Agent Based Modeling of Neurovascular Unit Development

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Horizons and Challenges in Organotypic Culture Models for Predictive Toxicology
Society of Toxicology Satellite Session
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This work does not necessary reflect EPA policy

Organotypic to Computational

- **Problem:** Multiscale modeling approach will improve toxicity predictions for chemicals from organotypic culture models

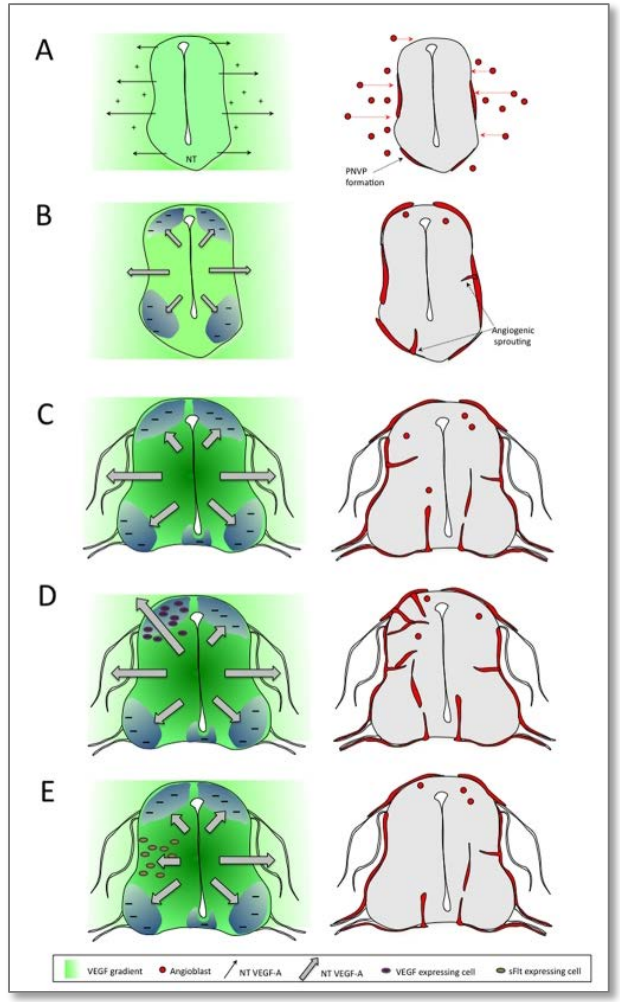
- **Hypothesis:** Use of computer models that recapitulate morphogenesis will improve analytically and theoretically based predictions of developmental toxicity.

- **Integration:** A model system which recapitulates the biology, and leverages both knowledge of cell-cell interactions and the available high-throughput *in vitro* profiling data

Computational neurovascular unit (cNVU) focus

- Vascularization of the neuroepithelium results from angiogenesis.
  - Sprouting from the perineural vascular plexus.
- Microglia, resident macrophages of the brain, meditate neurogenic and angiogenic signaling.
  - Are they mediators of developmental toxicity?
- A cellular-dynamic computational systems model of microglial function can improve our ability to understand and predict NVU DevTox.

mouse embryo
(GD9-12)



James et al. Development, 2009

Cell Agent-Based Modeling

- **Agent-Based Modeling and Simulation (ABMS):** a heuristic approach to reconstruct tissue dynamics using knowledge of biochemistry and cell-by-cell interactions.
  - Program each *agent* (cell) to follow specific rules
  - Interactions of agents gives rise to *emergent features* (phenotypic outcomes)
  - Qualify emergent feature with experimentally derived phenotypes (tissue level morphology)
  - Make toxicodynamic predictions by integrating biological knowledge & high throughput data

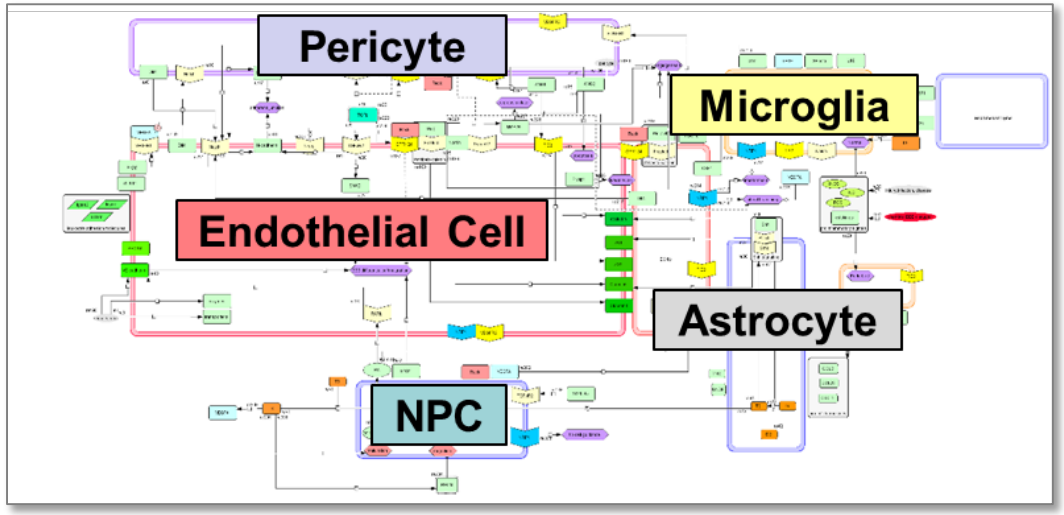
- **CompuCell3D*:** open source modeling environment
  - Rules (steppables) for distinct cell behaviors (growth, proliferation, apoptosis, differentiation, polarization, motility, ECM, signal secretion, …);
  - Rules coded in Python for cell-autonomous 'agents' that interact in shared microenvironment and self-organize into emergent phenotypes.

*James Glazier and colleagues, Indiana University

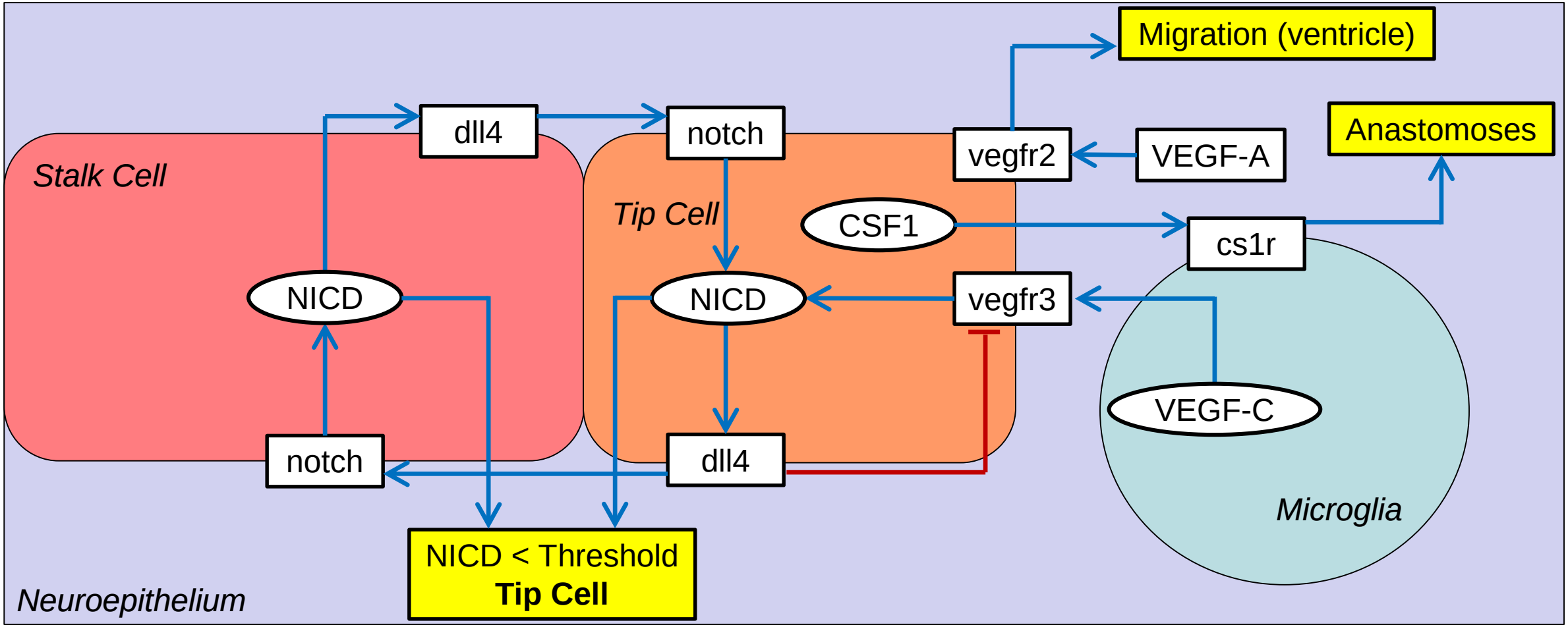
Agent-based model (ABM)

- **Goal**: build a cellular ABM that simulates microglia-mediated angiogenesis and neurogenesis.
- **Simulate**: exposure to ToxCast chemicals predicted to be neurovascular disruptors
  - Data from neurogenesis (ArunA) and angiogenesis (Vala)
- **Qualify**: simulation outputs against cell-based angiogenic and neurogenic assays.
  - proliferation, migration, tubulogenesis, branching, etc.

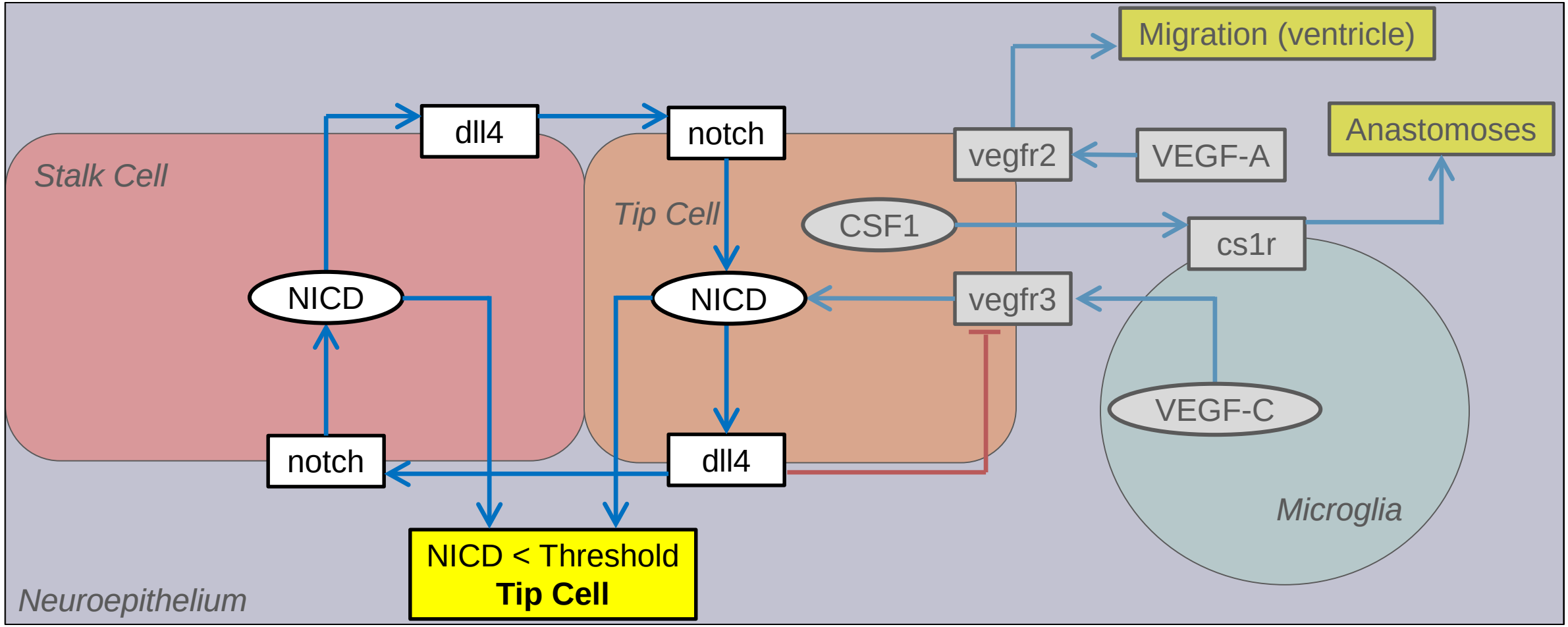
NVU systems map (K Saili, NCCT)



Cell-signaling network



1. Vessel Stabilization



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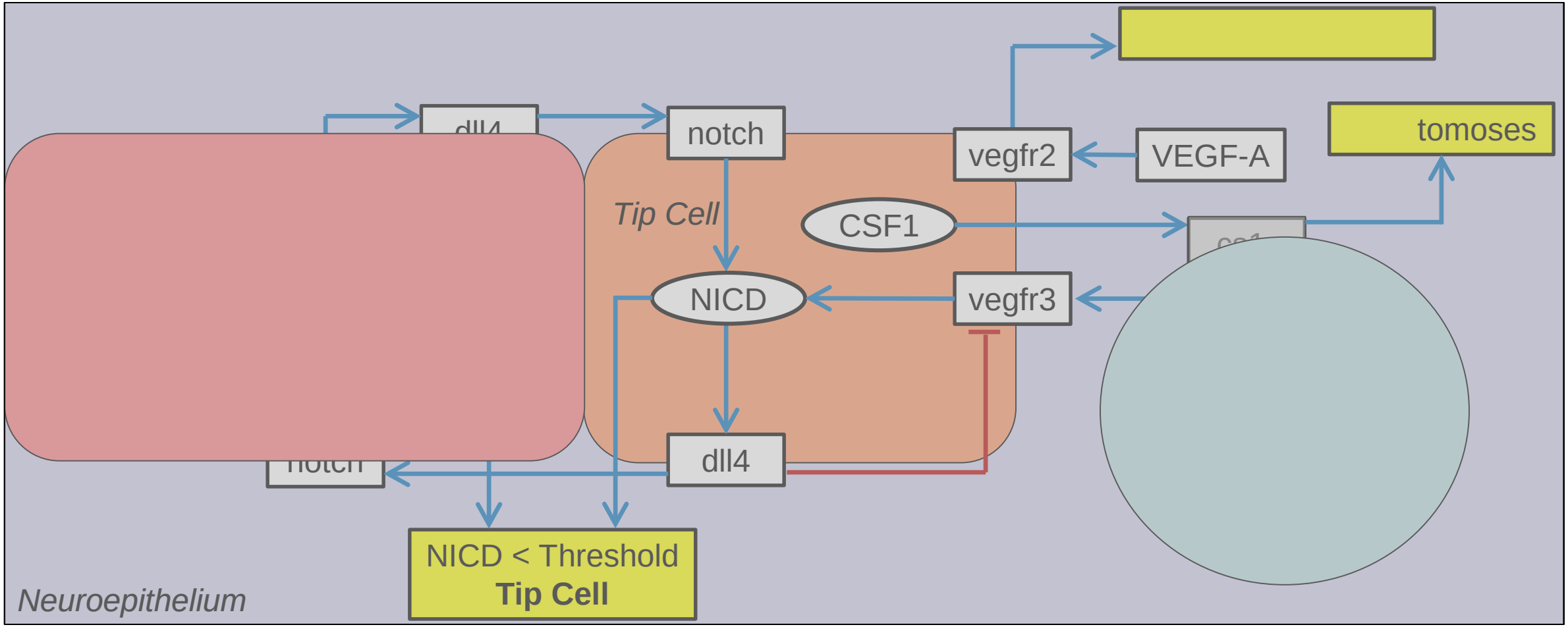
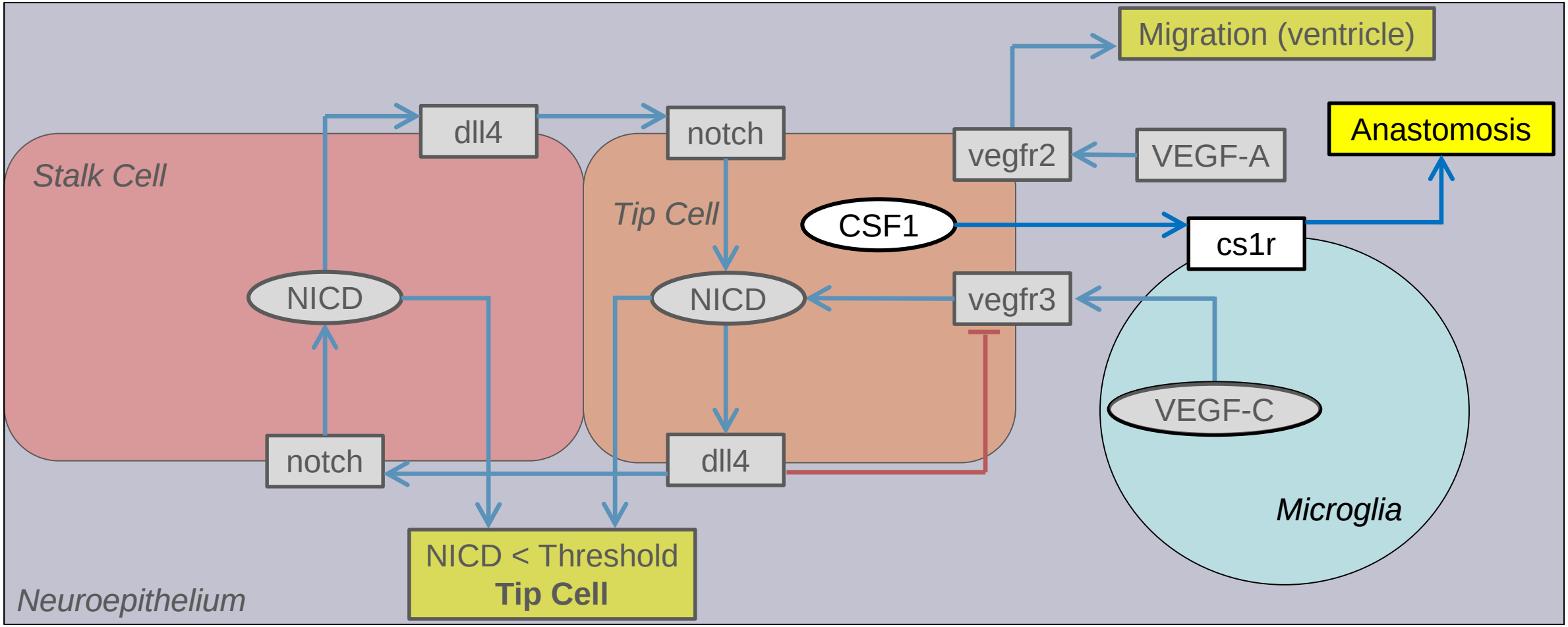
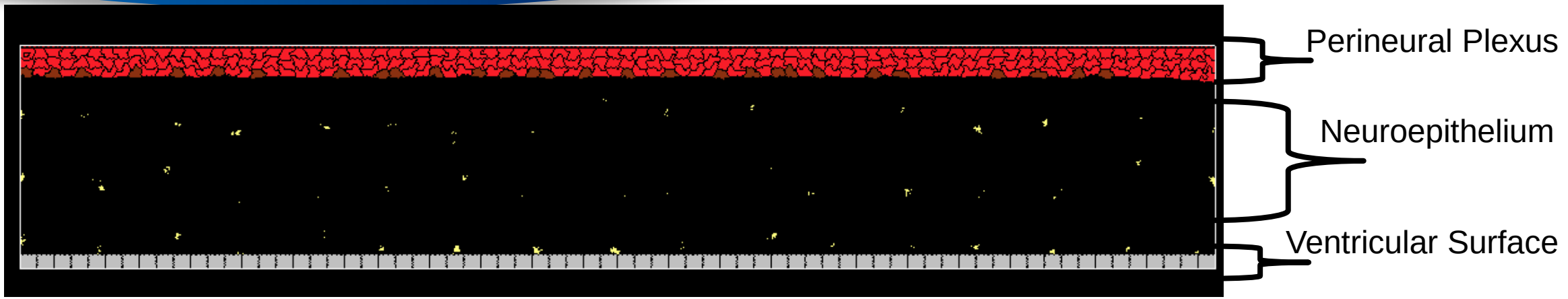
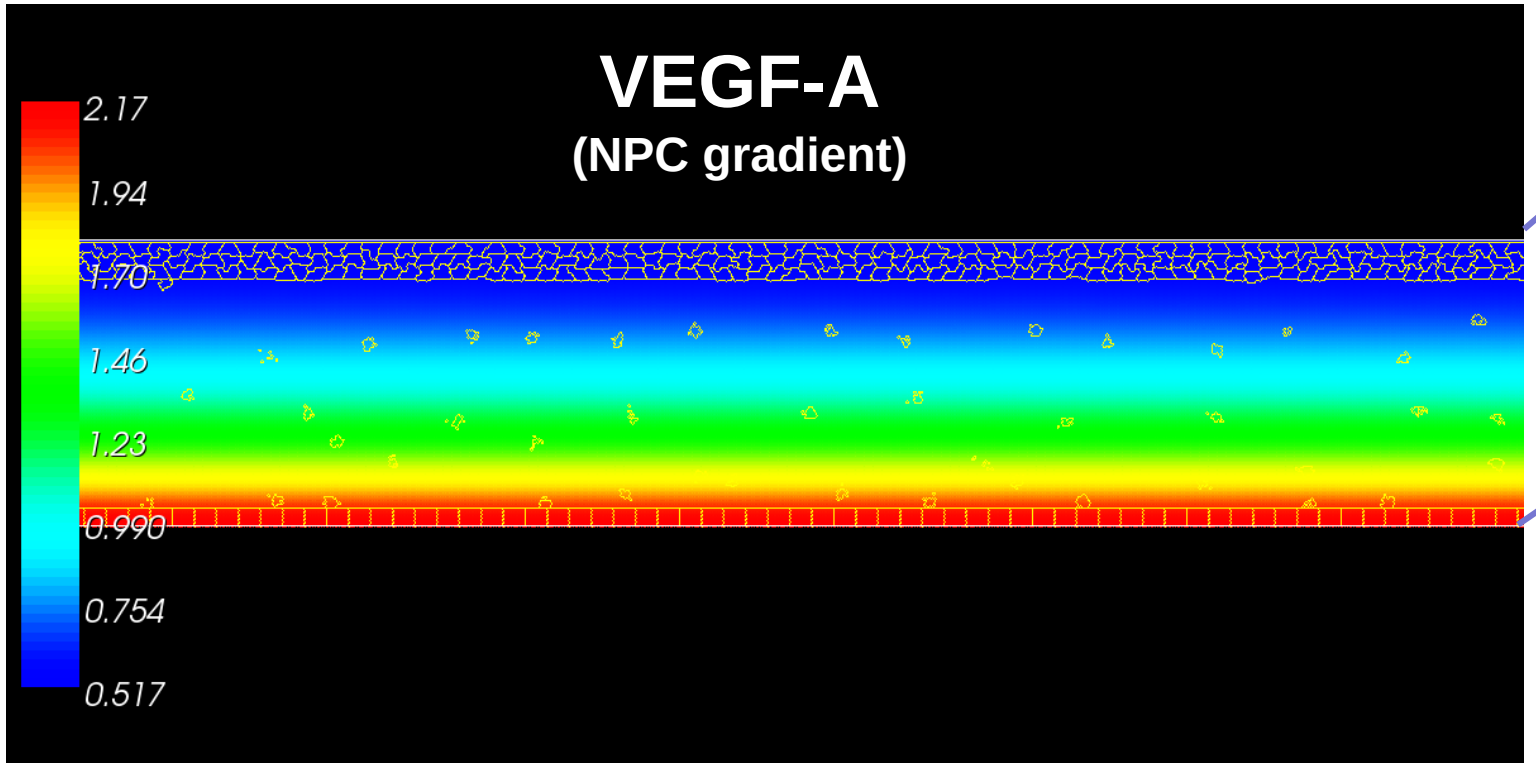


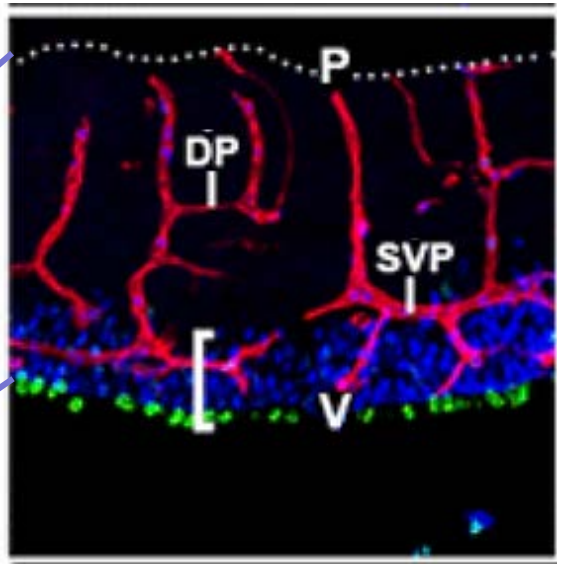
2. Microglia Anastomosis



cNVU boundary conditions

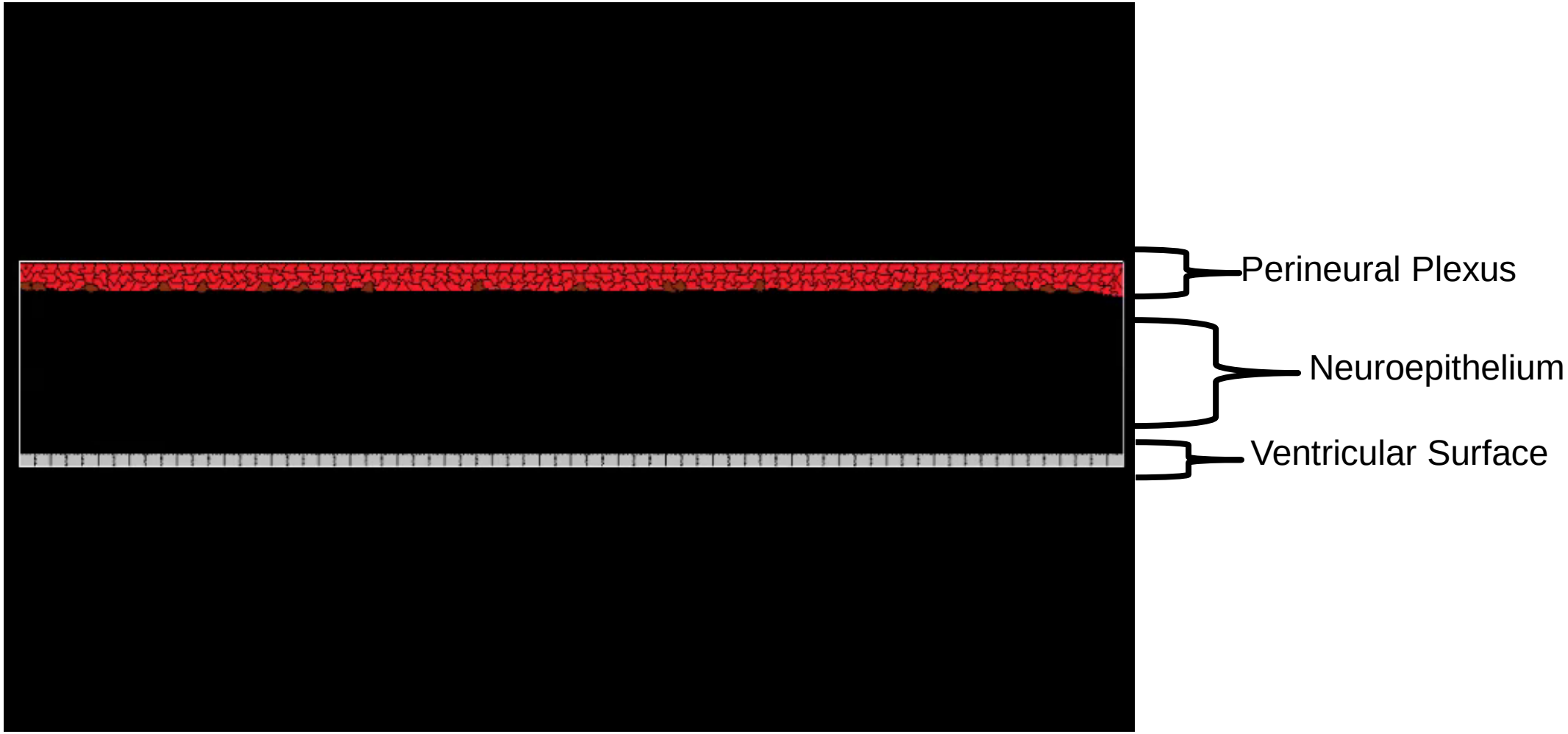




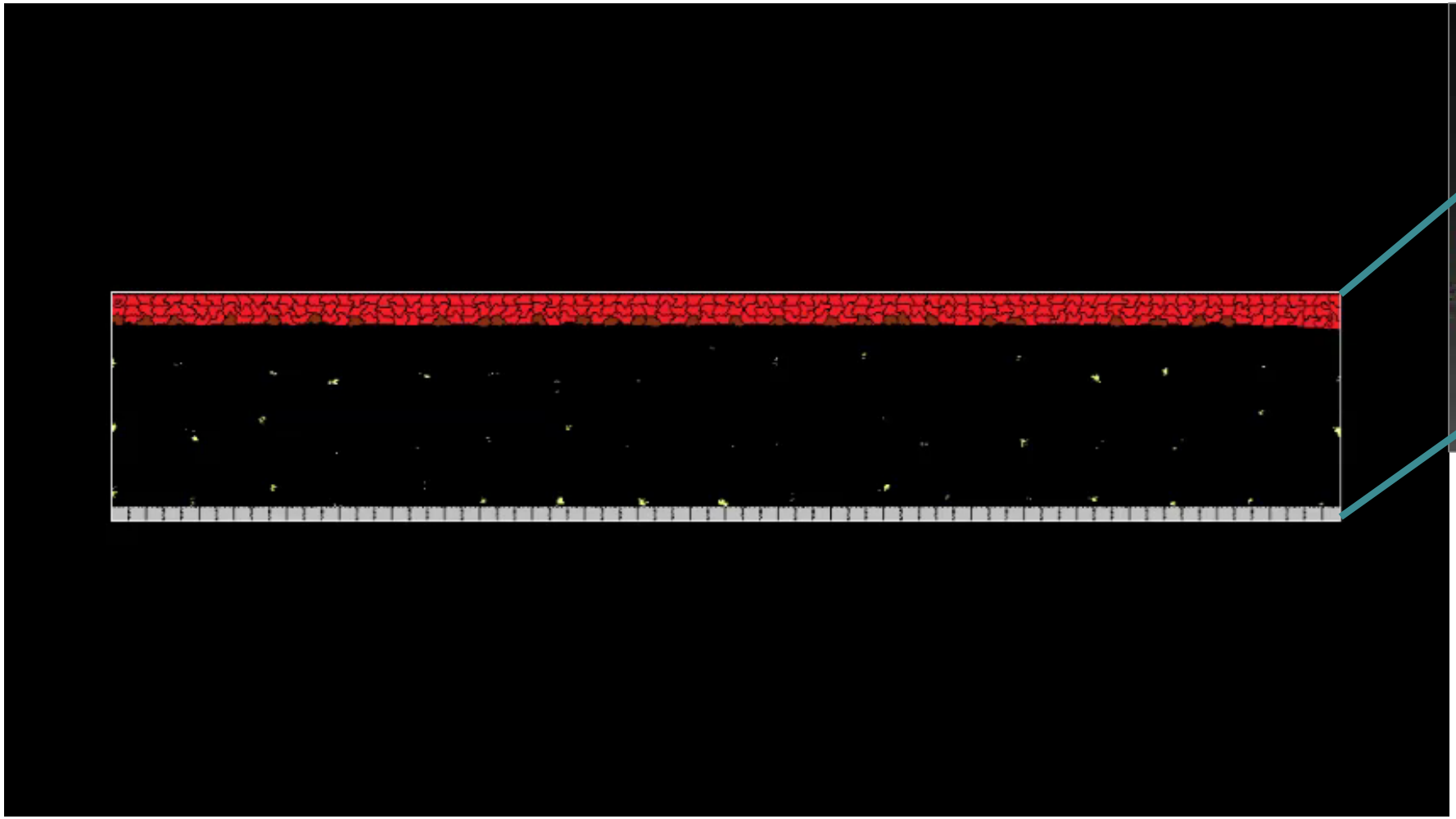


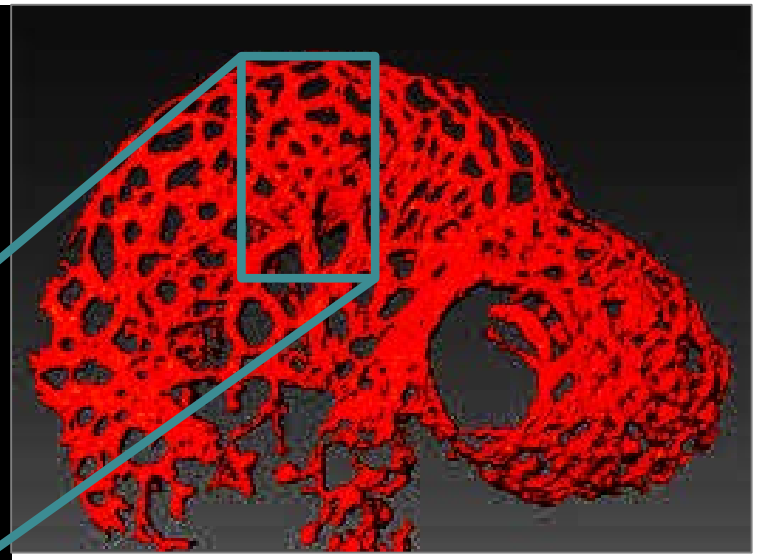
Tata et al., PNAS, 2016

Vascularization without microglia



cNVU Angiogenesis model

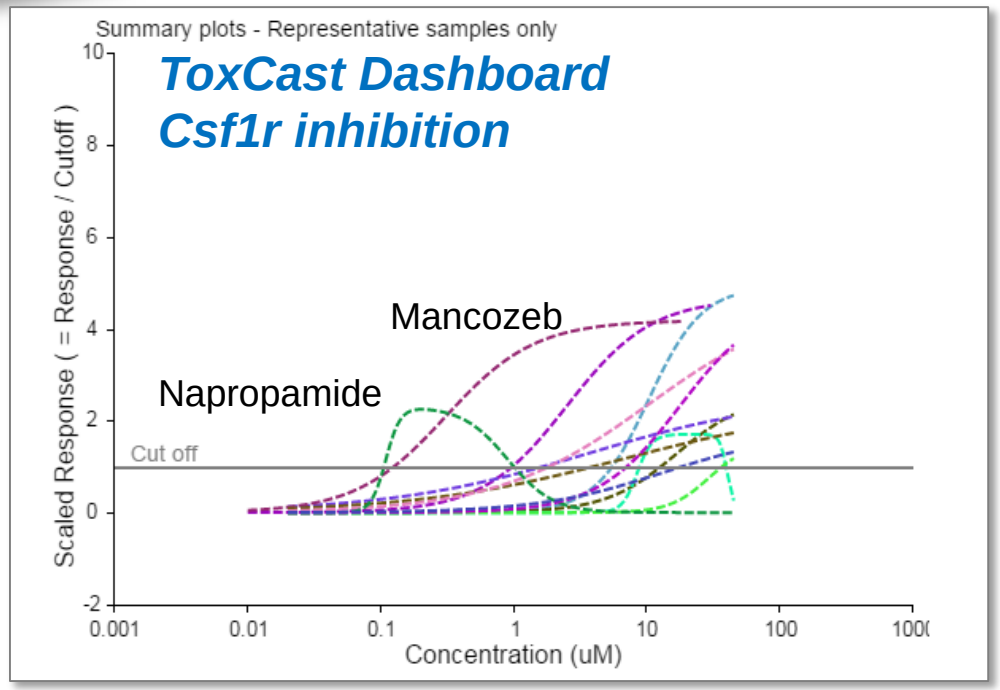




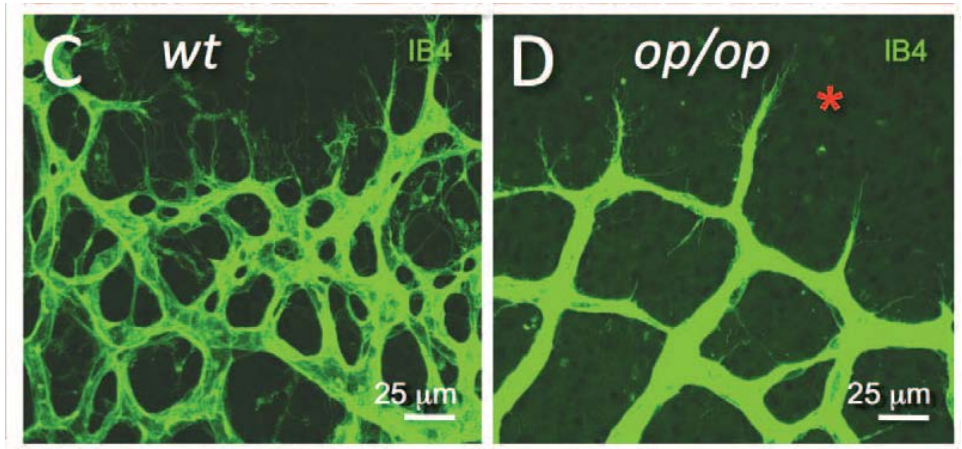
Embryonic vasculature

Toxicity-specific predictions

- Utilize concentration-response assays for *Csf1r* in ToxCast
  - *Csf1r* inhibition tied directly to microglia abundance (growth/survival)
  - *in vivo* studies demonstrate a decrease in vascular branching in the absence of microglia.



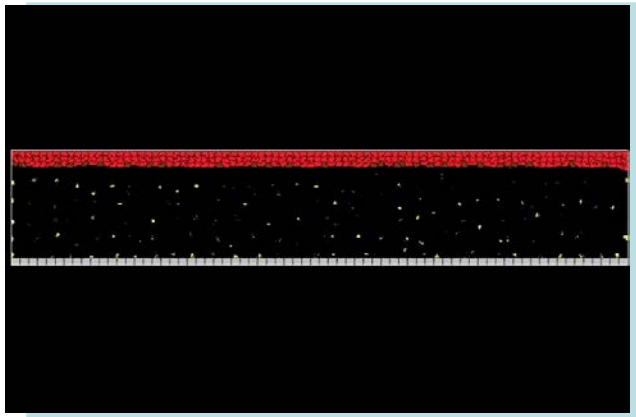
mouse retina



Rymo et al., PLoS one, 2011

Csf1$^{op/op}$: microglia "knockout"

Quantitative response: microglia abundance



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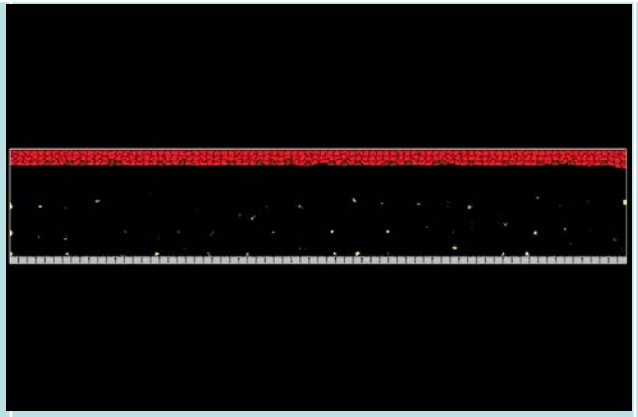

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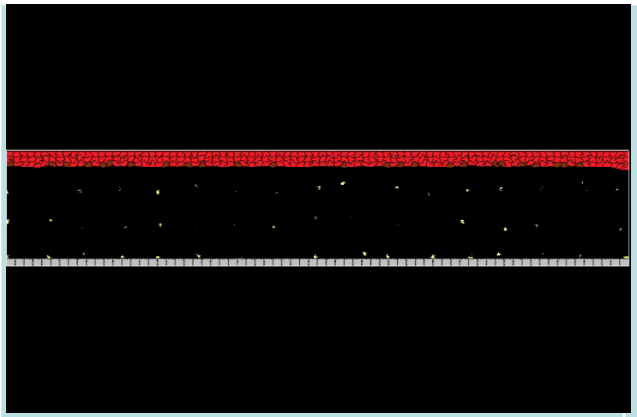
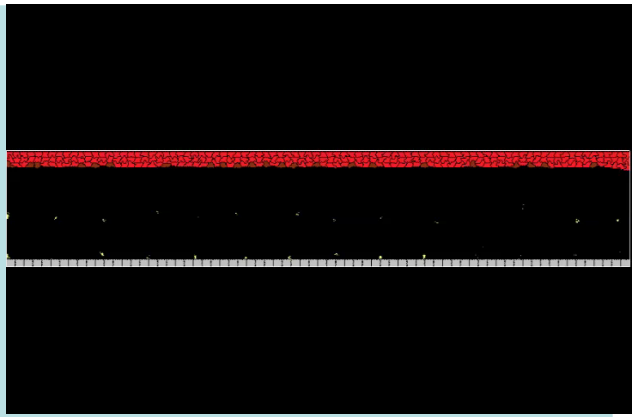


1x (prototype)



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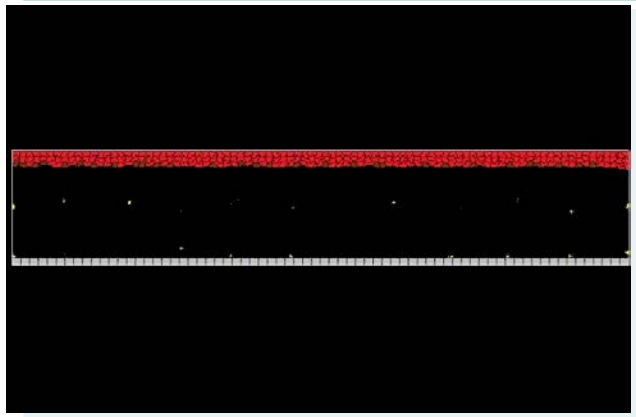

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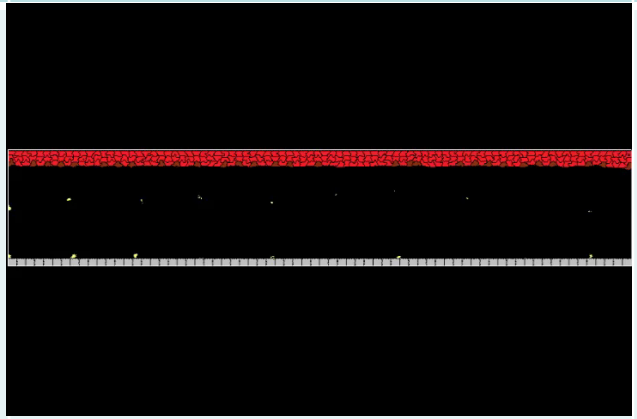

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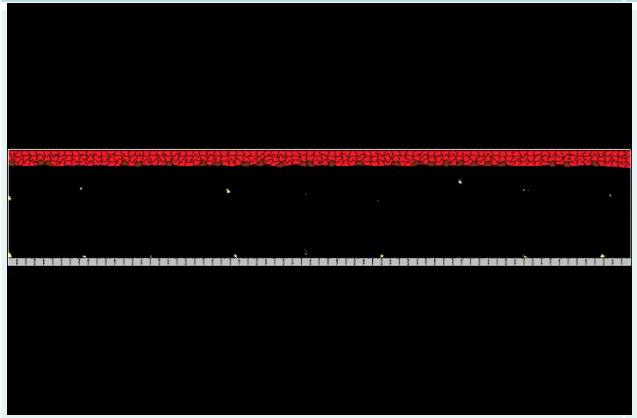

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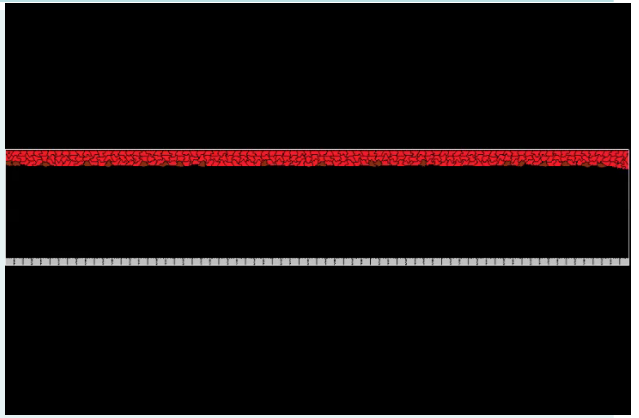

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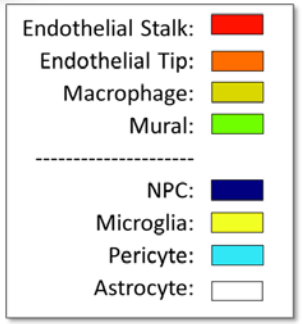
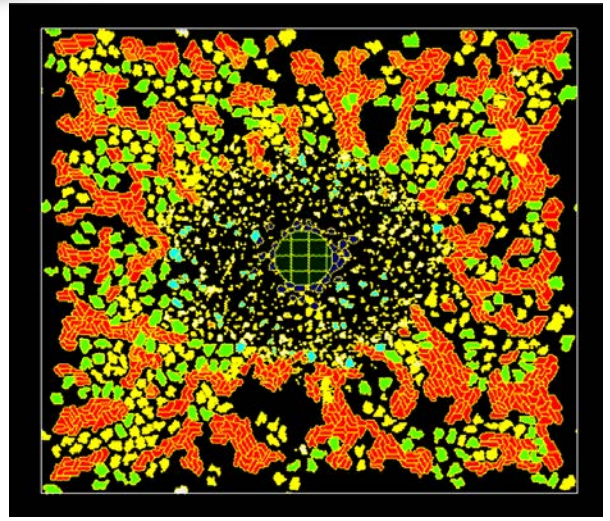
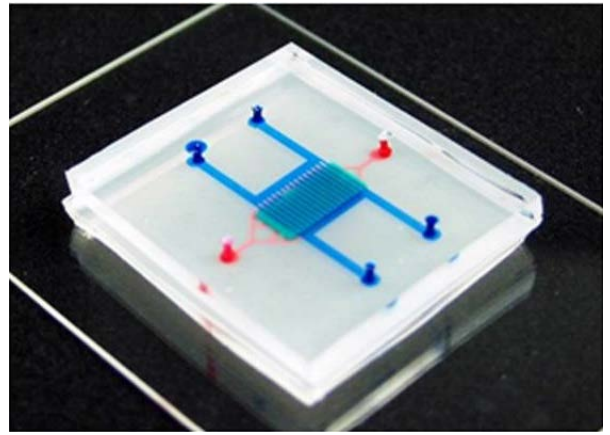
Towards a functional cNVU model

- Preliminary description of the role of microglial-endothelial interactions





- Next steps – include more cell types and features to better recapitulate NVU development
  - Capture neuroprogenitor cell NVU contribution
  - Incorporate 3D dynamics and vascular flow
  - Integrate available biological knowledge with HTS ToxCast data to simulate NVU developmental processes and toxicities



Brown et al., *Biomicrofluidics*. 2013

Acknowledgements

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Thank You

Questions?