# Disclaimer

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# Human Models for Analysis of Pathways (Human MAPs) Center


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Director, Human MAPs Center
Director, Forward BIO Institute
University of Wisconsin

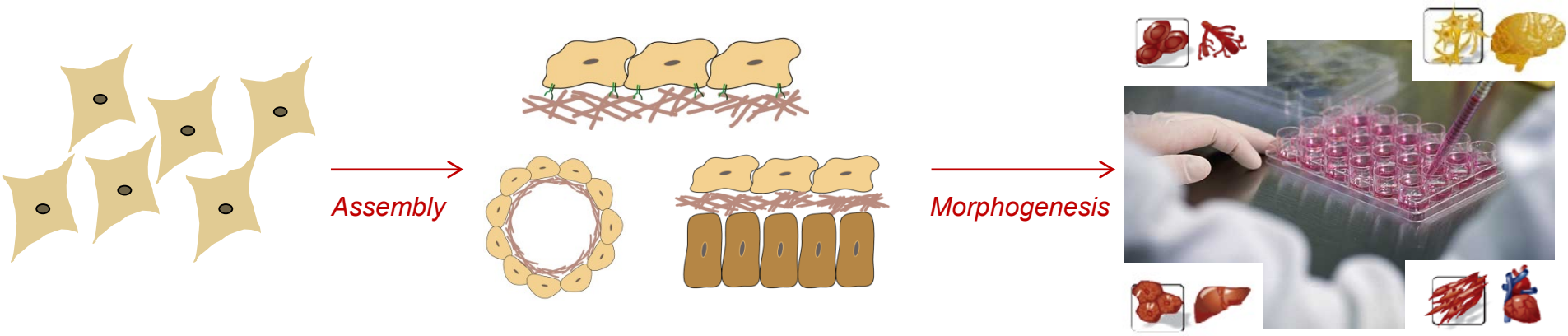



UW COLLEGE OF ENGINEERING

THE UNIVERSITY of WISCONSIN MADISON

UNIVERSITY of WISCONSIN MEDICAL SCHOOL

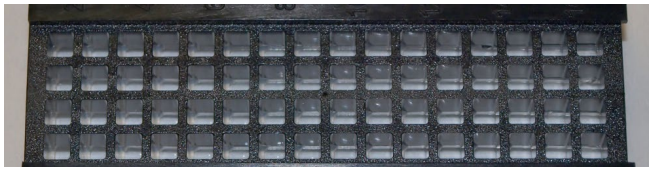
# Human MAPs Center: *Approach – practical innovation*



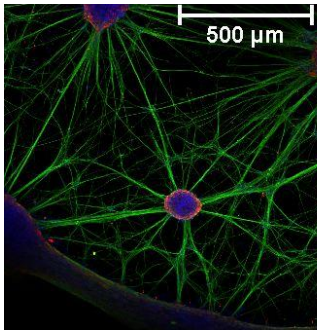

***Screening***

**Human vascular assay platforms**

EPA Toxcast (>1000 chemicals



**Human neural assay platforms**



# Human MAPs Center: *Objectives*

- *Generate pluripotent stem cell-derived cells that properly represent the diverse phenotypic characteristics of developing or mature human somatic cells*
- *Generate organotypic cell culture models that are robust and reproducible*
- *Translate organotypic cell culture models to microscale systems for HTS*
- *Combine genomic/epigenomic analyses with bioinformatics to gain molecular level insights into organotypic model assembly and the pathways influenced by toxins*

# Human MAPs Center: *Initial projects*

**Critical Obstacle:** Protocols are already available that direct hPSCs toward a hepatic fate, but resulting cells are not fully metabolically mature, limiting their current use in toxicological studies.
**Goal:** To generate organotypic models that represent mature liver tissue.
**Project PI Jamie Thomson**

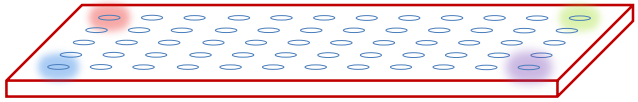
- first to isolate hESCs and iPSCs
- pioneer in pluripotent stem cell biology and applying hPSCs to form a variety of tissues, including liver
- team of leading experts in synthetic materials (Murphy), automated screening (Project Automation Scientist Brian McIntosh) and bioinformatics (Prof. Sushmita Roy, Dr. Ron Stewart).

## LIVER MAPS

**Critical Obstacle:** *In vitro* modeling of the human central nervous system (hCNS) is challenging due to the extensive diversity of its constituent phenotypes.
**Goal:** To develop a hPSC-derived screening platform that captures the phenotypic diversity of the developing hCNS (w/ rostrocaudal & dorsoventral specification).
**Project PI Randy Ashton**

- Expert on hPSCs differentiation into hCNS cells
- Focuses on using synthetic materials and microfluidics to control neuronal specification
- Team of leading experts in synthetic materials (Murphy), PSC biology (Thomson), automated HTS (Beebe, Brian McIntosh) bioinformatics (Roy, Dr. Stewart), and gene editing (Prof. Saha)

## BRAIN MAPS



## CANCER MAPS

**Critical Obstacle:** Urgent need for improved *in vitro* testing tools that can more efficiently evaluate a broad spectrum of chemicals in conditions that closely mimic human mammary ducts.
**Goal:** Apply a novel organotypic *in vitro* approach to recapitulate ER-mediated breast cancer, and to develop an AOP to identify chemical contributors.
**Project PI David Beebe**

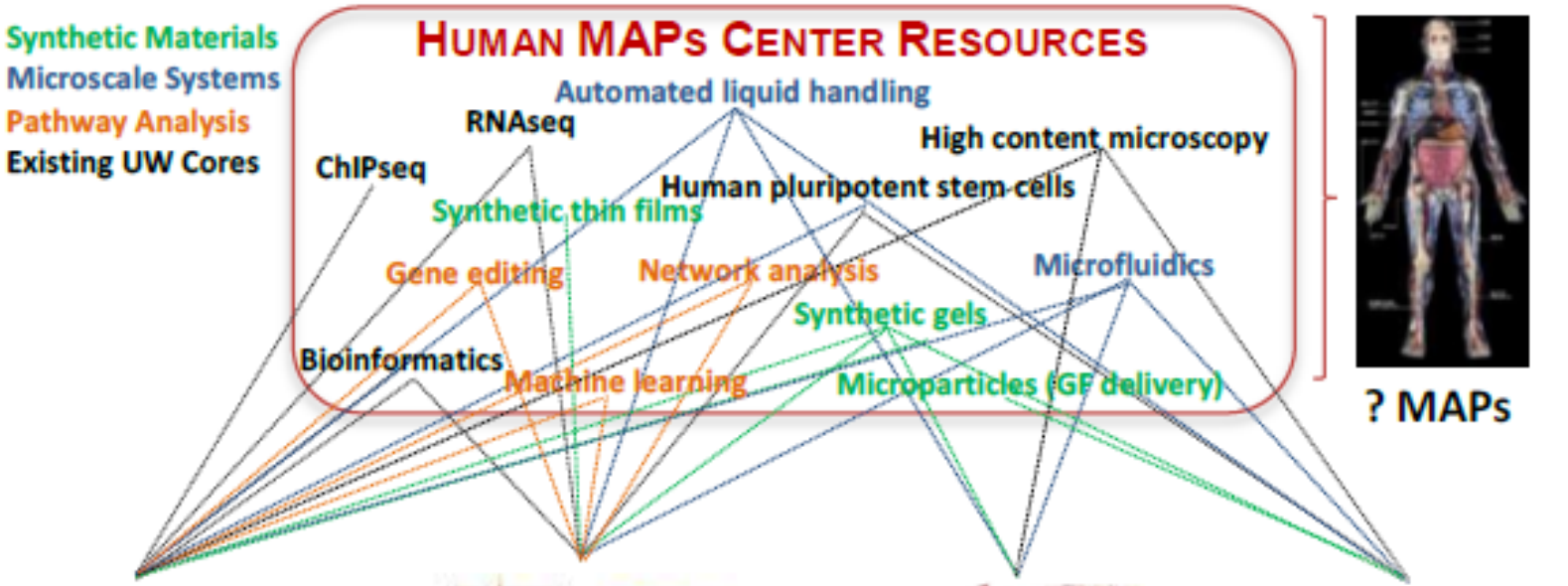
- world leader in microscale systems for high throughput screening in biological applications
- pioneer in human cancer biology applications
- team of leading experts in synthetic materials (Murphy), high-throughput screening (Dr. Kyung Sung), and cancer biology (Prof. Linda Shuler)

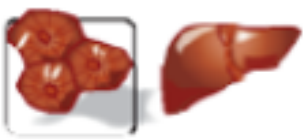
## VASCULAR MAPS

**Critical Obstacle:** *In vitro* models of the human neurovasculature do not properly capture critical interactions between endothelial cells and other cell types of importance to tox screening.
**Goal:** Develop hPSC-derived organotypic vascular networks (w/ pericytes/astrocytes) for toxin HTS.
**Project PI Nader Sheibani**

- Recognized leader in developmental and pathological angiogenesis
- Focuses on studying chemical disturbances of vascular and neurovascular function
- Team of leading experts in synthetic materials (Murphy, Dr. Ali Saghiri), PSC biology (Thomson), and automated HTS (Beebe)

# Human MAPs Center: *Evolution of Projects*



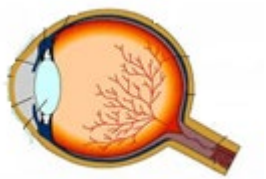



Liver MAPs

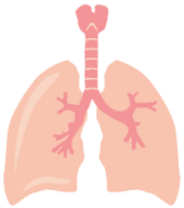
Brain MAPs

Cancer MAPs

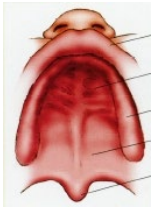
Vascular MAPs



Eye MAPs



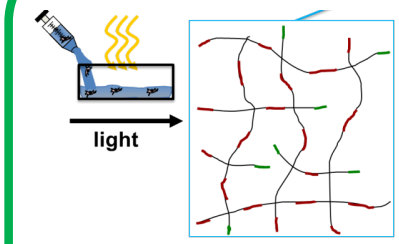
Lung MAPs



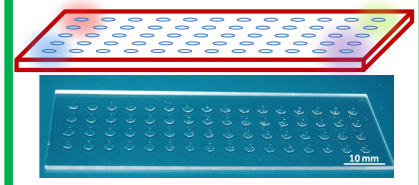
Palate MAPs

Disease MAPs

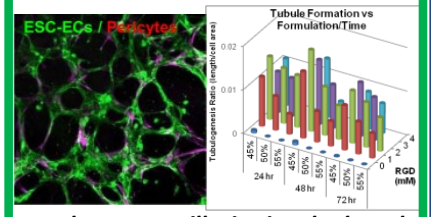
# Human MAPs Center: *Evolution of Cores*




*Adaptable synthetic chemistries*

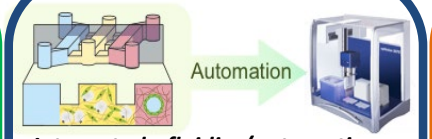



*Synthetic matrix arrays*

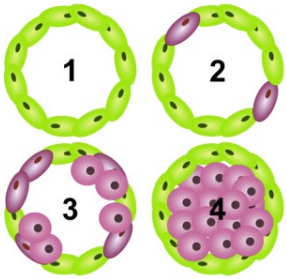



*e.g. human capillaries in a hydrogel*

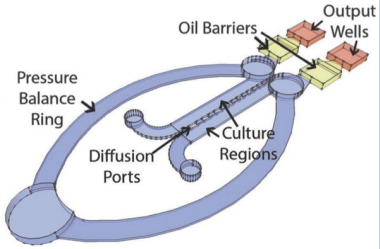
**Synthetic Matrices**




*Integrated µfluidics/automation*

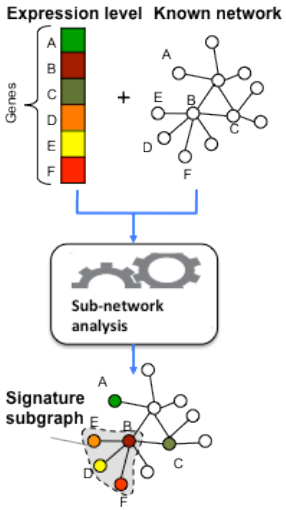



*µscale organotypic assembly*

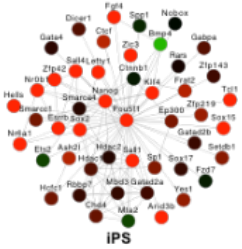



*"On chip" analysis - iFAST*

**Microscale Systems**




*Identifying key pathways*




*Phenotypic analysis*

**Pathway Analysis**

***Innovative Technology Cores (ITCs)***

***Metabolomics/secretome*** ***Metabolic imaging*** ***Embedded biosensors***

# Human MAPs Center: *Initial Partners*

***Public***

University of Wisconsin
SCHOOL OF MEDICINE AND PUBLIC HEALTH
Department of Orthopedics & Rehabilitation

Graduate School
UNIVERSITY OF WISCONSIN–MADISON

LUDWIG INSTITUTE FOR CANCER RESEARCH

WARF
Wisconsin Alumni Research Foundation

Stem Cell & Regenerative Medicine Center
UNIVERSITY OF WISCONSIN–MADISON

UW COLLEGE OF ENGINEERING

WISCONSIN INSTITUTES FOR DISCOVERY

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

***EPA H-MAPs Center***

***Private***

Cellular Dynamics international

TRS Tissue Regeneration Systems

Stem Pharm

SIGMA-ALDRICH

BellBrook LABS

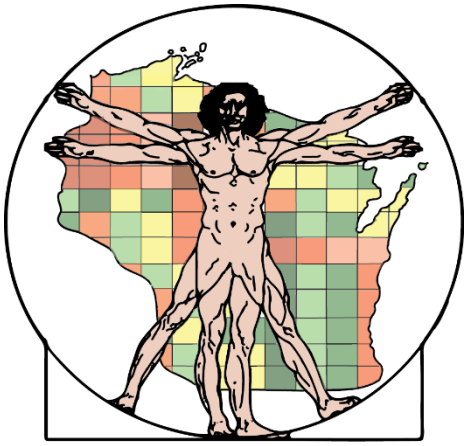
Ibidi

MORGRIDGE INSTITUTE FOR RESEARCH

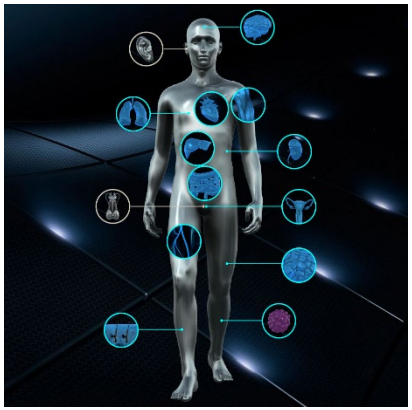
SCIKON INNOVATION INC

GILSON

# Human MAPs Center: *β Testing Partners*



Human MAPs Center



**NCATS TC Testing Centers**

***EPA H-MAPs Center***

GLADSTONE INSTITUTES

Washington University

CEDARS-SINAI

MORGRIDGE INSTITUTE FOR RESEARCH

Cellular Dynamics international

Stem Pharm

ONEXIO

BellBrook LABS

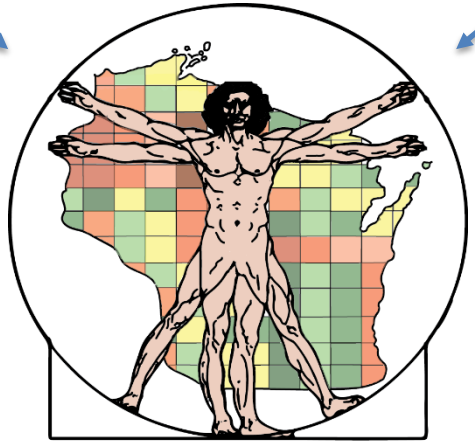
Ibidi

America's Biopharmaceutical Companies

# Human MAPs Center: *partners, reciprocal interactions*

- **In silico insights regarding cell/tissue assembly**
- **In silico insights regarding compound prioritization**
- **Suggest compounds to be tested based on mechanism**
- **Provide compound libraries for blinded testing**

- **Unique resources for model development**
- **Specific Voice of Customer and market information**
- **Identification of "non-starters" for broad end users**
- **Conduit for broad dissemination of technologies**



Human MAPs Center

- **New technologies**
- **New assays**
- **Experimental data**
- **Outstanding trainees**

# EPA-funded Human MAPs Center: Outputs (2015 – 2018)

**Publications**

- Over 70 publications

**Patents:**

- 14 patents filed

**Presentations:**

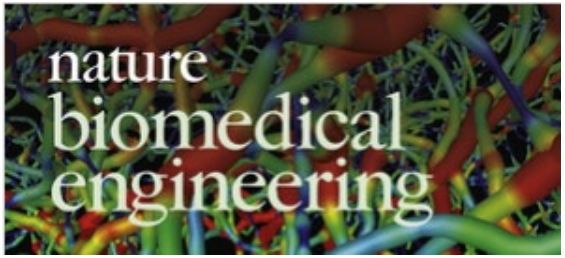
- Over 200 public presentations

Genome Research

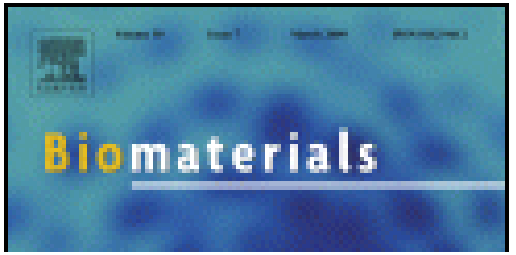
I.F. 11.351

Current Opinion in Biotechnology

I.F. 9.294 (3 articles)




I.F. 17.135 (2 articles)



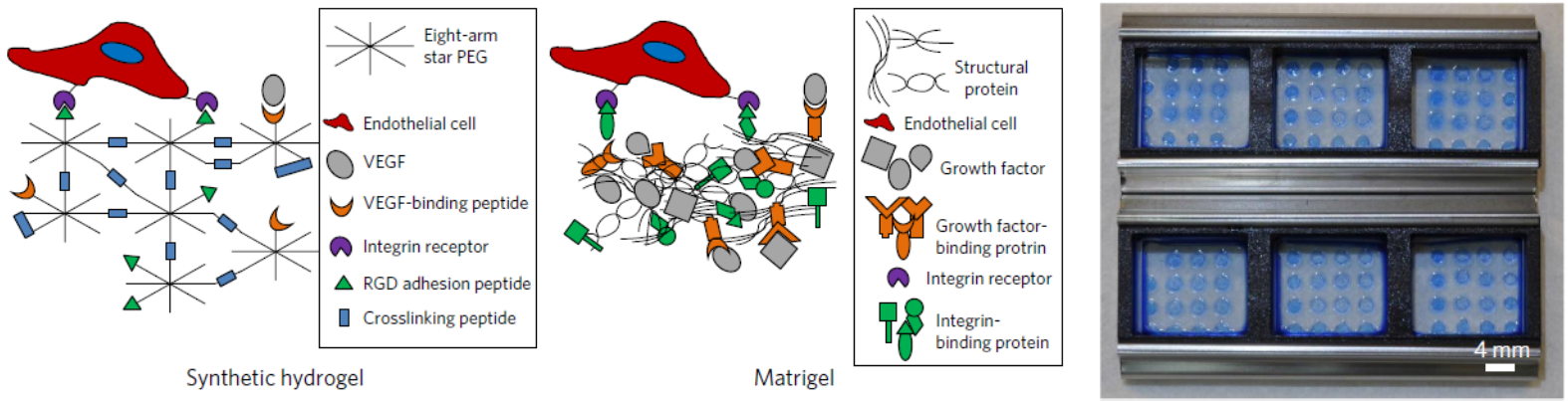

I.F. 8.402 (2 articles)

Pharmacology & Therapeutics

I.F. 11.127

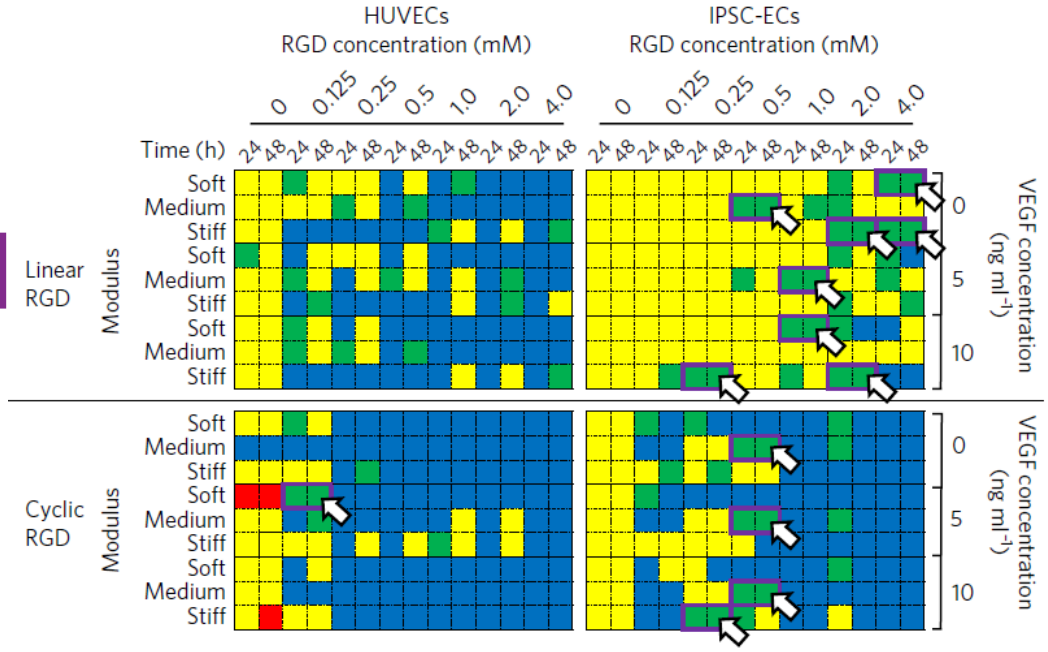

I.F. 8.2 (3 articles)

# Simple Example: Replacing Matrigel in vascular screening




nature biomedical engineering
ARTICLES
PUBLISHED: 11 JULY 2017 | VOLUME: 1 | ARTICLE NUMBER: 0096

**Versatile synthetic alternatives to Matrigel for vascular toxicity screening and stem cell expansion**



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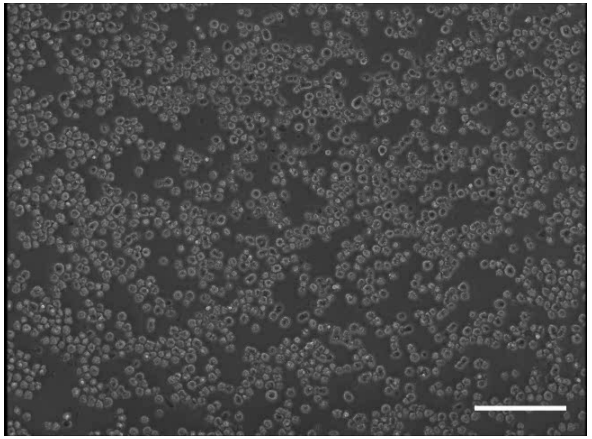
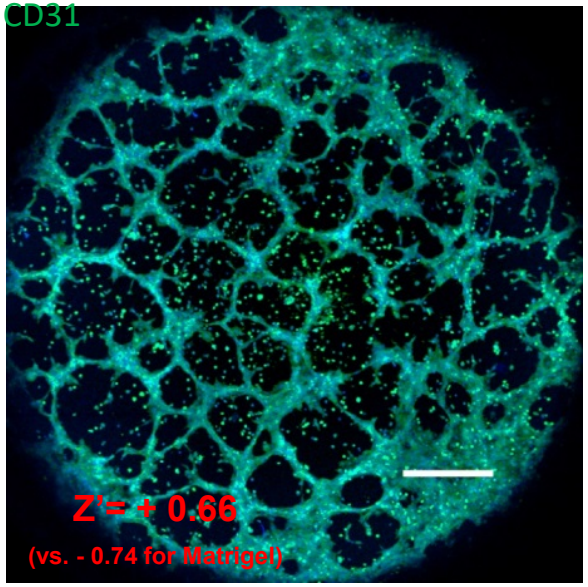





| Chemical Name: | Matrigel | Synthetic | pVDC score |
|---|---|---|---|
| 1,2,4-Trichlorobenzene | 0 | 0 | 0.000 |
| Decane | 0 | 0 | 0.000 |
| Tris(2-chloroethyl) phosphate | 0 | 0 | 0.000 |
| 1,2,3-Trichloropropane | 0 | 0 | 0.002 |
| Pymetrozine | 0 | 0 | 0.002 |
| Methimazole | 0 | 0 | 0.002 |
| Diethanolamine | 0 | 0 | 0.002 |
| Imazamox | 0 | 0 | 0.007 |
| D-Mannitol | 0 | 0 | 0.007 |
| Methylparaben | 0 | 0 | 0.010 |
| Valproic acid | 0 | 0 | 0.016 |
| 2,4-Diaminotoluene | 0 | 0 | 0.069 |
| Bisphenol A | 0 | 0 | 0.146 |
| Haloperidol | 0 | 0 | 0.177 |
| Tris(2-eth l) phosphate | 0 | 0 | 0.182 |
| Tris(1,3-d -2-propyl)phosphate | 0 | 0 | 0.188 |
| Cladribine | 0 | 0 | 0.196 |
| TNP-470 | 0 | 0 | 0.238 |
| Oxytetracycline dihydrate | 0 | 0 | 0.260 |
| Celecoxib | 0 | 1 | 0.269 |
| Docusate sodium | 0 | 0 | 0.304 |
| C.I. Solvent Yellow 14 | 0 | 1 | 0.306 |
| Reserpine | 0 | 0 | 0.307 |
| Quercetin | 0 | 1 | 0.309 |
| Phenolphthalein | 0 | 0 | 0.327 |
| 5HPP-33 | 1 | 0 | 0.327 |
| tert-Butylhydroquinone | 0 | 0 | 0.336 |
| Triclocarban | 1 | 1 | 0.362 |
| Triclosan | 0 | 1 | 0.372 |
| Pyridaben | 0 | 1 | 0.379 |
| 1-Hydroxypyrene | 1 | 1 | 0.386 |
| Sodium dodecylbenzenesulfonate | 0 | 0 | 0.429 |
| Disulfiram | 1 | 1 | 0.432 |
| Fluazinam | 1 | 1 | 0.434 |
| Octyl gallate | 0 | 1 | 0.450 |
| Bisphenol AF | 0 | 1 | 0.457 |
| PFOS | 0 | 0 | 0.460 |
| 4-Nonylphenol, branched | 0 | 0 | 0.461 |

pVDC Score: Non-Inhibitory Inhibitory

| | Synthetic | Matrigel |
|---|---|---|
| True Positives | 11 | 5 |
| False Positives | 0 | 0 |
| True Negatives | 12 | 12 |
| False Negatives | 15 | 21 |
| **Accuracy** | **61 %** | **45 %** |

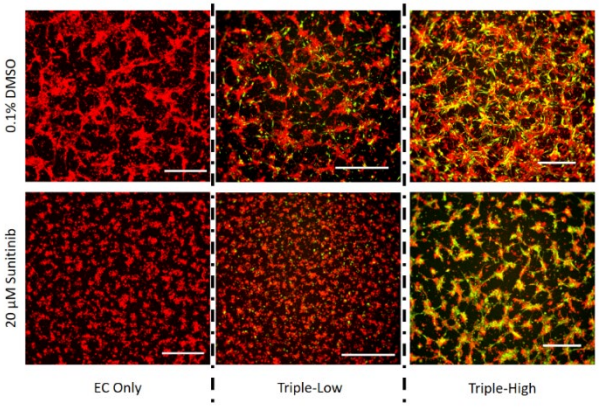
nature biomedical engineering

ARTICLES

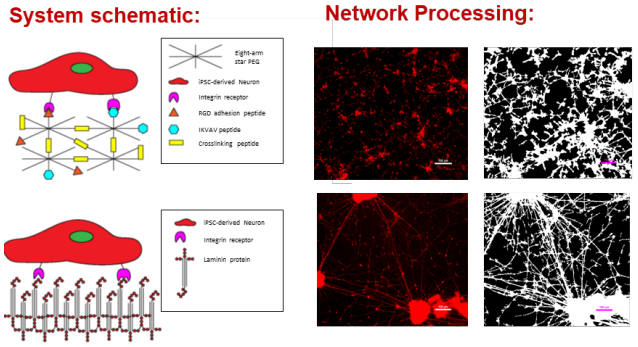
PUBLISHED: 11 JULY 2017 | VOLUME: 1 | ARTICLE NUMBER: 0096

**Versatile synthetic alternatives to Matrigel for vascular toxicity screening and stem cell expansion**

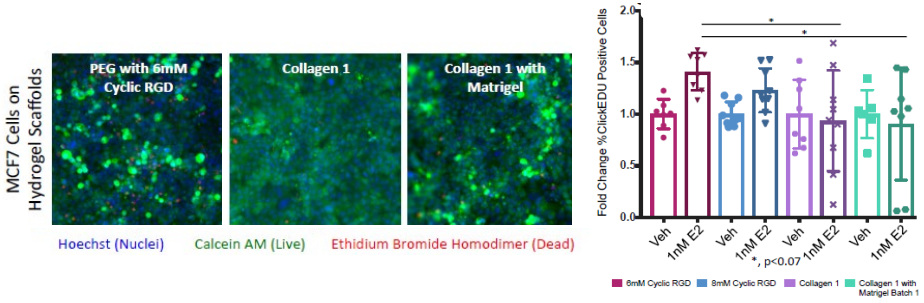
# Synthetic alternatives to naturally derived ECMs: screening applications




**Neurovascular (iPS-ECs, -PCs, -Astrocytes)**
Nguyen, et al. ***Applied In Vitro Toxicology***, 2019.

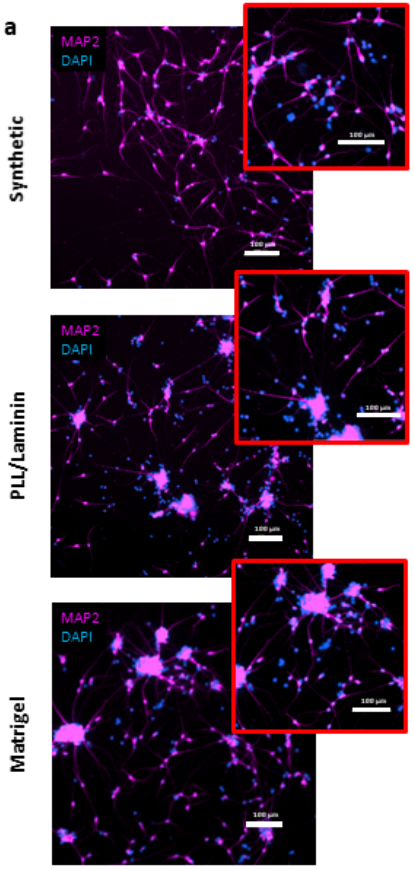


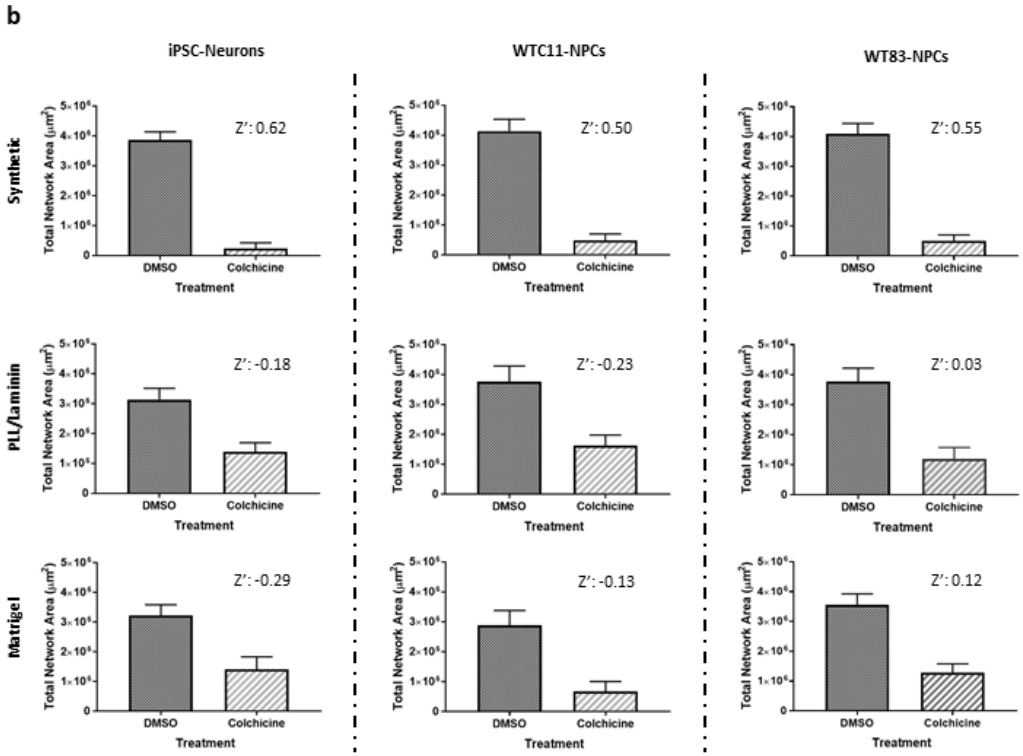

**Neural (iPS-neurons)**
Evans, Daly, et al., 2019




**Breast Cancer (MCF-7 cells)**
Livingston, et al., 2019.

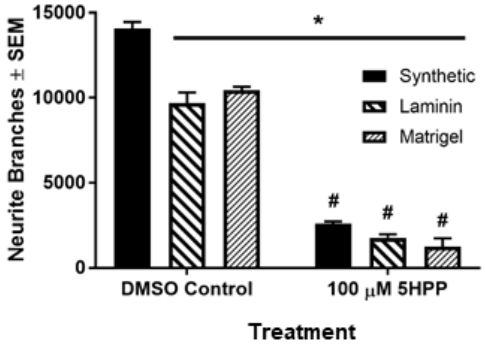
# Neural model 1.0: neurogenesis

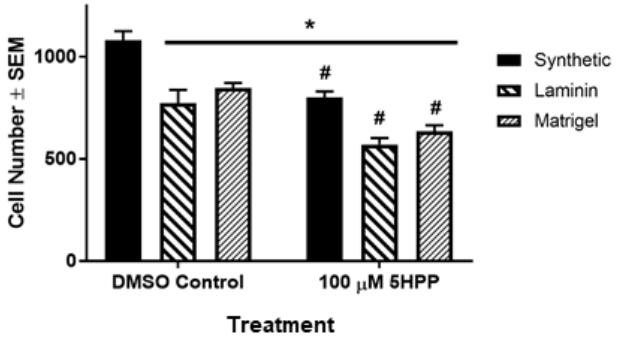


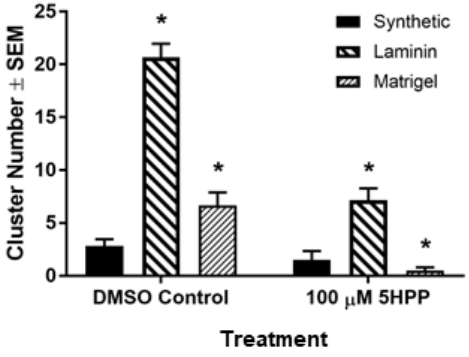



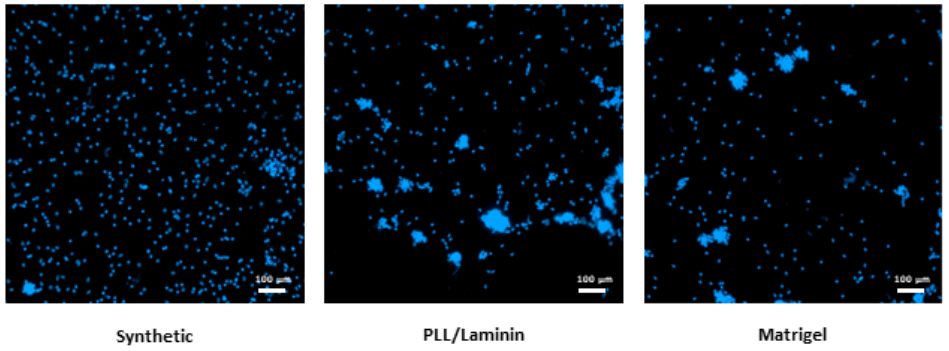

**Neural (iPS-neurons)**
Evans, Daly, et al., 2019
"High-throughput toxicity screening of iPSC-derived neurons on synthetic hydrogels"

# Neural model 1.0: neurogenesis




**Neural (iPS-neurons)**
Evans, Daly, et al.
"High-throughput toxicity screening of iPSC-derived neurons on synthetic hydrogels"
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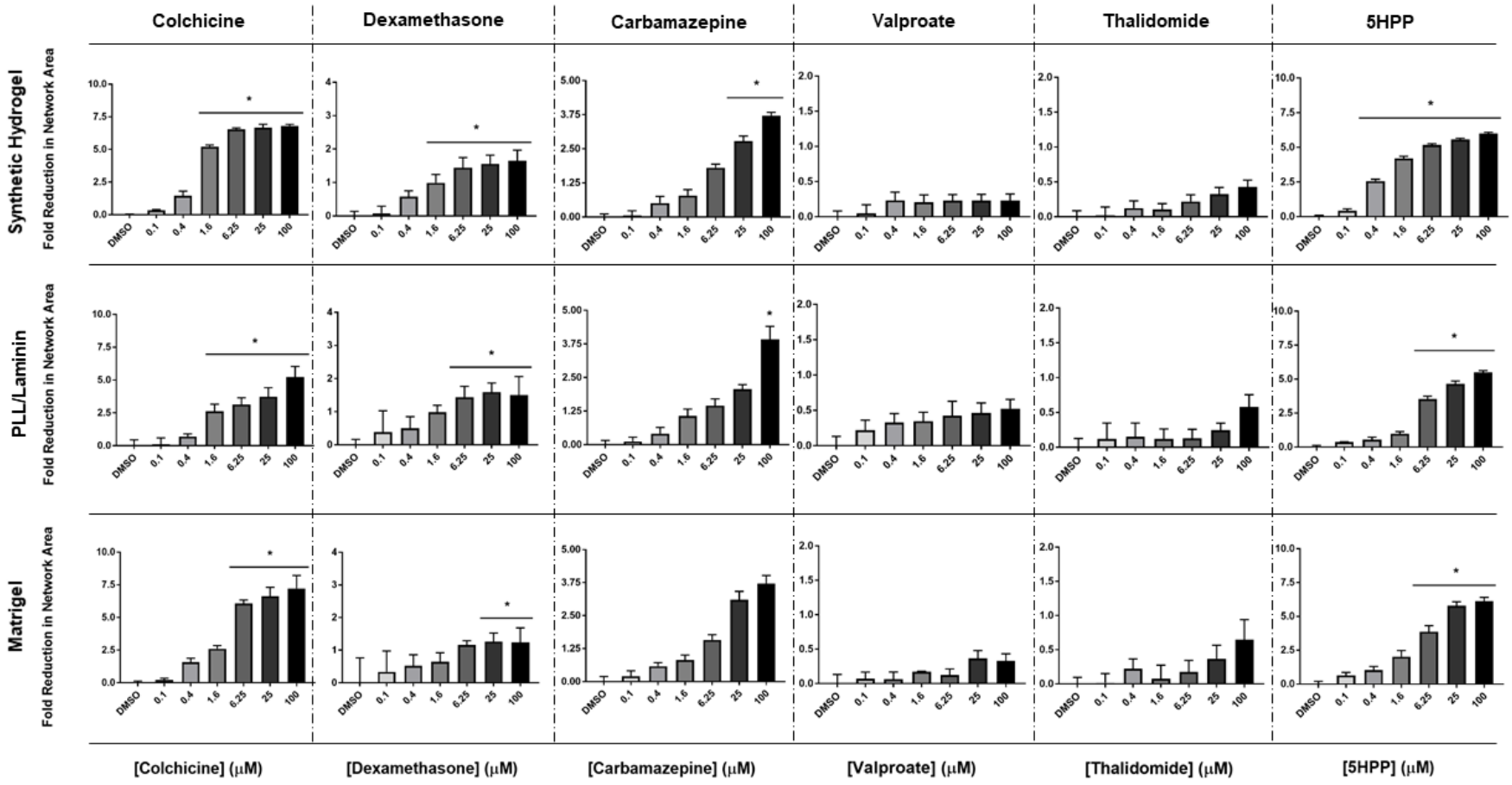
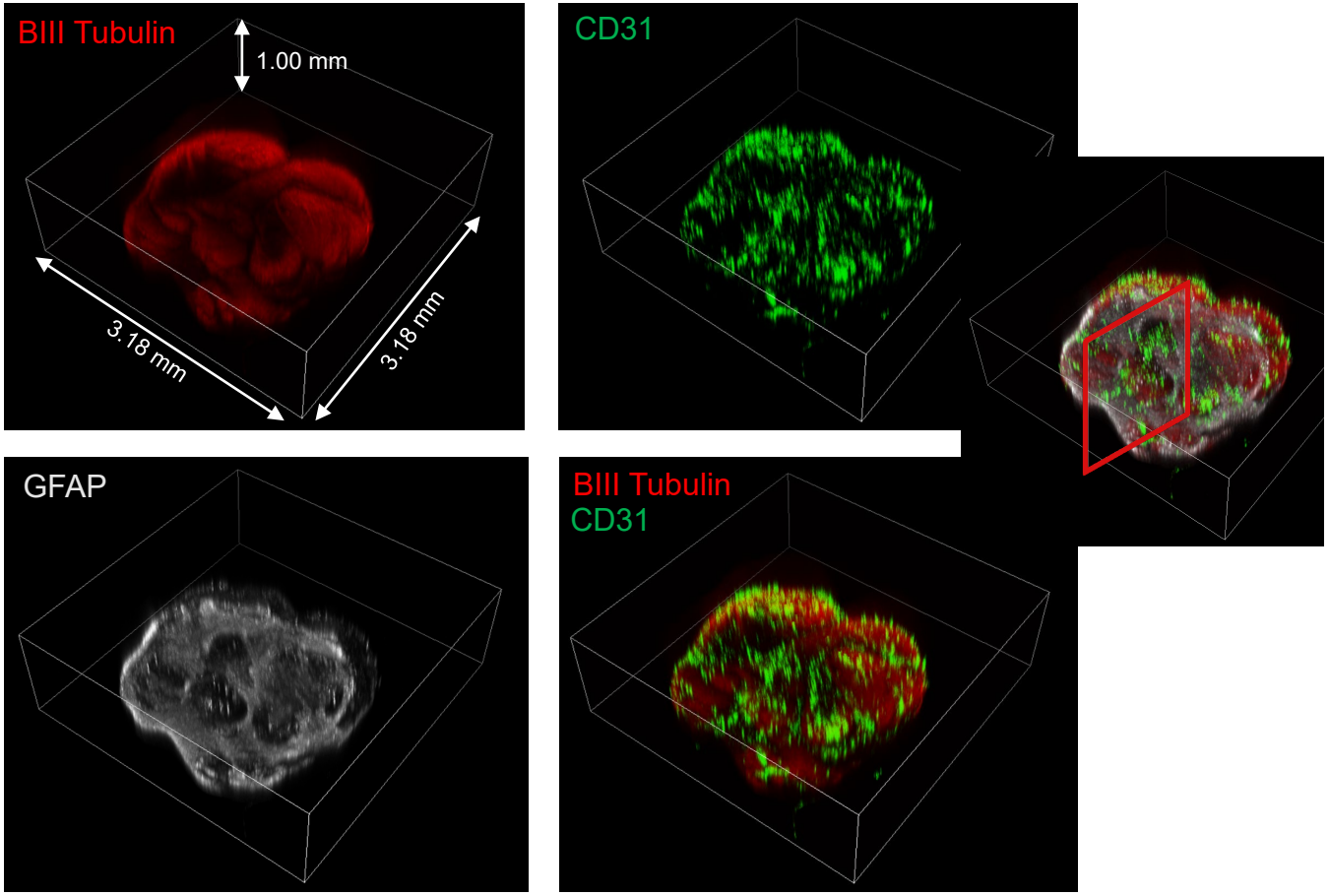
# Neural model 1.0: neurogenesis



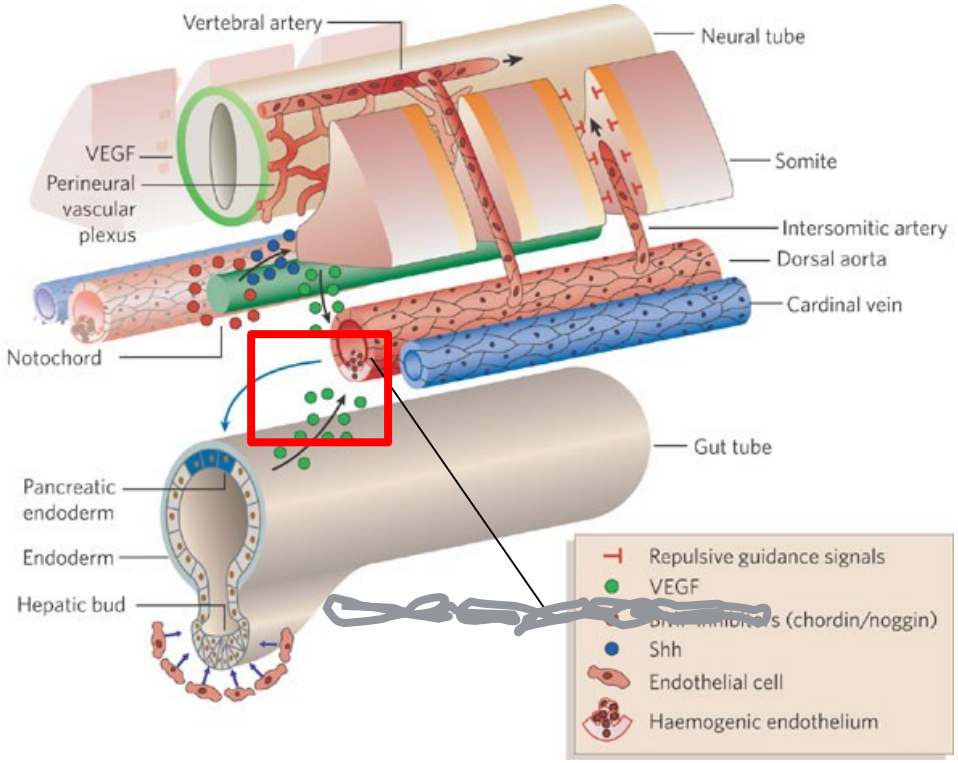

**Neural (iPS-neurons)**
Evans, Daly, et al.
"High-throughput toxicity screening of iPSC-derived neurons on synthetic hydrogels"
.

# Neural model 2.0: Perineural Vascular Plexus



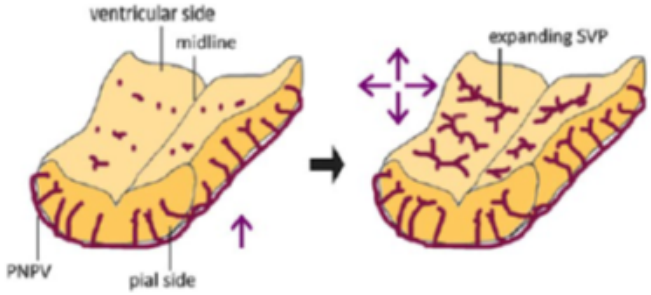

Day 21 - 96 wells

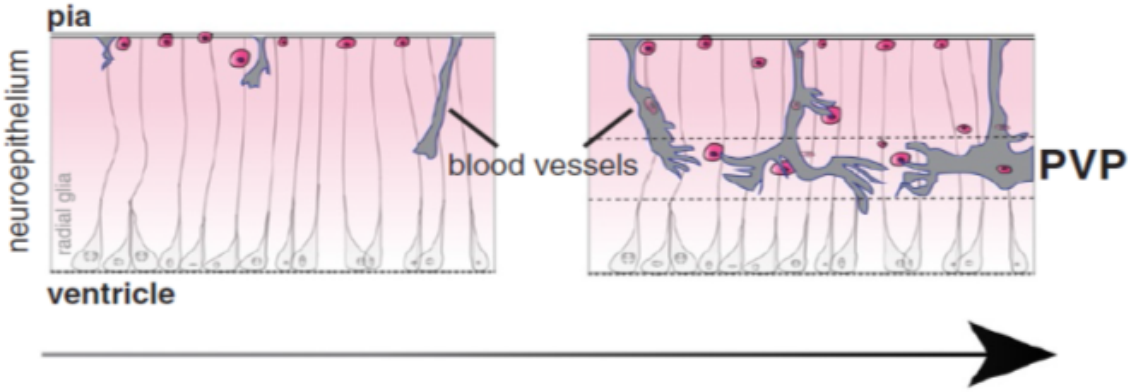
# Neural model 2.0: Perineural Vascular Plexus




**Key Players in this process:**

- NPCs, radial glia and neurons
- Endothelial cells
- Pericytes
- Microglia

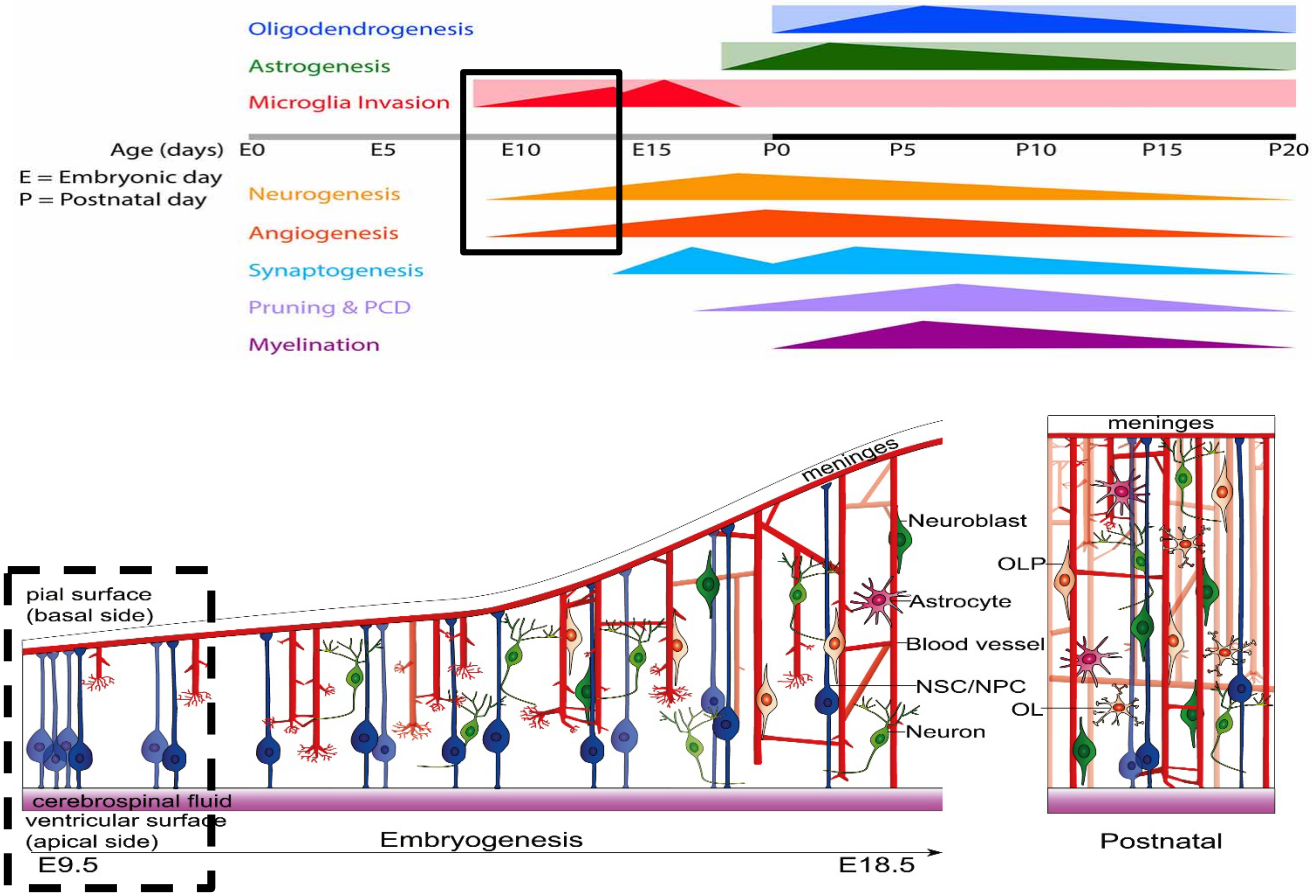



Coultas *et al* Nature 2015

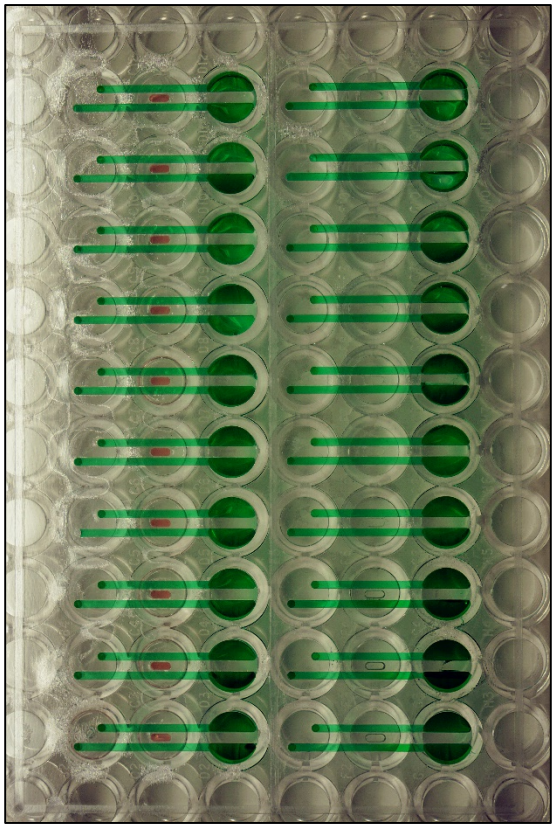
Reemst et al 2016 Frontiers in Human Neuroscience

# Neural model 2.0: Perineural Vascular Plexus




Adapted from Reemst *et al.* 2016 Front. Hum. Neurosci.; Paredes et al. 2018, Cell

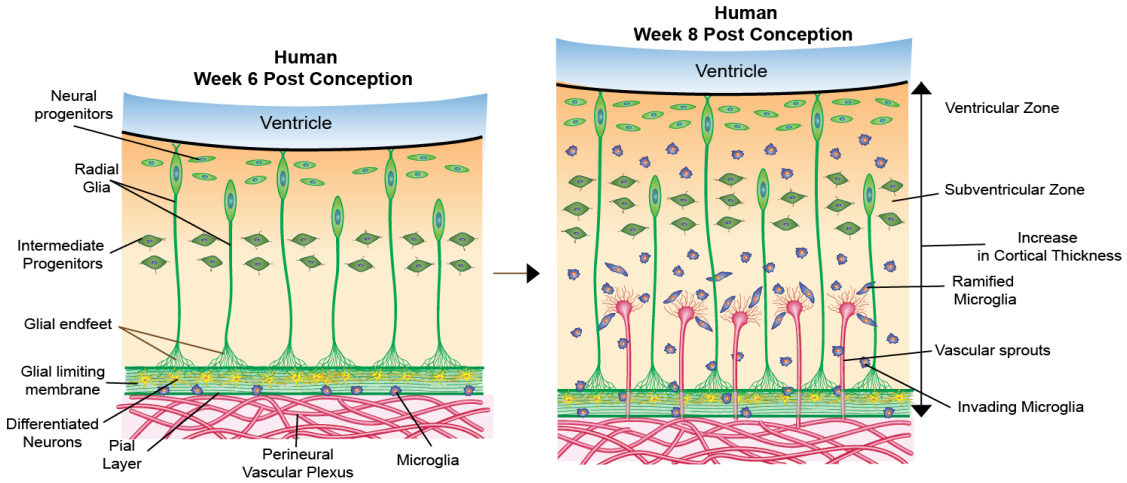
# Neural model 2.0: Perineural Vascular Plexus

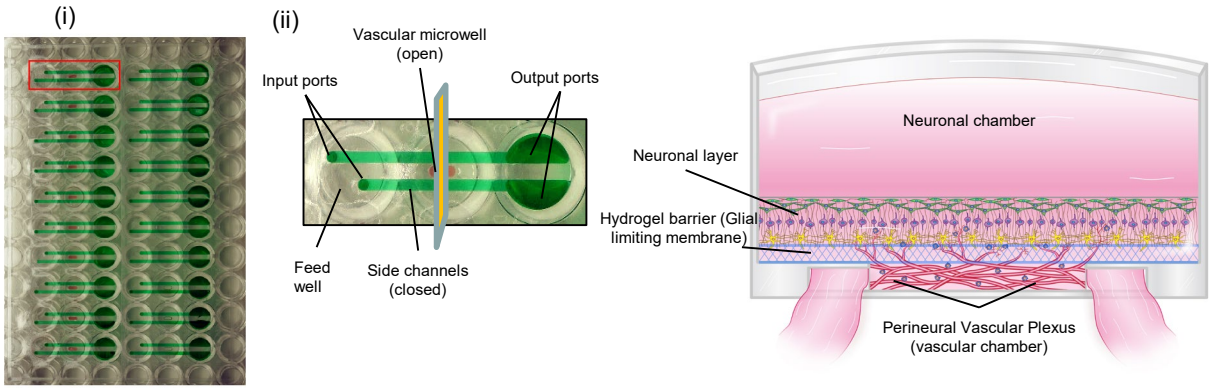


- Pumpless, tubeless
- 96 well format
- Short production time
- Optically transparent
- Increased outputs
- Closed format for vascularization
- Open format for organoid assembly
- Low media and cell volumes

UW: David Beebe, Brian Johnson

# Neural model 2.0: Perineural Vascular Plexus



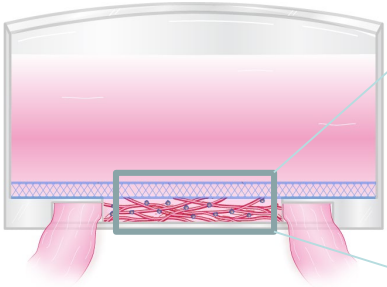



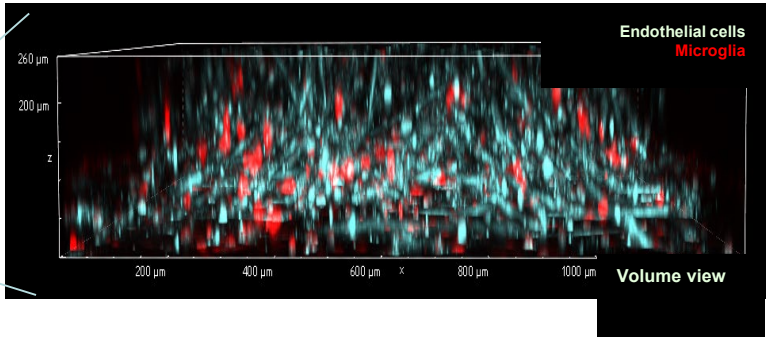

**20 Device Microfluidics Plate (96 well format)**

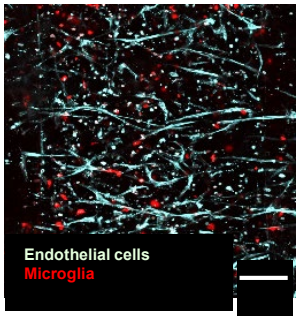
**Cross-Section of 1/20 Device**

# Neural model 2.0: Perineural Vascular Plexus

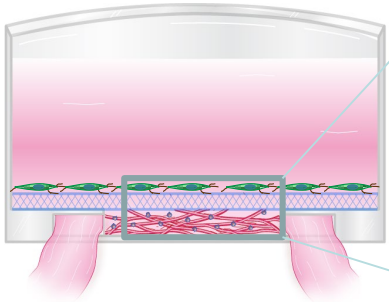
Day 5:

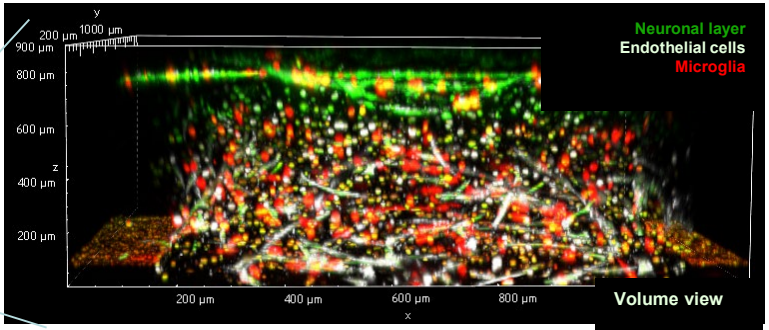


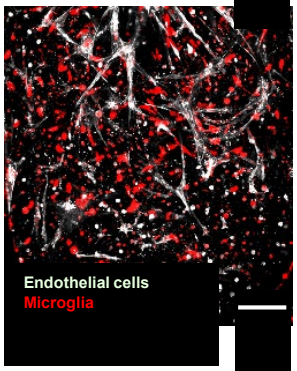


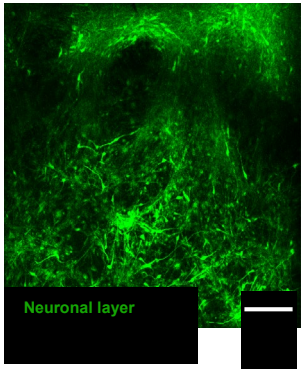




Day 14:

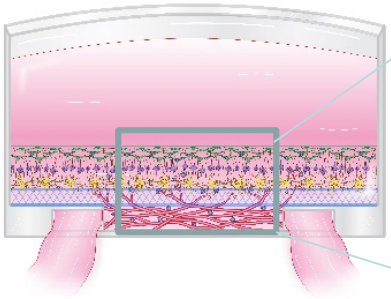


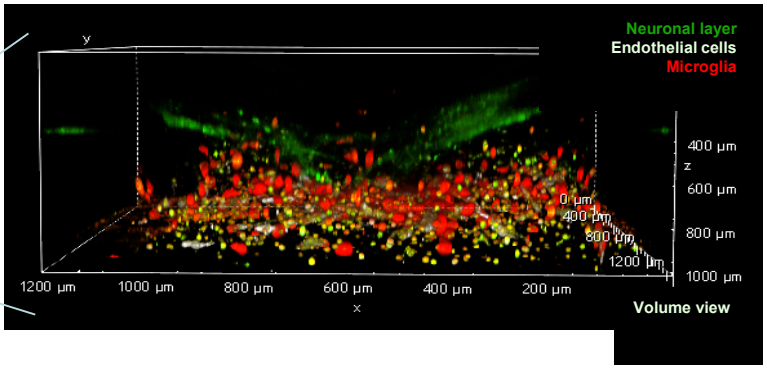


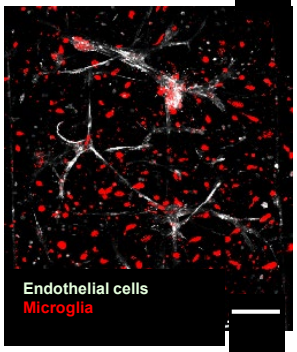



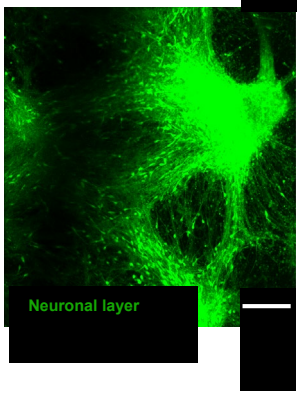




Day 21:

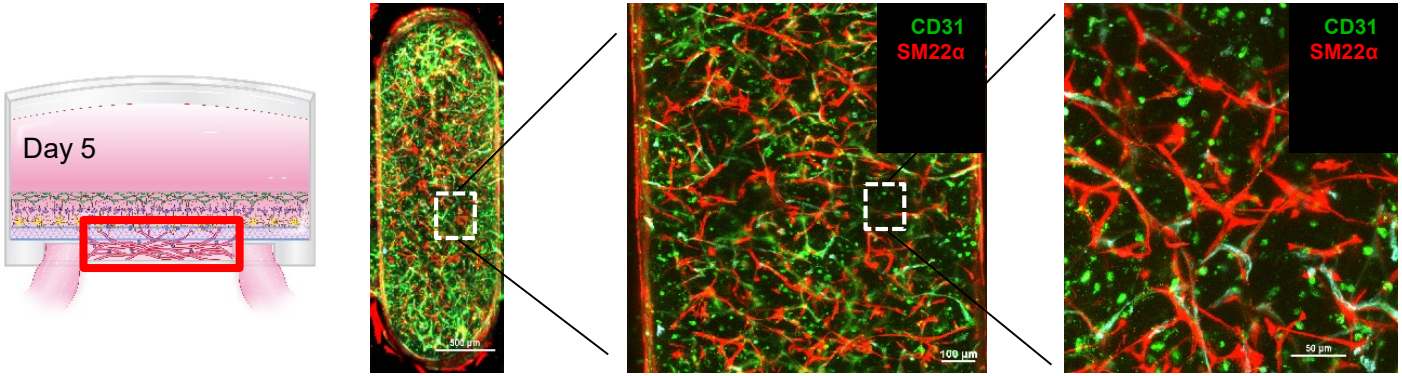




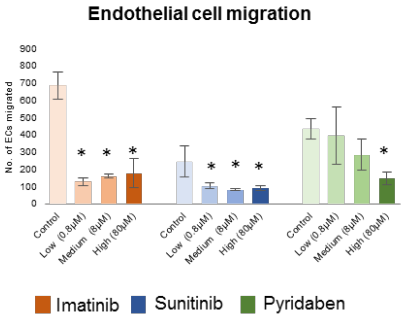



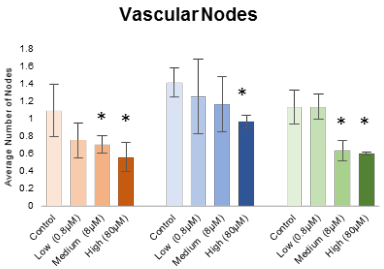
# Neural model 2.0: Perineural Vascular Plexus (VDCs)

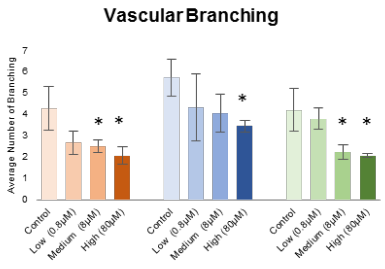


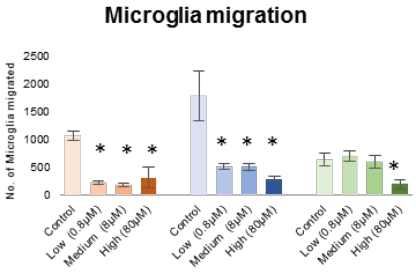

*Primary toxin effects*

*Secondary effects*

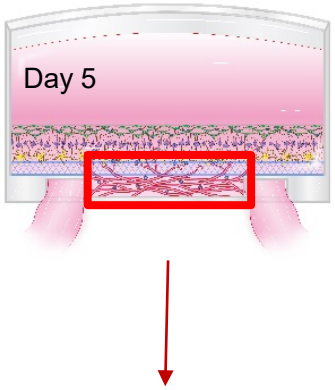


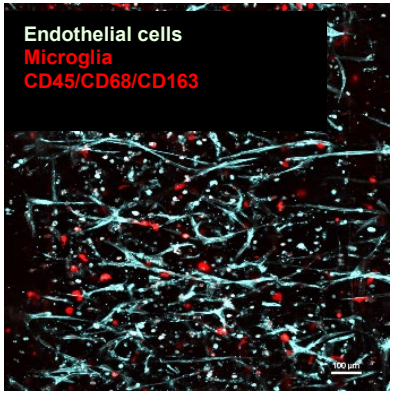



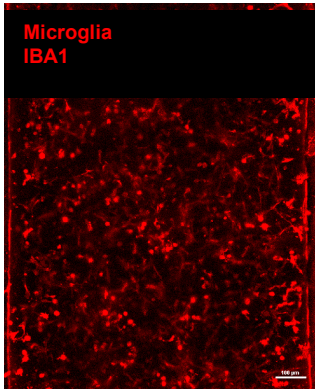



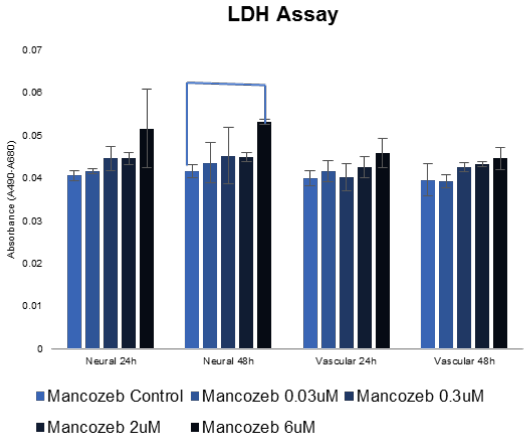
# Neural model 2.0: Perineural Vascular Plexus (Mancozeb)

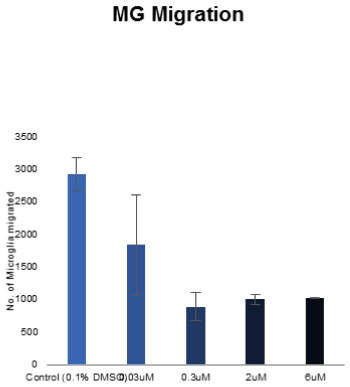


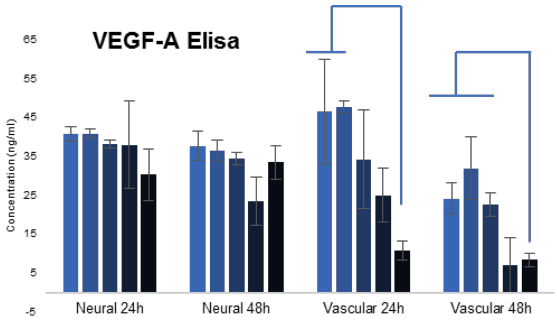



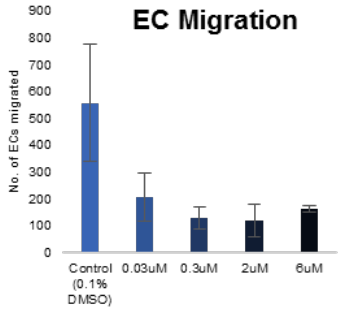

*Primary toxin effects*



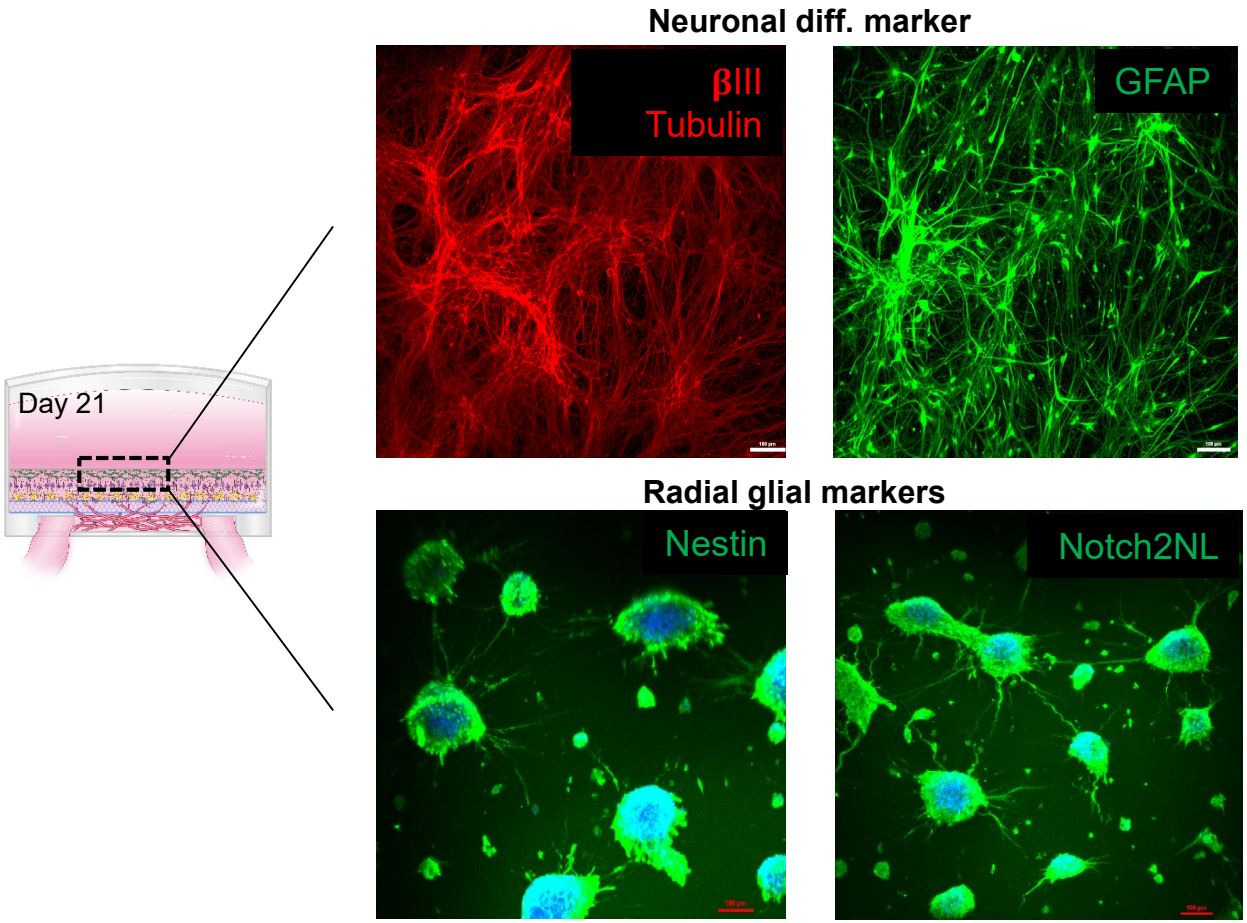




*Secondary effects*

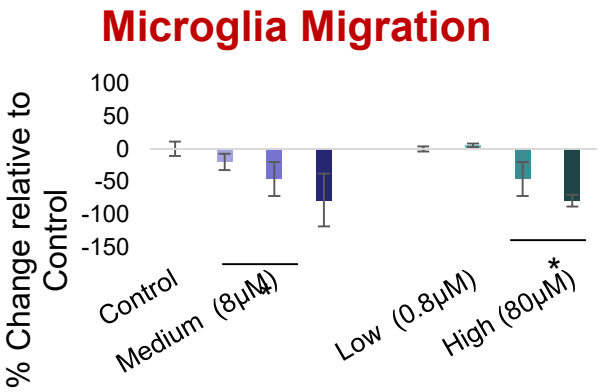


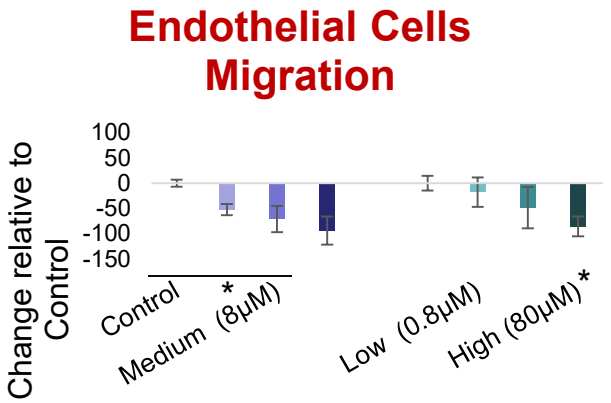



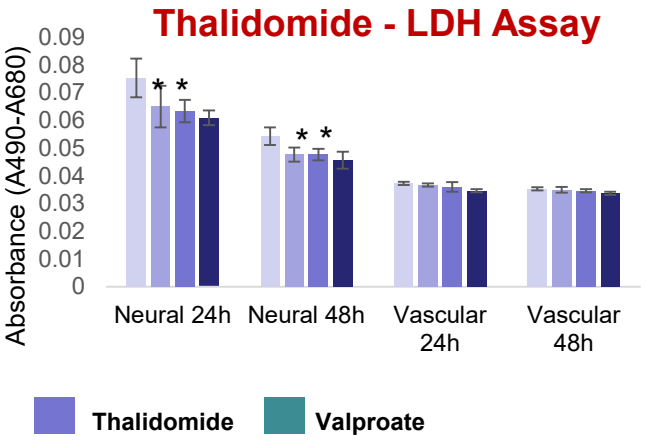
# Neural model 2.0: Perineural Vascular Plexus

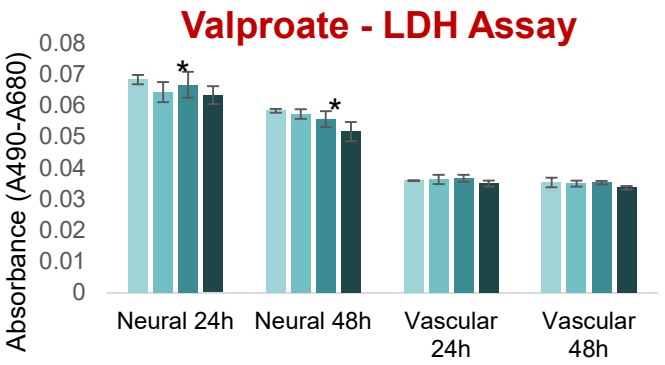


# Neural model 2.0: Perineural Vascular Plexus (teratogens)

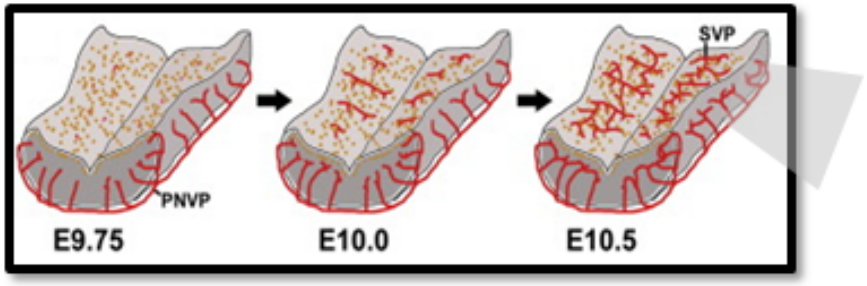


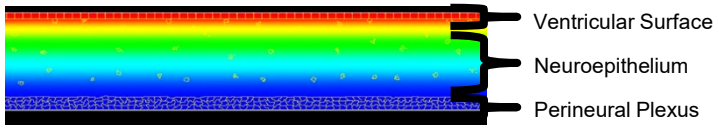



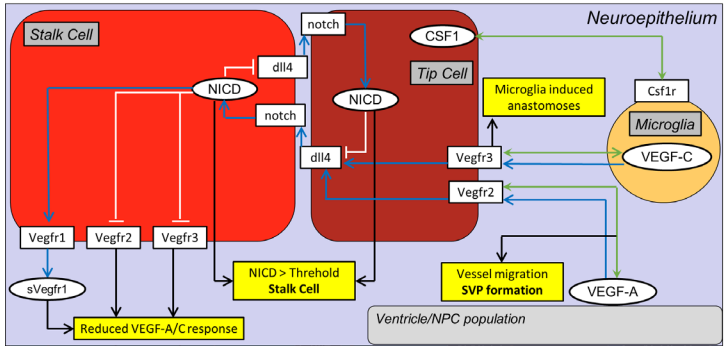



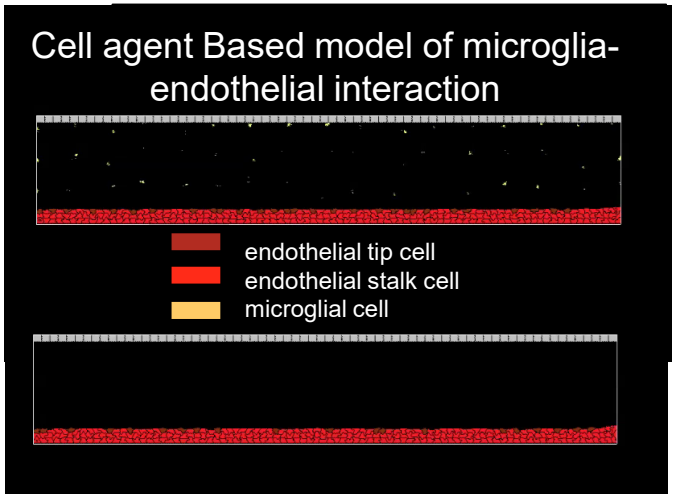
# Neural model 2.0: Perineural Vascular Plexus (cell agent based modeling)




*VEGF-A gradient*: NPCs in the subventricular zone

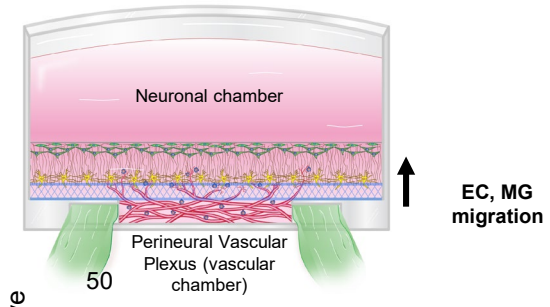


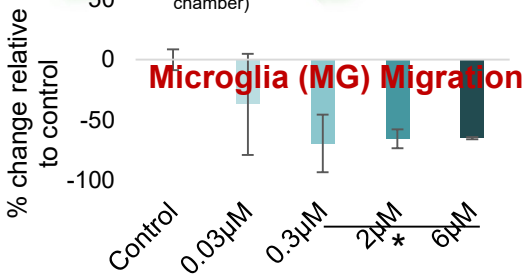



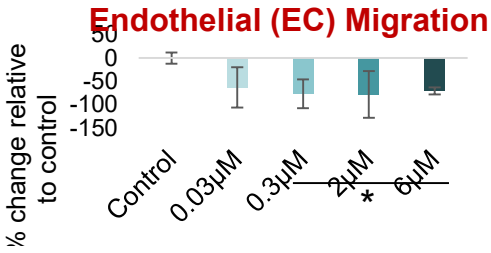



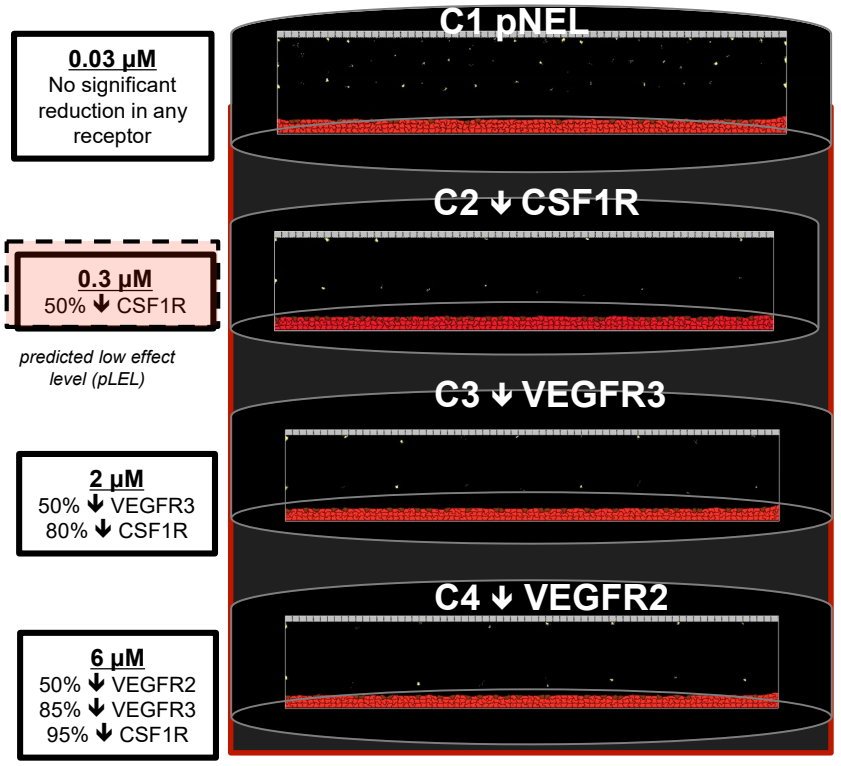

**K. Saili, T. Zurlinden, T. Knudsen, NCCT/ORD/EPA**

# Neural model 2.0: Perineural Vascular Plexus (cell agent based modeling)



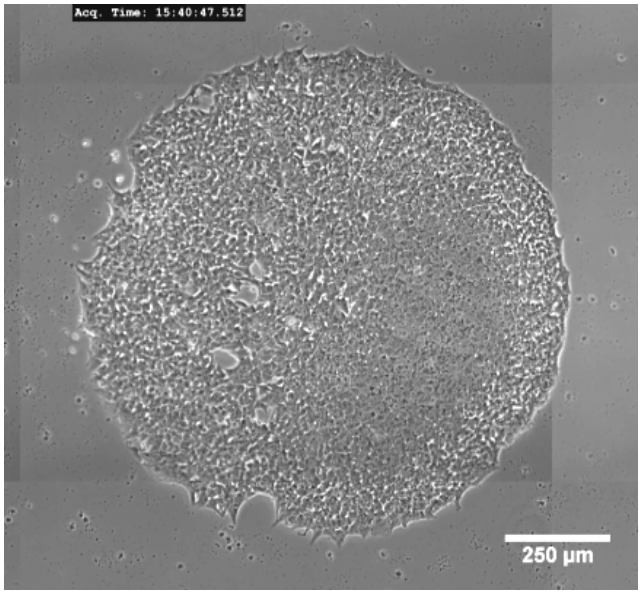



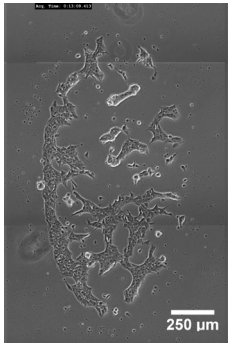



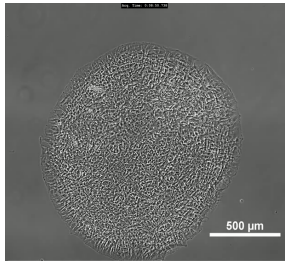



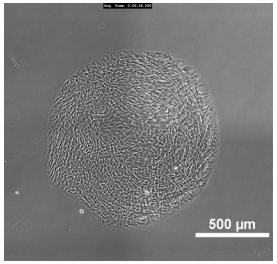

K. Saili T. Zurlinden, T. Knudsen, NCCT/ORD/EPA, G. Kaushik UW Madison

# Neural model 3.0: Human Brain Organoid

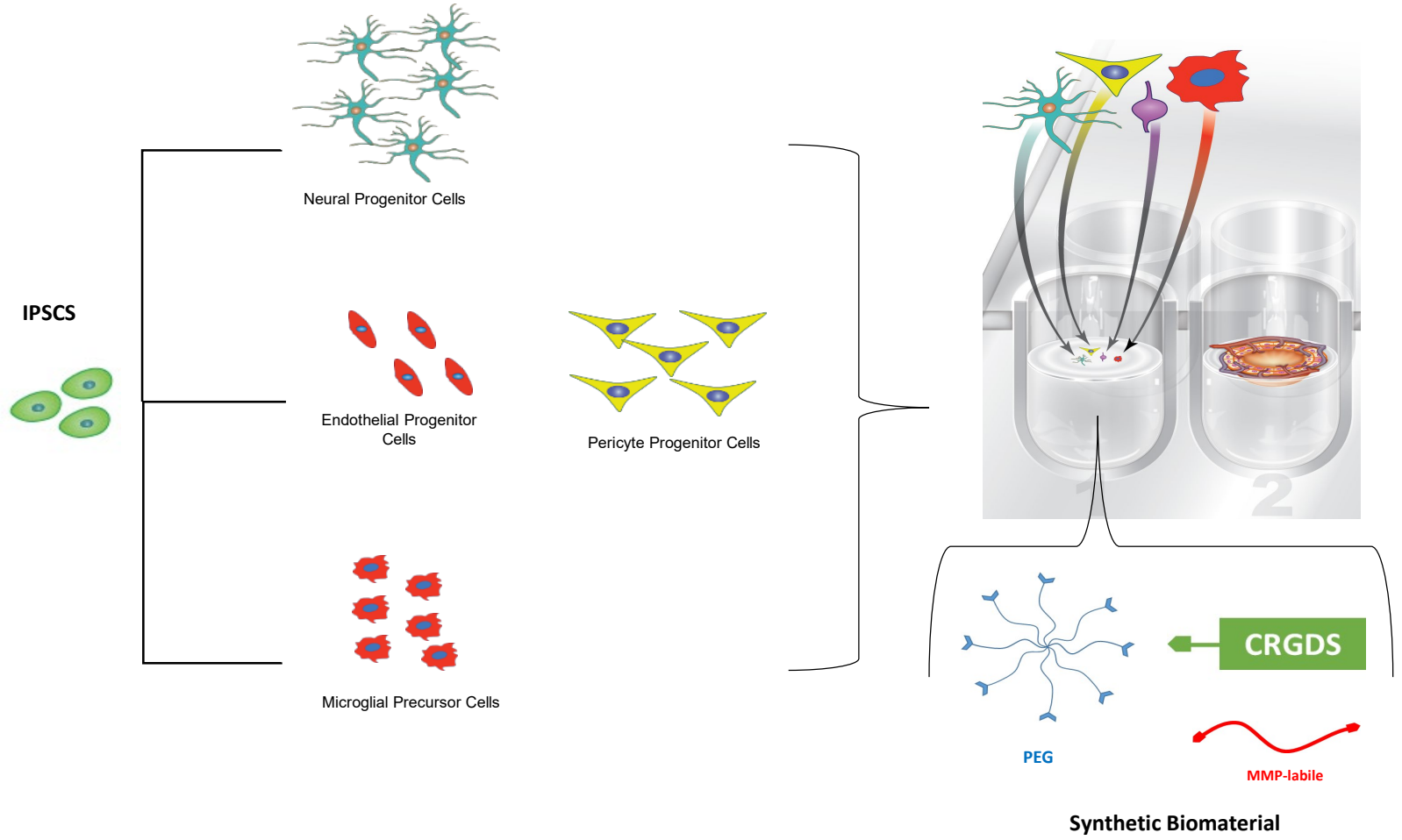


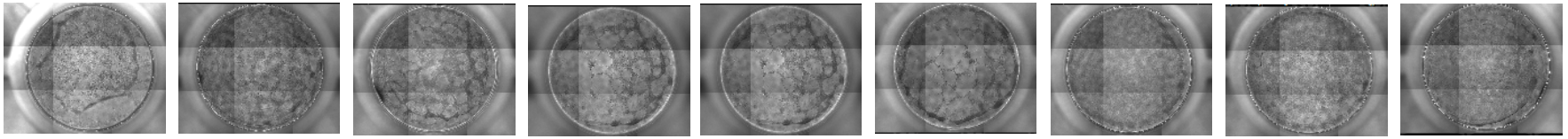



# Neural model 3.0: Human Brain Organoid

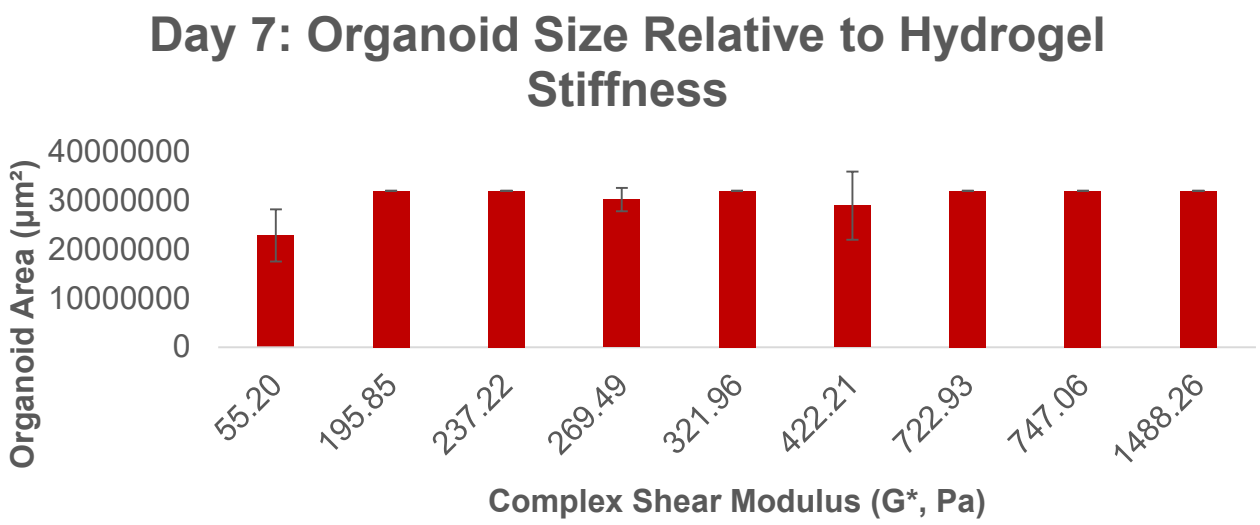


# Neural model 3.0: Human Brain Organoid

Increasing complex shear modulus (G*) – increasing hydrogel stiffness

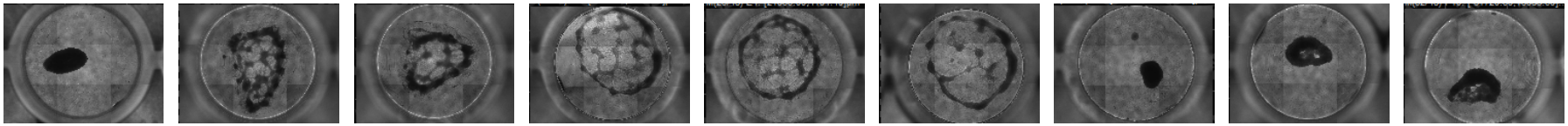


55 Pa | 195 Pa | 237 Pa | 269 Pa | 321 Pa | 422 Pa | 722 Pa | 747 Pa | 1488 Pa

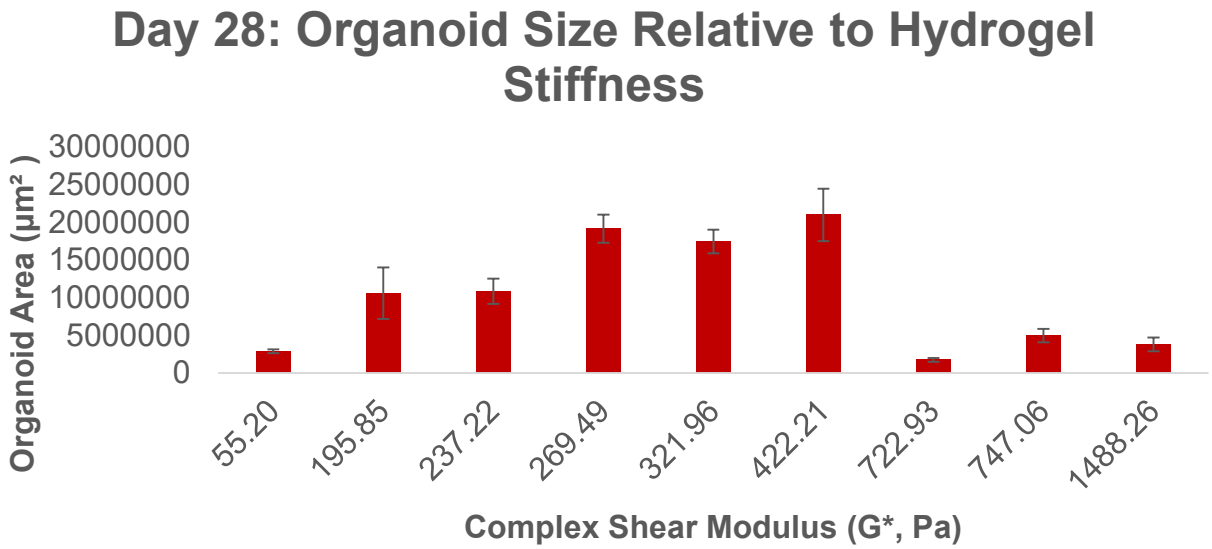


# Neural model 3.0: Human Brain Organoid

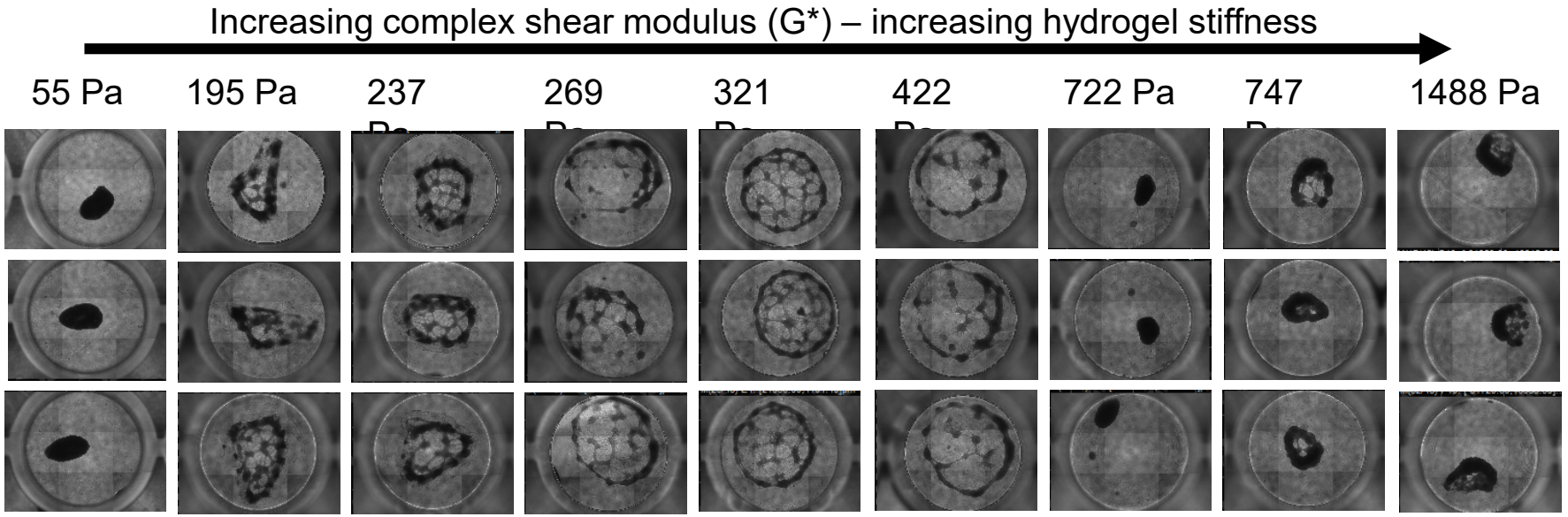
Increasing complex shear modulus (G*) – increasing hydrogel stiffness



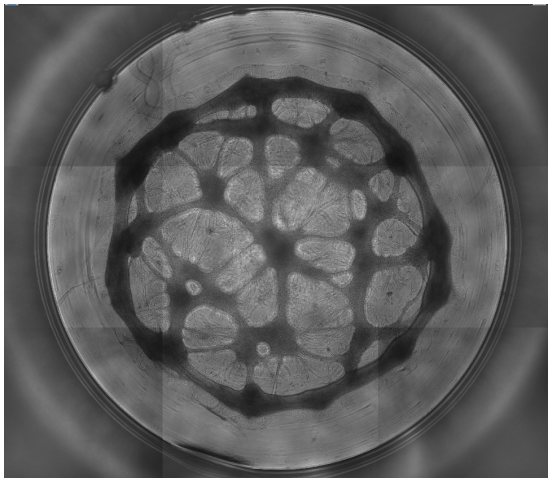
55 Pa | 195 Pa | 237 Pa | 269 Pa | 321 Pa | 422 Pa | 722 Pa | 747 Pa | 1488 Pa

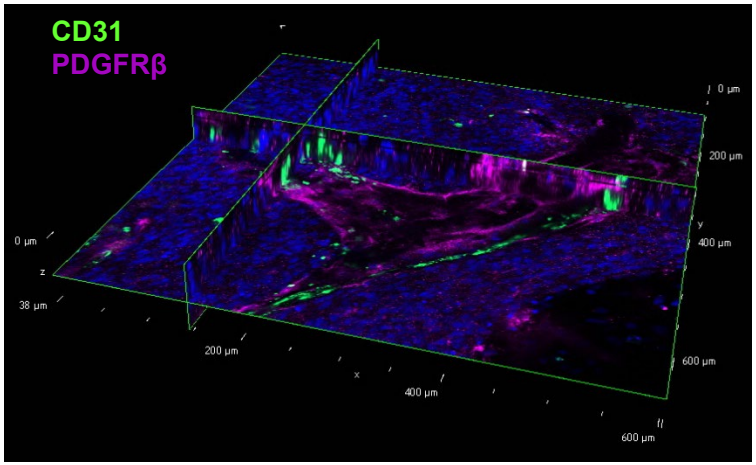


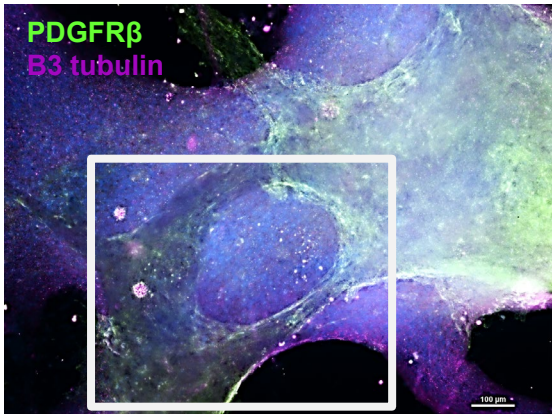
# Neural model 3.0: Human Brain Organoid

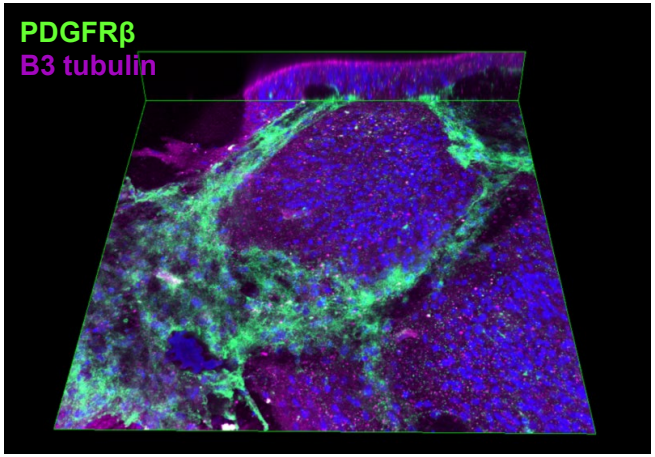


# Neural model 3.0: Human Brain Organoid



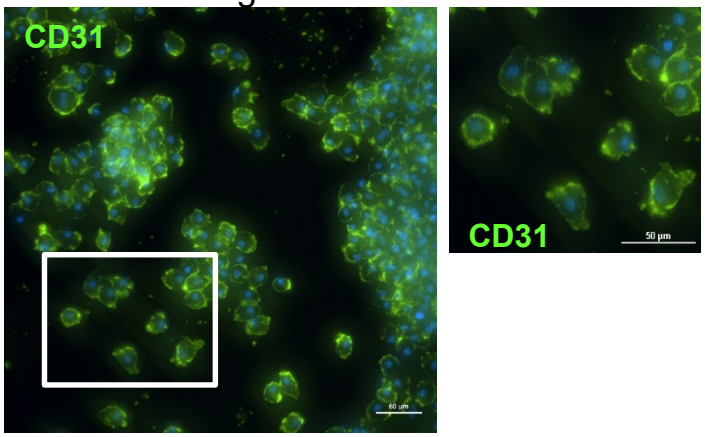


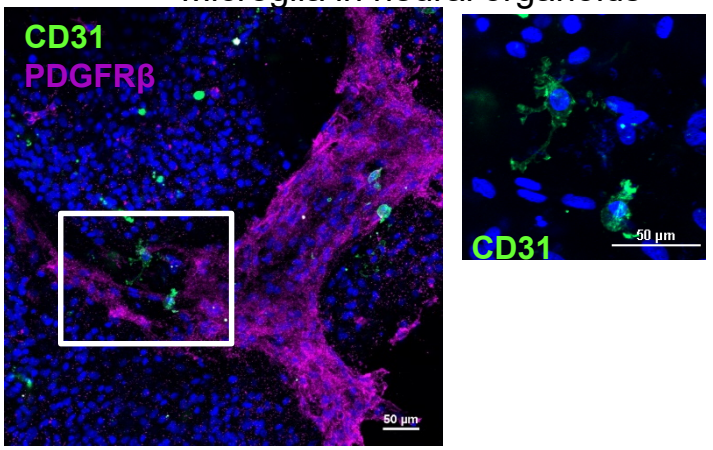



# Neural model 3.0: Human Brain Organoid

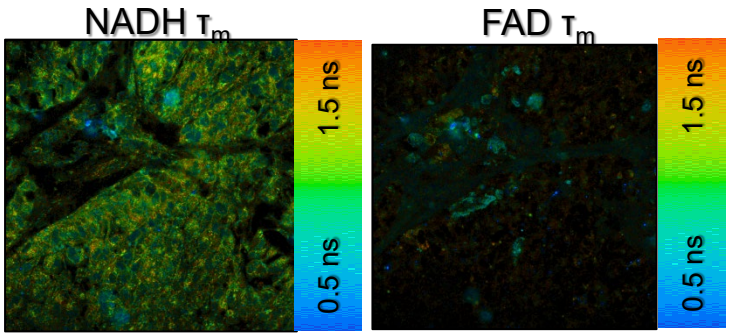
Microglia in culture

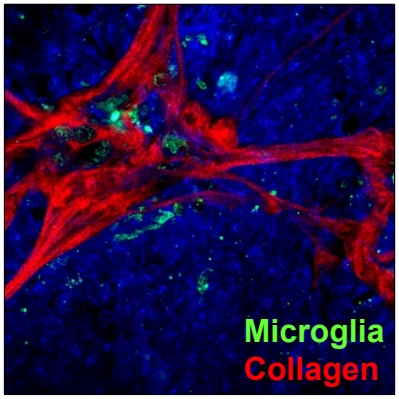



Microglia in neural organoids

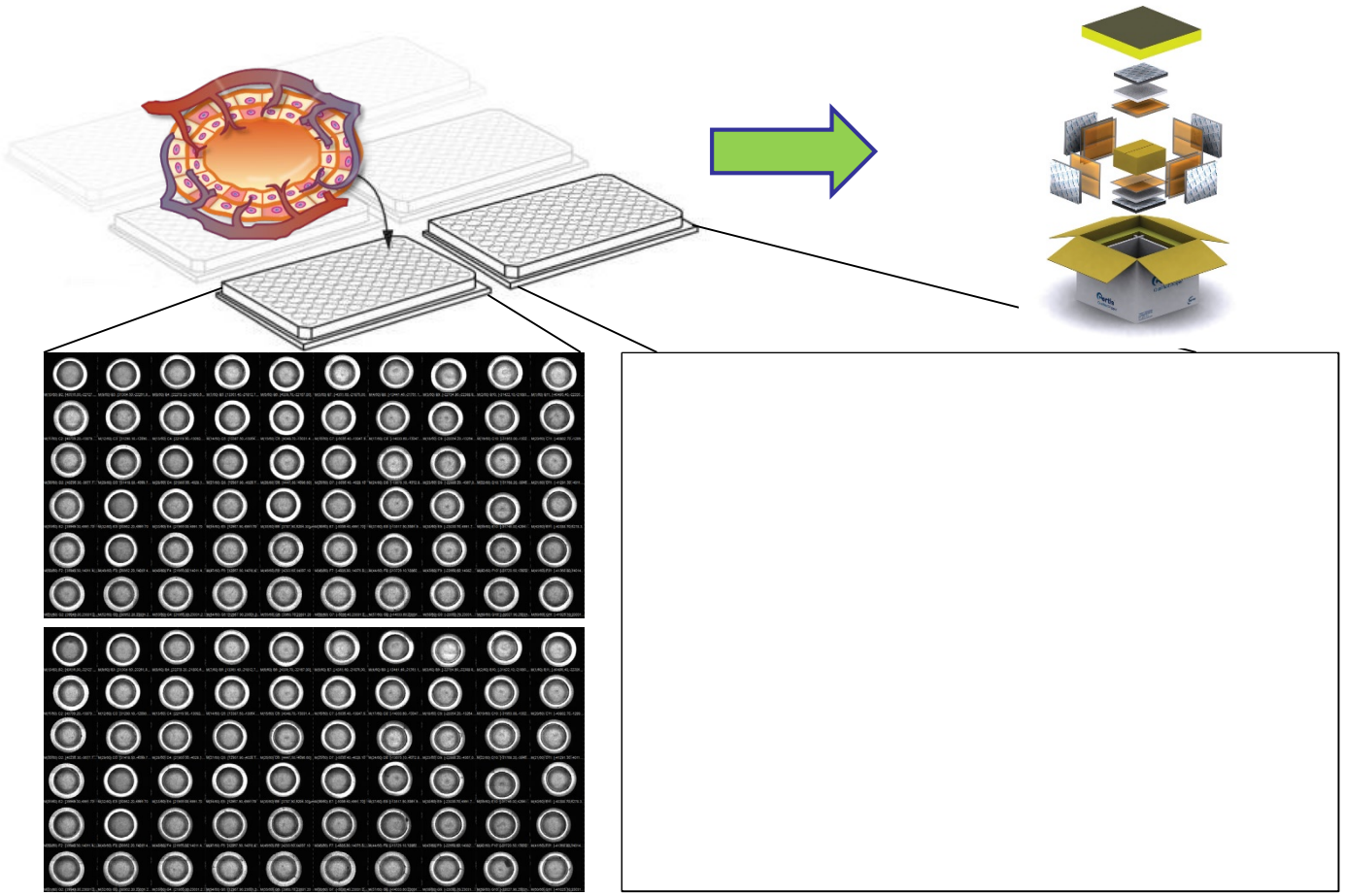



Metabolic Imaging of Microglia in Organoids



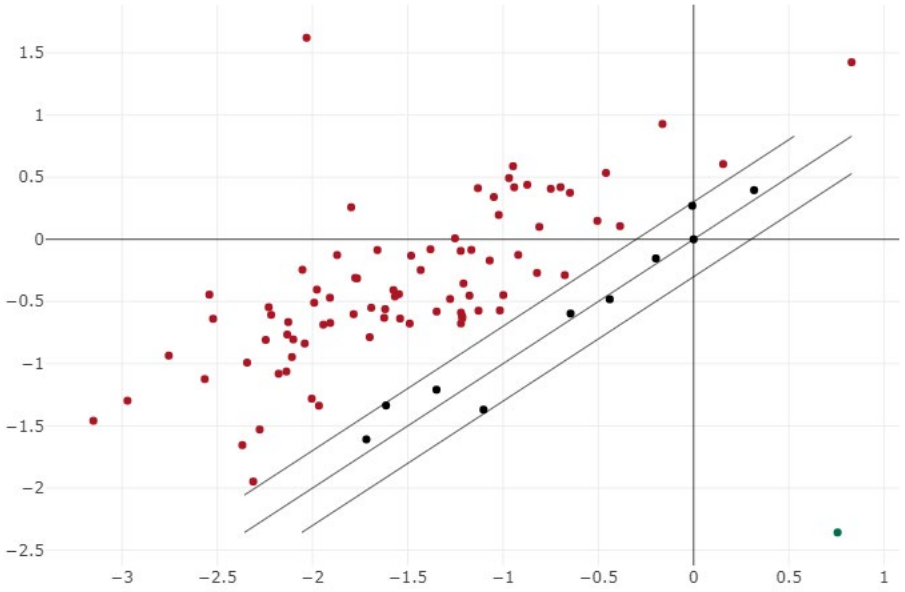



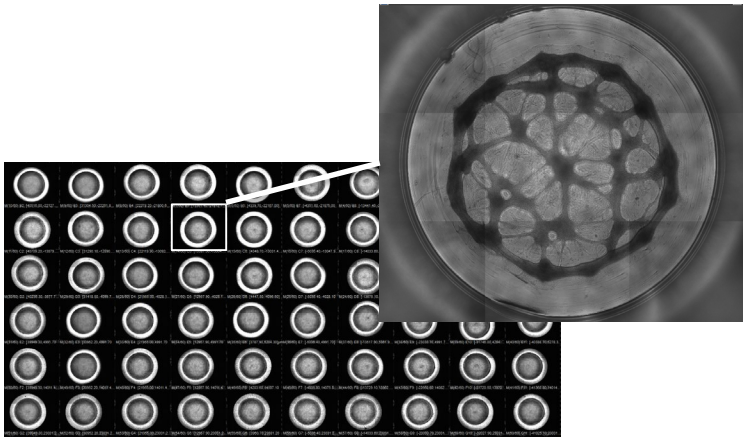
# Neural model 3.0: Human Brain Organoid



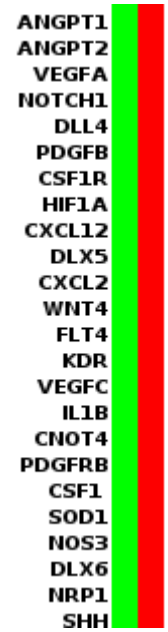
10 Plates, 960 Organoids, Testing of FDA approved Drugs and Neurotoxins at Three Doses – Cmax, 10 x Cmax, 100 x Cmax

# Neural model 3.0: Human Brain Organoid



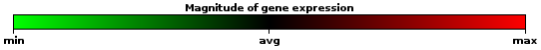




Neural

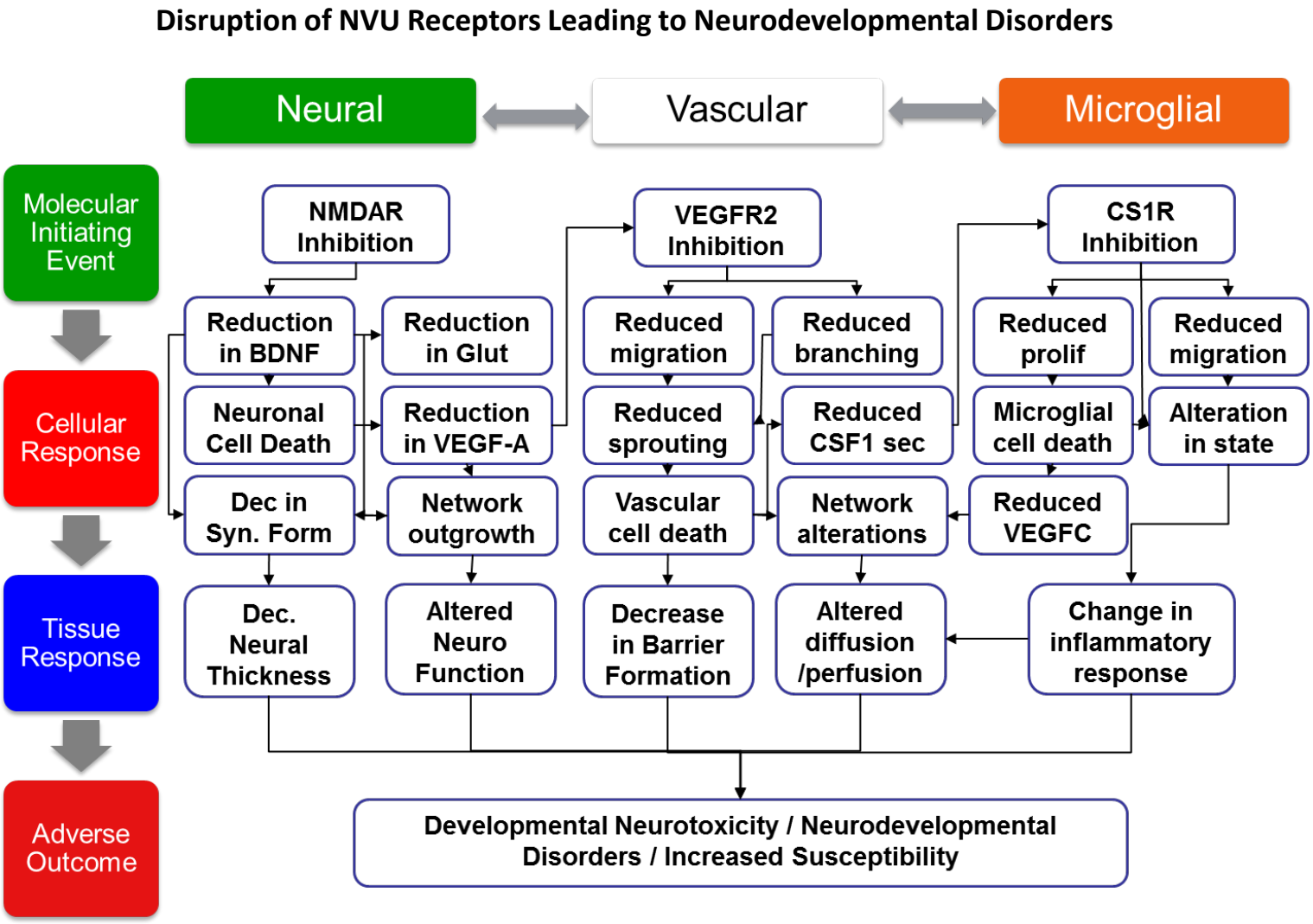



Neurovascular


Inflammatory



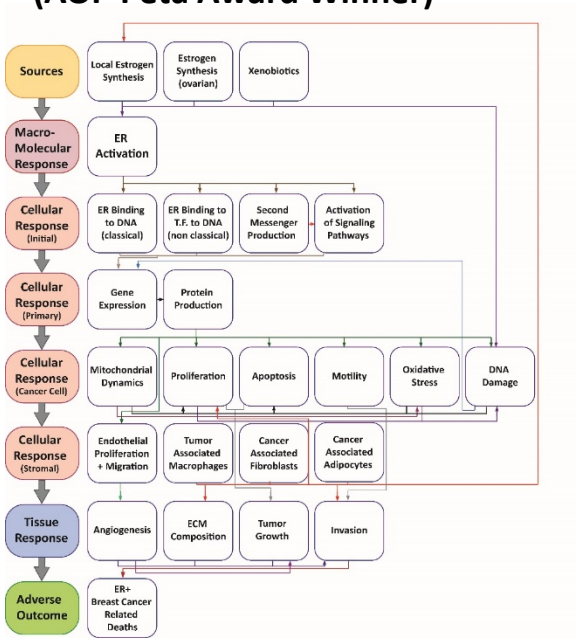
# DEVELOP AOPs in order to focus on specific important outcomes



# DEVELOP AOPs in order to focus on specific important outcomes

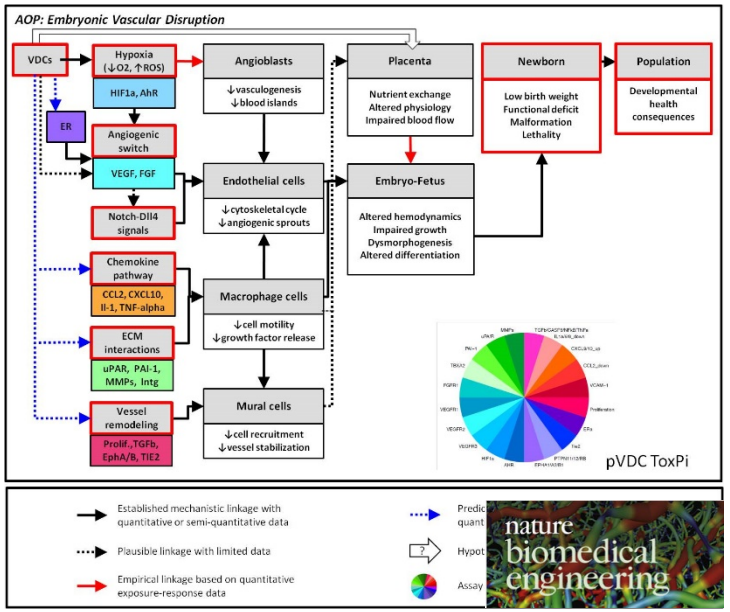
## Estrogen Receptor Activation Leading to Breast Cancer (AOP Peta Award Winner)





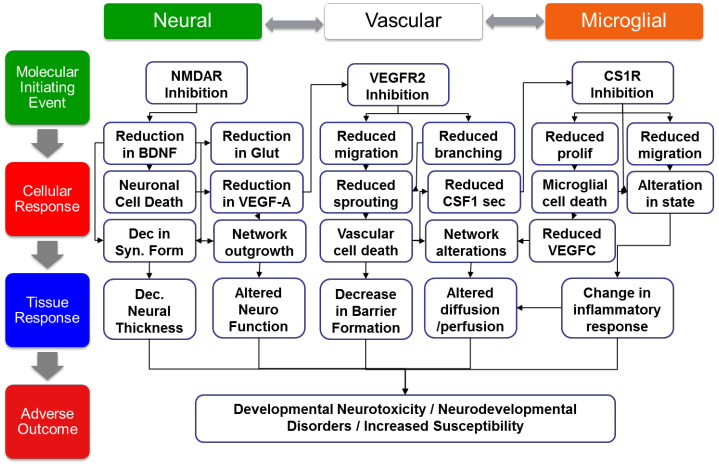

https://aopwiki.org/aops/200

## Disruption of VEGFR Signaling Leading to Developmental Defects

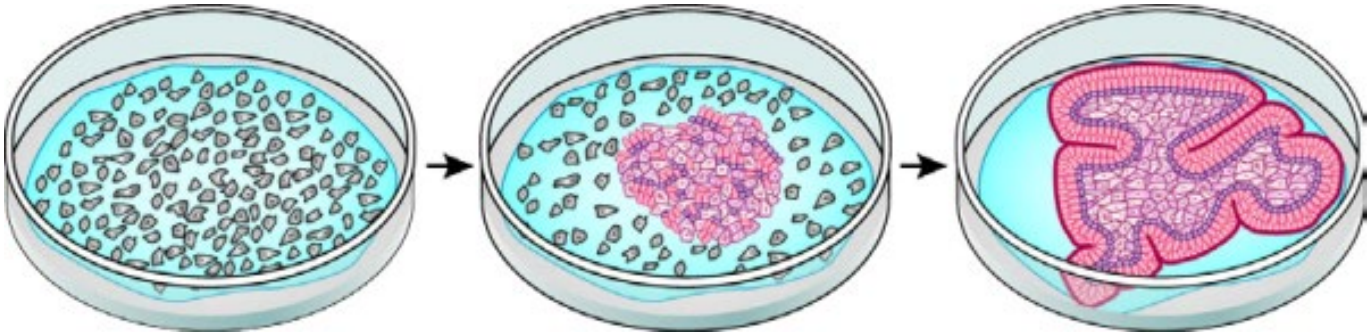




https://aopwiki.org/aops/43

## Disruption of NVU Receptors Leading to Neurodevelopmental Disorders


# LEVERAGE the mindset of industry to improve the science

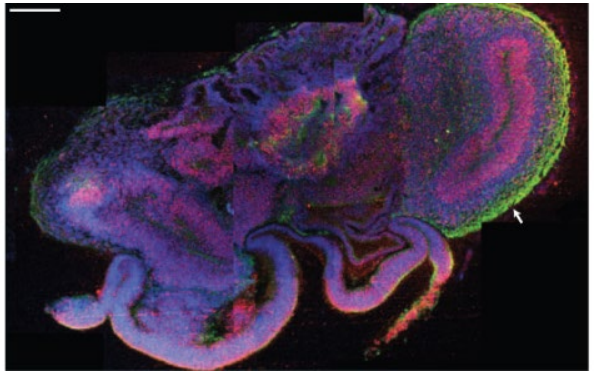


***Nature Methods*** 2014 – News (Natalie DeSouza)

**Optic cup**

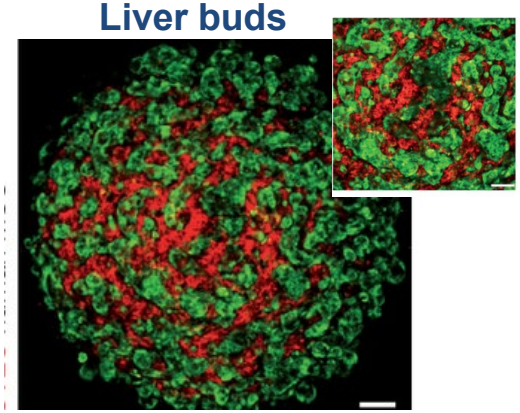

Eiraku et al. ***Nature,*** 2011

**"Brain organoid"**



Lancaster ***Nature*** 2013

**Liver buds**



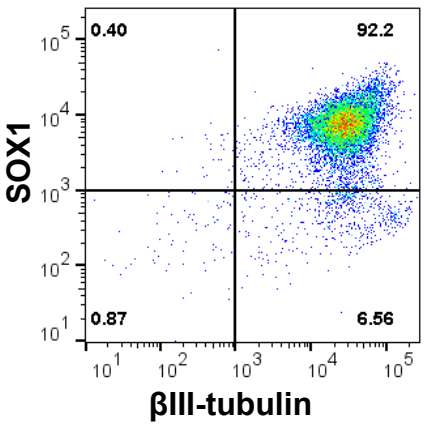
Takebe et al., ***Nature*** 2014

- **Challenge – user independent reproducibility**
- **Challenge – generating robust quantitative data**
- **Challenge – transferrability to pharma & toxicology**

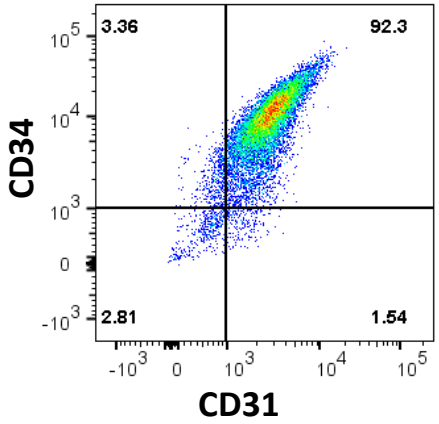
# PARTNER in areas of complementary interest/expertise

Cellular Dynamics international

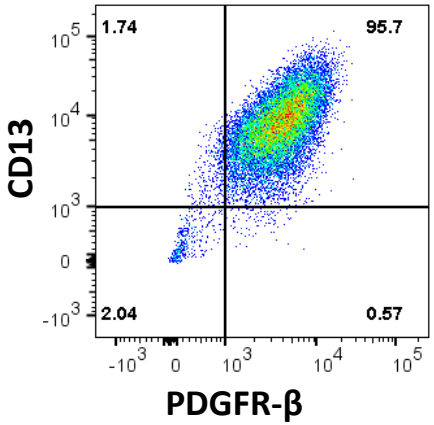
**Neural Progenitor Cells**



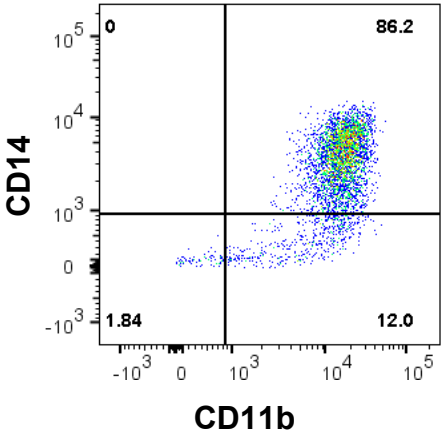

**Endothelial Cells**




**Mesendodermal Cells**



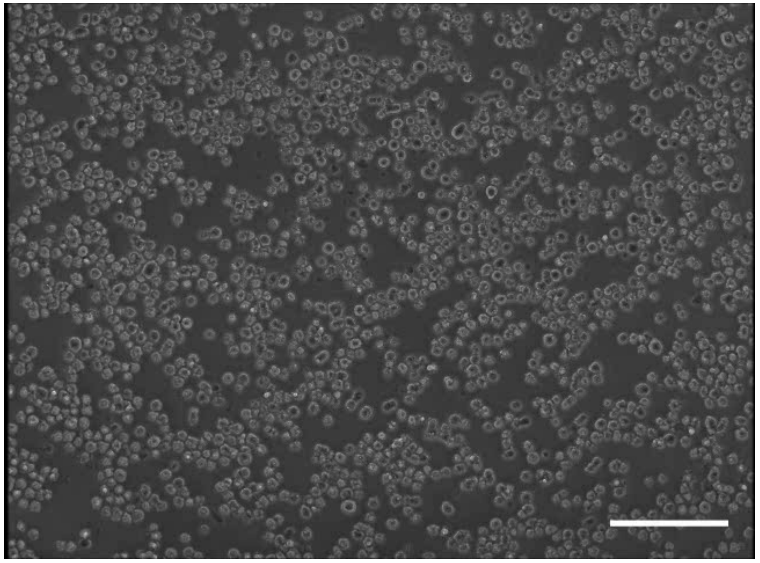

**Microglia Precursors**




*> 90 % purity for all cell types*

- All components derived from human ES and iPS cells in defined conditions
- Purity of cell components verified by FACS
- **We develop → they may license**
- **They develop → we demonstrate utility**

# TRANSFER new technologies for broad dissemination



ORIGINAL ARTICLE

## High-Content Assay Multiplexing for Vascular Toxicity Screening in Induced Pluripotent Stem Cell-Derived Endothelial Cells and Human Umbilical Vein Endothelial Cells

Yasuhiro Iwata,[1] William D. Klaren,[1] Connie S. Lebakken,[2] Fabian A. Grimm,[1] and Ivan Rusyn[1]

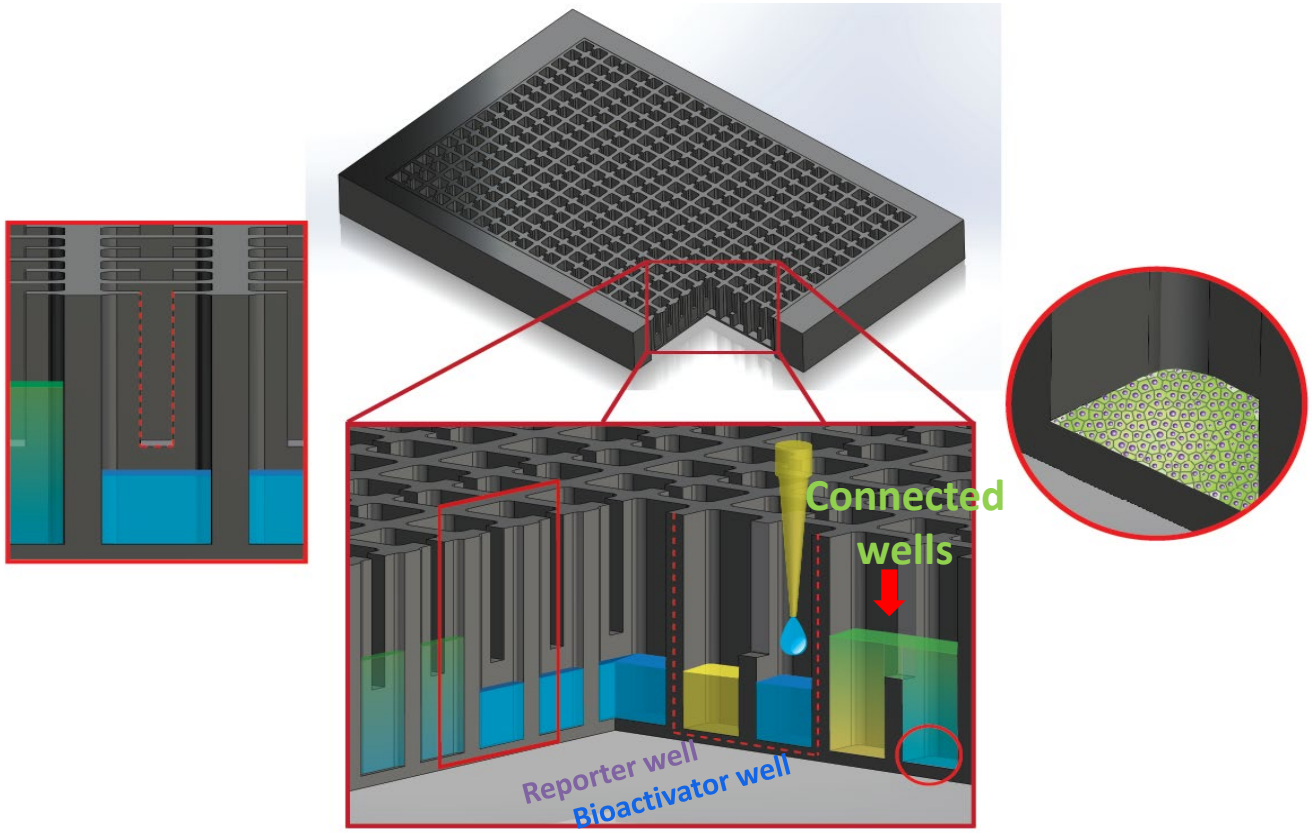
Keywords: endothelial cells, high-throughput, angiogenesis, iPSC-derived cells

## Assessment of Drug-Induced Toxicity Biomarkers in the Brain Microphysiological System (MPS) Using Targeted and Untargeted Molecular Profiling

Sara G. Mina[1†], Begum Alaybeyoglu[1†], William L. Murphy[2], James A. Thomson[3,4], Cynthia L. Stokes[5] and Murat Cirit[1*‡]

# TRANSFER new technologies for broad dissemination

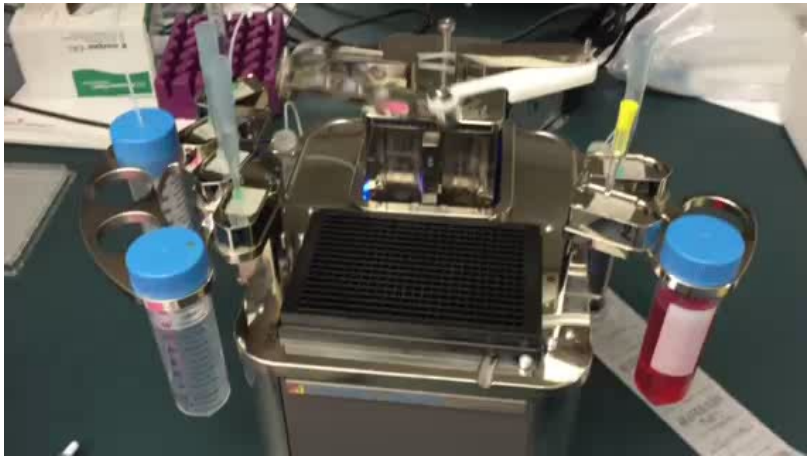
## MICRO-MT High-throughput co-culture




TRANSFORM TOX TESTING CHALLENGE
INNOVATING FOR METABOLISM

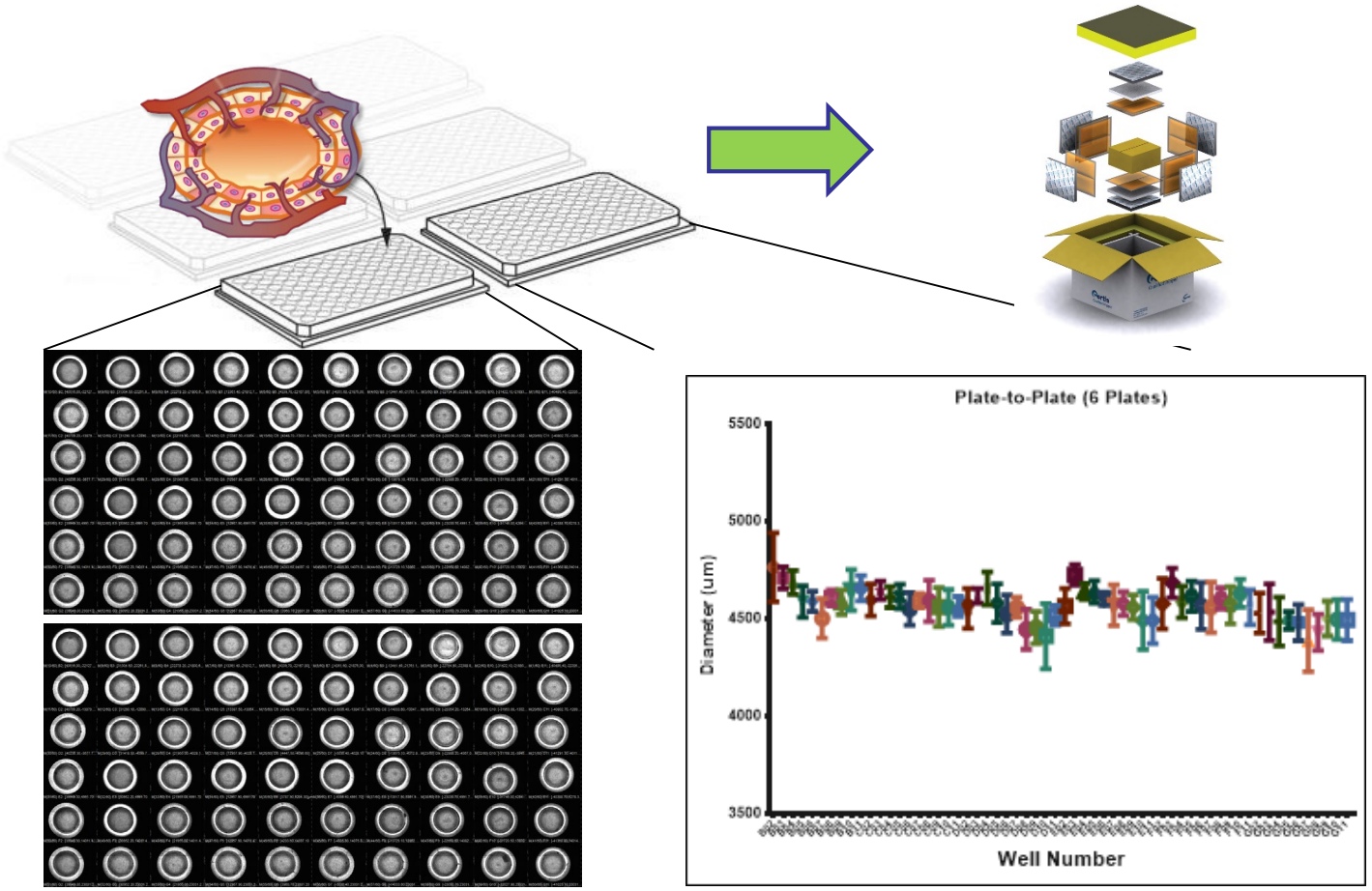
Stage 1 NIH EPA Transforming Tox Challenge Awarded
Stage 2 NIH EPA Transforming Tox Challenge Awarded

# EMPHASIZE testing scenarios that are likely to be of broad end user interest



***Transferrable, Scalable, Adaptable***

# EMPHASIZE testing scenarios that are likely to be of broad end user interest




10 Plates, 960 Organoids, Testing of FDA approved Drugs and Neurotoxins at Three Doses – Cmax, 10 x Cmax, 100 x Cmax

# Are we there yet? What will it take for technologies to be broadly used in tox testing?

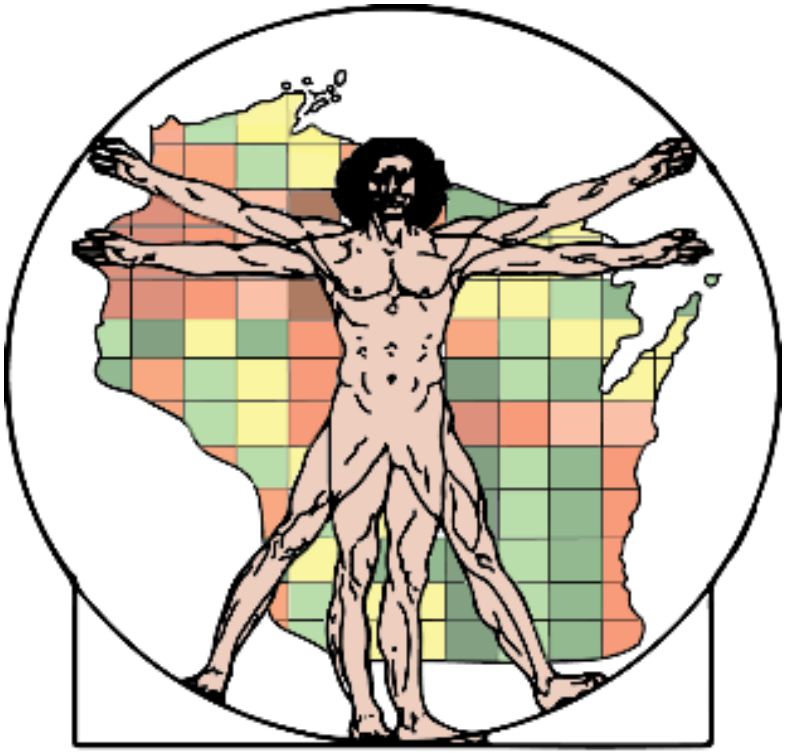
- TEMPLATE pathways from initial technology discovery to broad implementation
  - OECD guidelines? Health and Environmental Sciences Institute (HESI)?
  - iPSC CM – Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative?
- SPECIFIC scenarios that would demonstrate unique physiological relevance
  - A specific perturbation and associated response that uniquely occurs in vivo
  - Specific compound sets that provide opportunity for blinded screening (EPA?)
- UNDERSTAND technical issues that will limit transferrability
  - Use prior industry experience to appreciate pain points
  - Work to gain broad voice of customer (Tox-focused subcommittee of IQ Consortium?)
- USE computational data sets and associated insights to provide scenarios for validation
  - Developmental scenarios that can be modeled in silico and recapitulated in experiment
  - Coalesce experimental data sets that combine distinct biological mechanisms (VTM)
- DEVELOP and use AOPs in order to focus on specific important outcomes
  - Ensure that the most important biological outcomes are readily/robustly quantifiable
  - Build in the appropriate level of complexity, but no more…
  - Leverage other high value applications to develop systems for toxicity testing?

# Driving DISSEMINATION and VALIDATION

***From Previous HMAPs SAC Discussions:***

- "How to best identify unmet needs? What is the best mechanism to source this info and input from Pharma?"
    - "Present systems to broader audience of target users and generate a due diligence checklist with our regulatory and pharmaceutical partners with a focus on scalability, reproducibility, etc…. give feedback on what they want to see (e.g. biomarkers)."
    - "[company] has checklists for liver, kidney, and skin. May have the data for other systems, but not necessarily consolidated."
    - "Need VOC/end user feedback – application and workflow integration should have influence on the design."
- "What general insights can help us to create adoptable approaches/technologies?"
    - "Focus on Fit for purpose vs perfected systems. Evaluate the systems in that context or drive application to that unmet need."

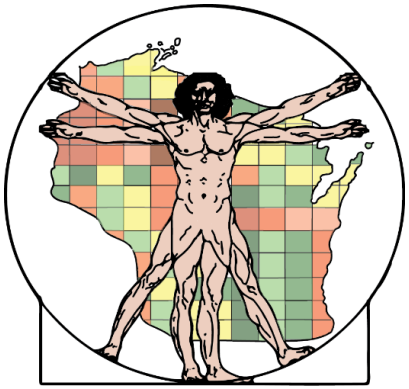
# Derive, Detect, Discover: *Next Generation Human Biology Models*




- *Critical mass of innovative models in HMAPs*
- *Critical mass of key partners from industry*
- *Emergence of new UW-Madison initiatives*
  - *Forward BIO Initiative*
  - *WARF Human Therapeutics Program*
  - *ICTR Office of Therapeutics Discovery*
  - *UW Data Science Institute*
- ***What is the scope of the opportunity?***
- ***What form of UW initiative would be most beneficial?***
- ***What is the most productive way to partner with EPA?***

# Bioinspired Materials Laboratory (http://bioinspired.engr.wisc.edu)

*Collaborators*
James Thomson (Morgridge)
Linda Griffith (MIT)
John Wikswo (Vanderbilt)
Connie Lebakken (Stem Pharm)
David Page (UW)
Ron Stewart (Morgridge)
David Gamm (UW)
David Beebe (UW)
Melissa Skala (Morgridge)
David Mann (FCDI, DMW)
Ivan Rusyn (Texas A&M)
Nader Sheibani (UW)
Randolph Ashton (UW)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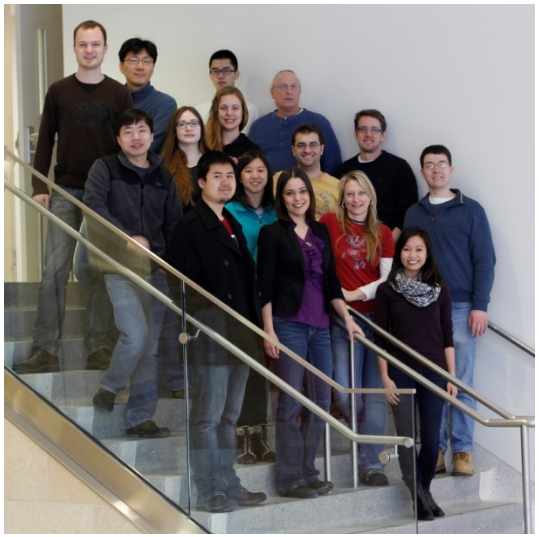
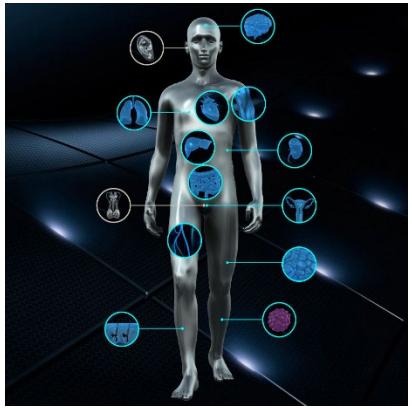
Tremaan Spearman-White
Victoria Harms
Junsu Yun

THE UNIVERSITY of WISCONSIN MADISON



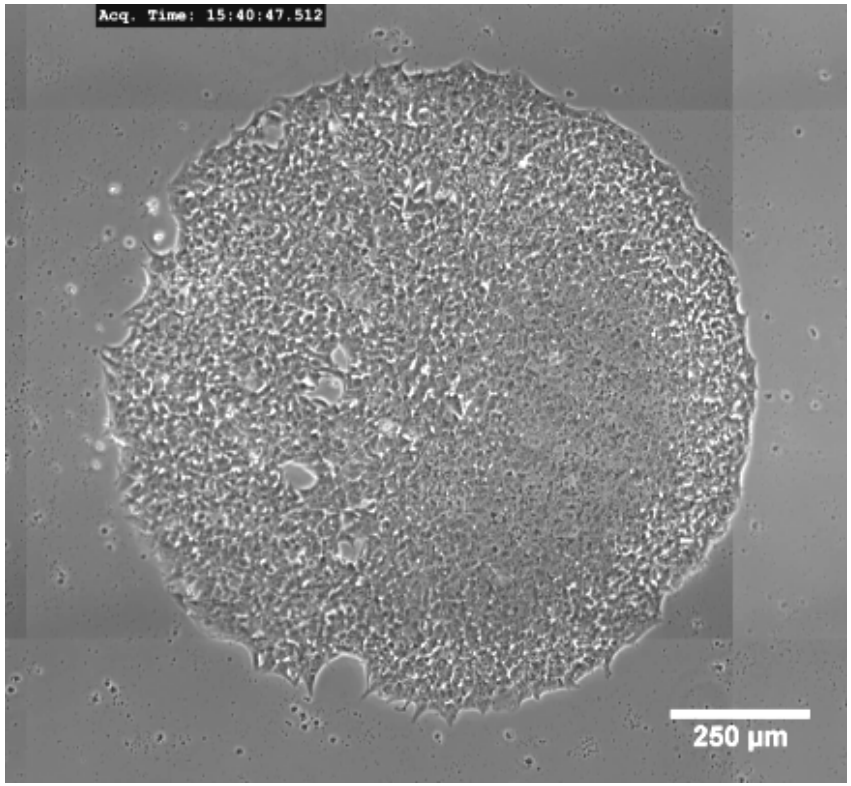

NIH MPS Program

**This research is funded by US EPA STAR Grant #835737**

Stem Pharm

Cellular Dynamics international FUJIFILM Value from Innovation

# Derive, Detect, Discover: *Next Generation Human Biology Models*




- *Appropriate Complexity (but no more)*
- *Reproducibility*
- *Output Detection and Tracking*
- *Interface with Computational Modeling*
- *Transferability/Commercialization*