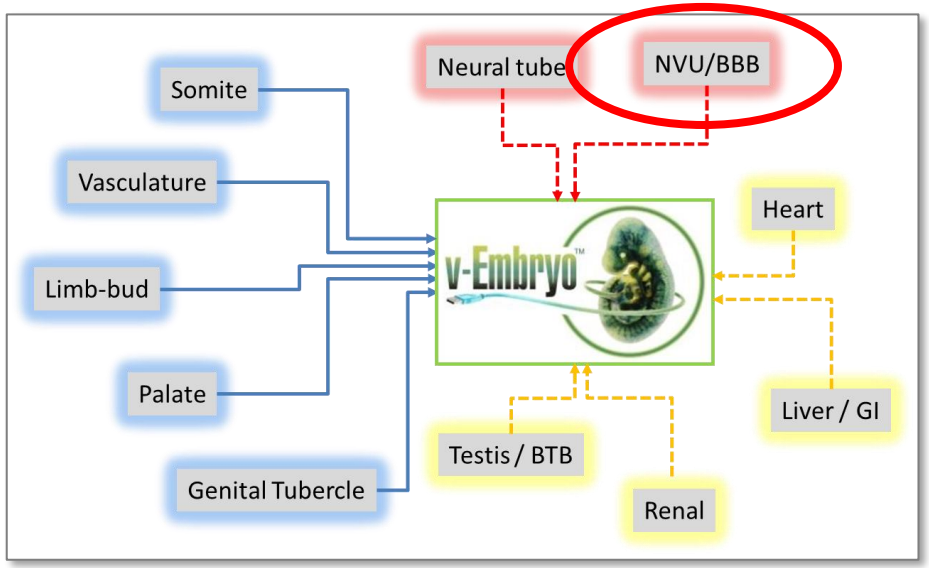
Hypothesis: microglial states (M0, M1, M2) may be important sentinels for neurodevelopmental effects, through impacts to developmental vascularization and/or local cytokine signaling.

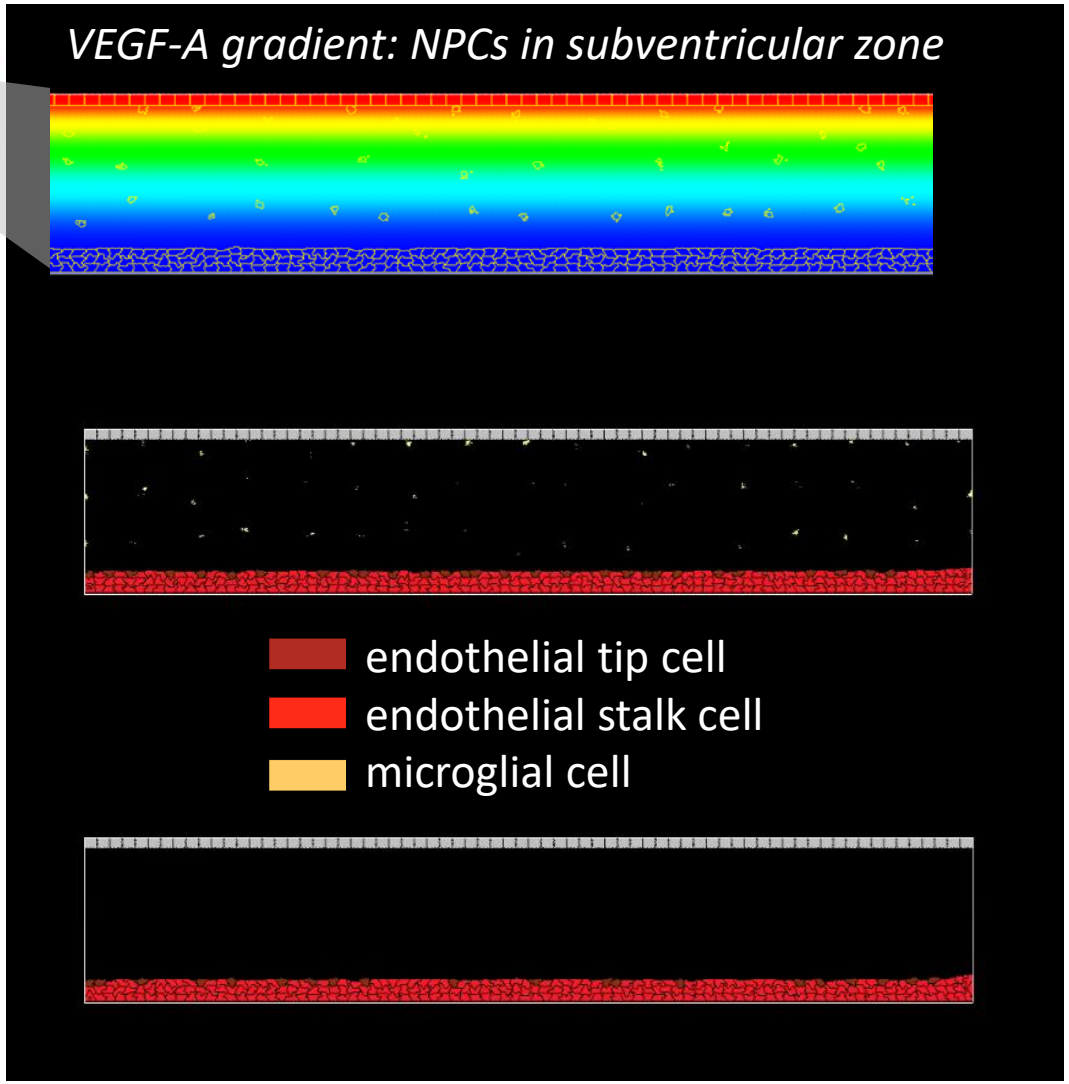
*EPA-A*STAR collaboration with A Silvin, F Ginhoux – A*STAR/SIgN, work in progress*

Computational neurovascular unit (cNVU)



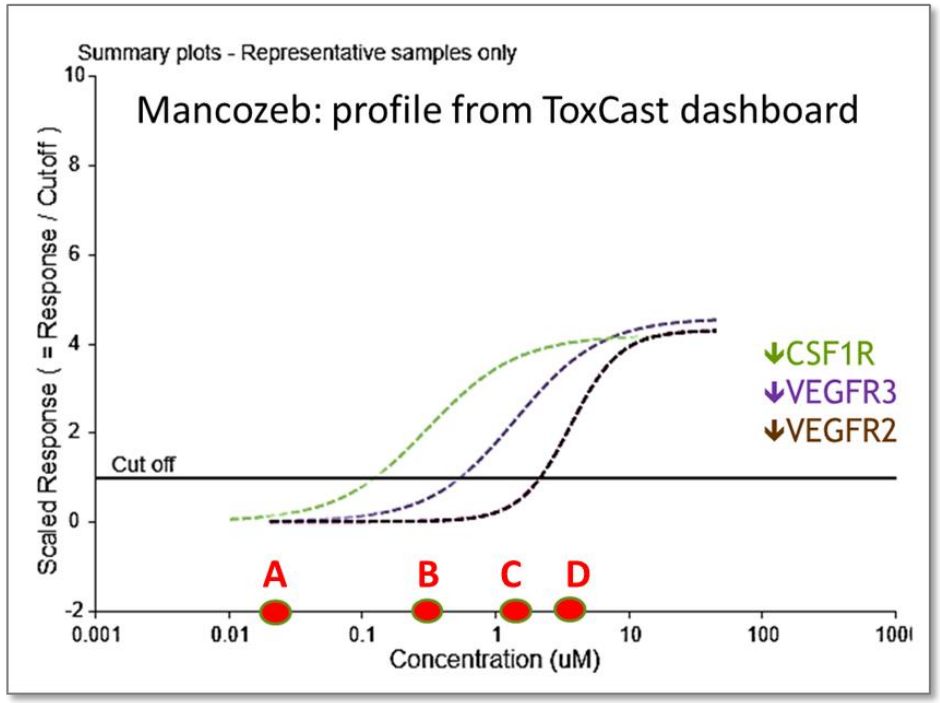
Tata et al. (2015), Mech Dev

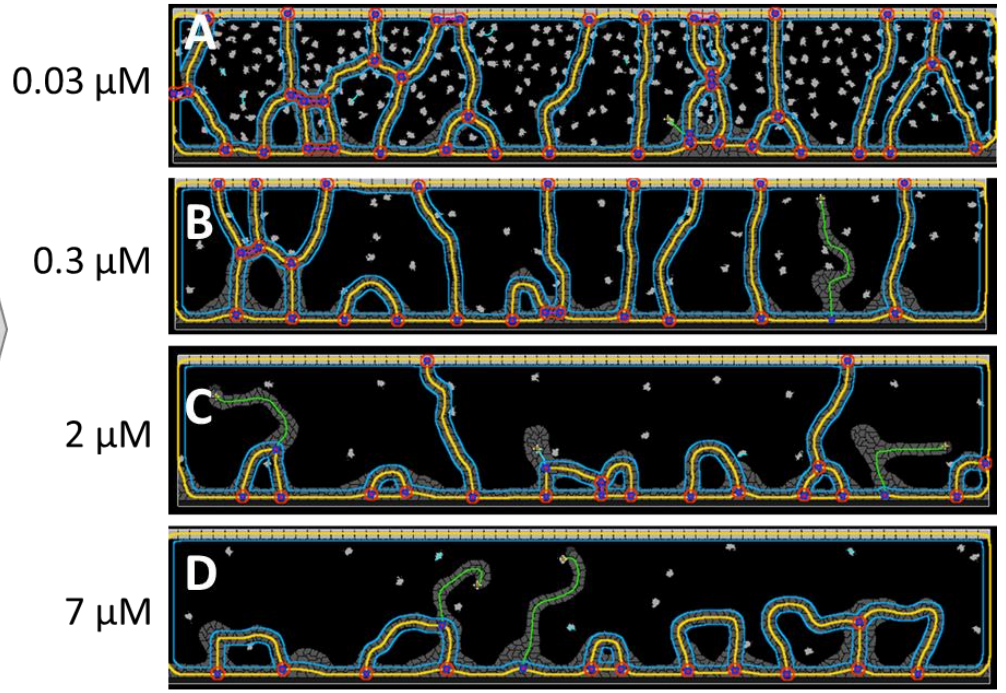




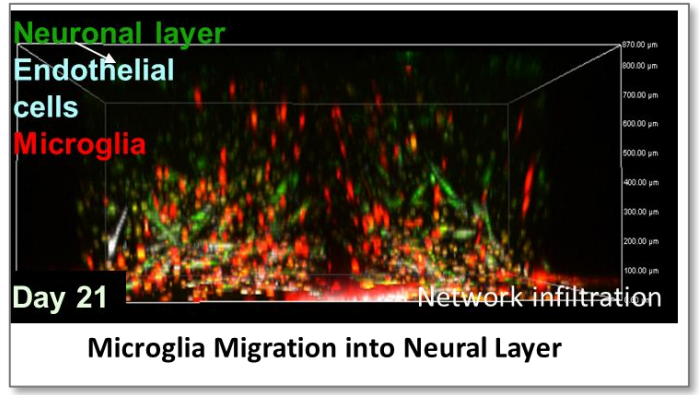
Compucell3D model (manuscript in preparation)

Translation of HTS concentration-response into phenotype





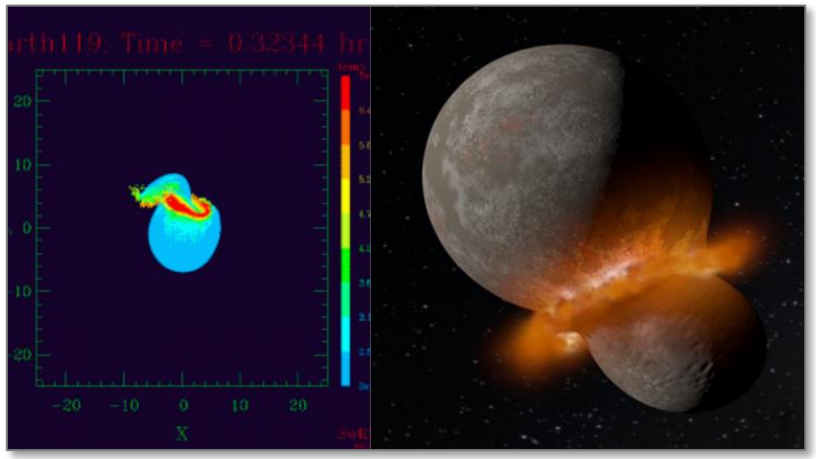
- HTS bioactivity profile for three receptors known to mediate microglial-endothelial interactions (LEL = 0.5 µM).
- Critical effect observed in an engineered PNVP microsystem for microglial migration (LEL = 0.3 µM) [Kaushik et al. (2020)].



Microglia Migration into Neural Layer

Computational Dynamics → Cinematic Representation

- Simulating complex systems with cellular ABMs can uniquely translate biomolecular data from HTS assays into computable phenotype (AOPs) for mechanistic modeling and quantitative prediction.
- Computational intelligence: ABMs are editable, customizable, and through fuzzy logic can fill-in for missing, incomplete, or uncertain biological information (curation and confidence).
- Putting 'artificial life' into realistic motion with interactive Cinematic Scientific Visualization (iCSV) may be both aesthetically pleasing and operationally impactful for stakeholder engagement.



Same data with traditional and cinematic representation

Birth of the Earth
(… can we build iCSV for the Embryo?)

CSV video kindly provided by Kalina Maria Borkiewicz, National Center for Supercomputing Applications (NCAS), University of Illinois

Special Thanks

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