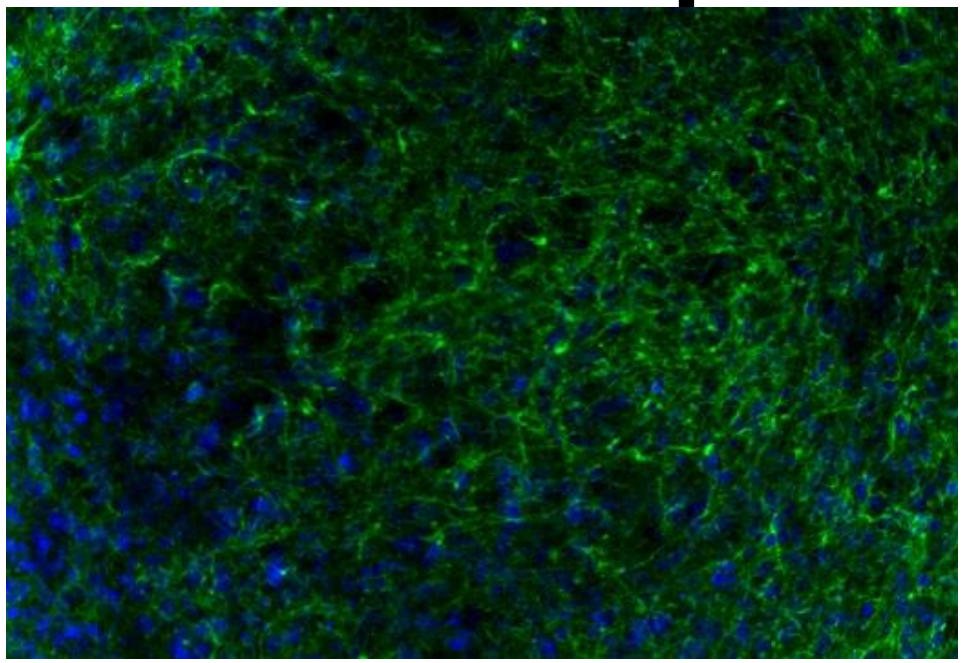
Human Brain Organoids as a Tool for Assessing Neurodevelopmental Toxicity



Gurugowtham (Guru) Ulaganathan

Duke University

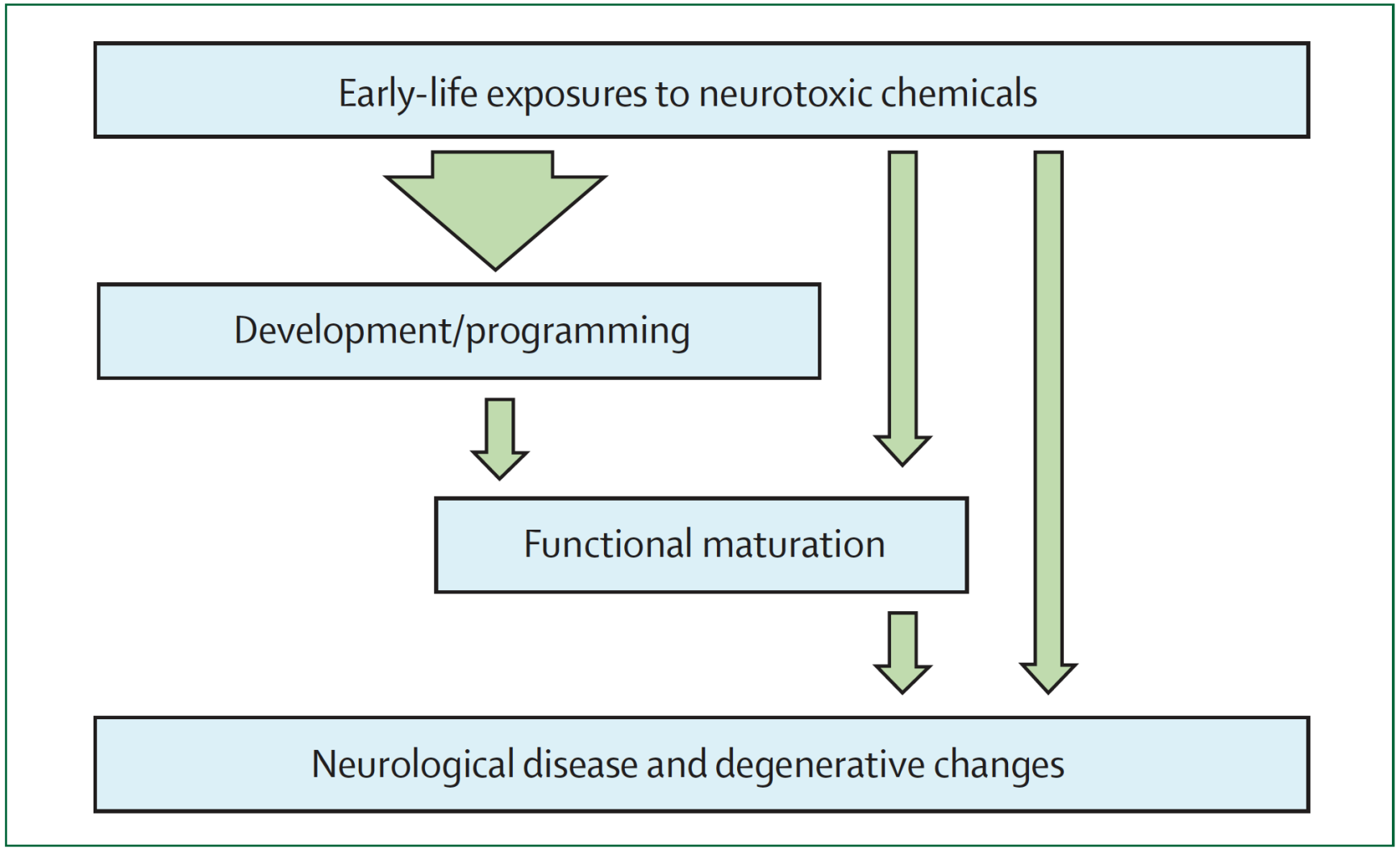
January 21, 2026

Duke | NICHOLAS SCHOOL of the ENVIRONMENT

Duke UNIVERSITY | SUPERFUND Research Center

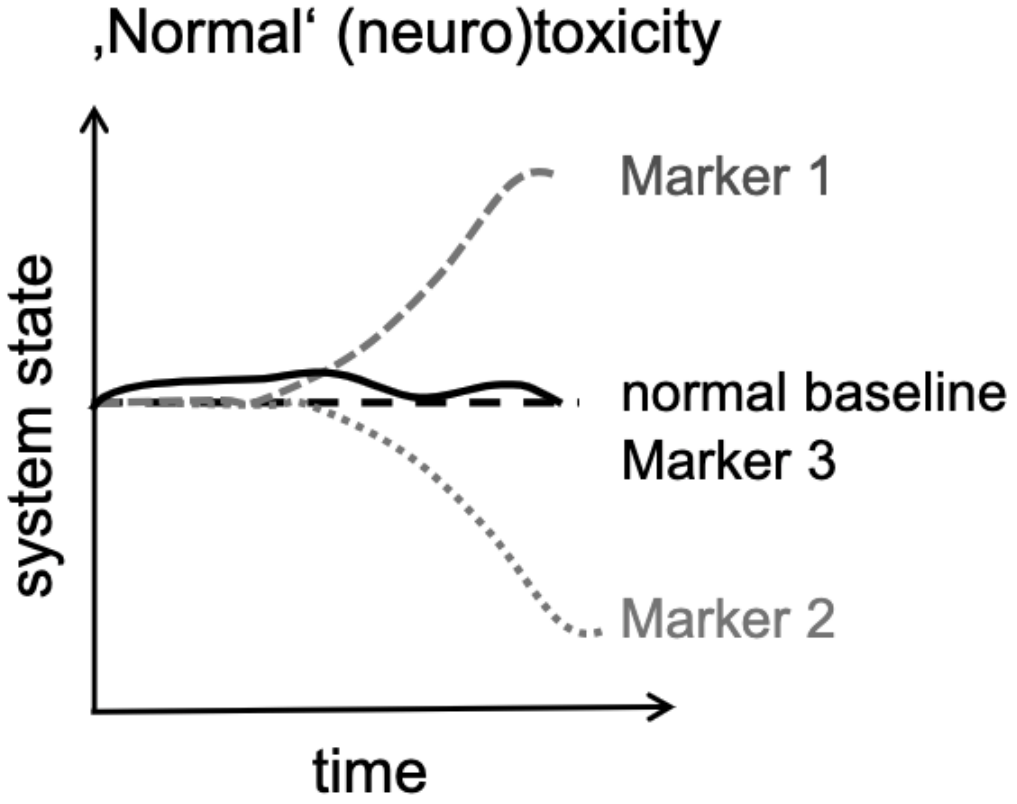
early life exposures, later life consequences

What is DNT?

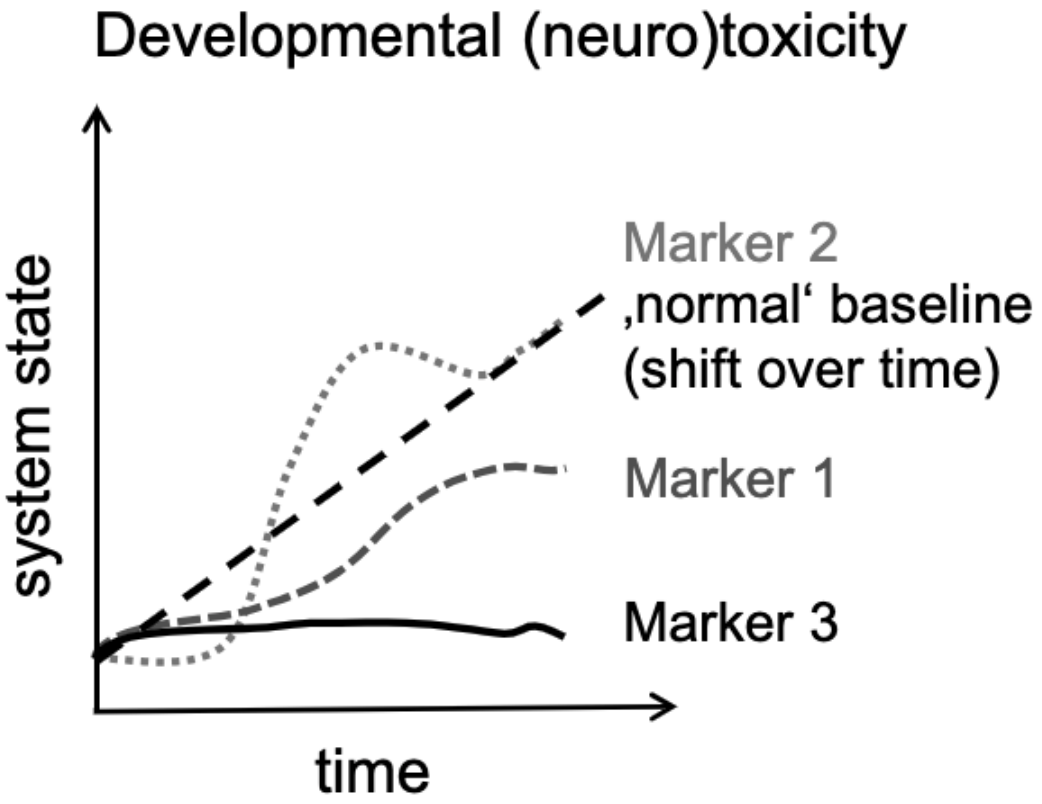


Grandjean et al. (2006)

What makes DNT complex?



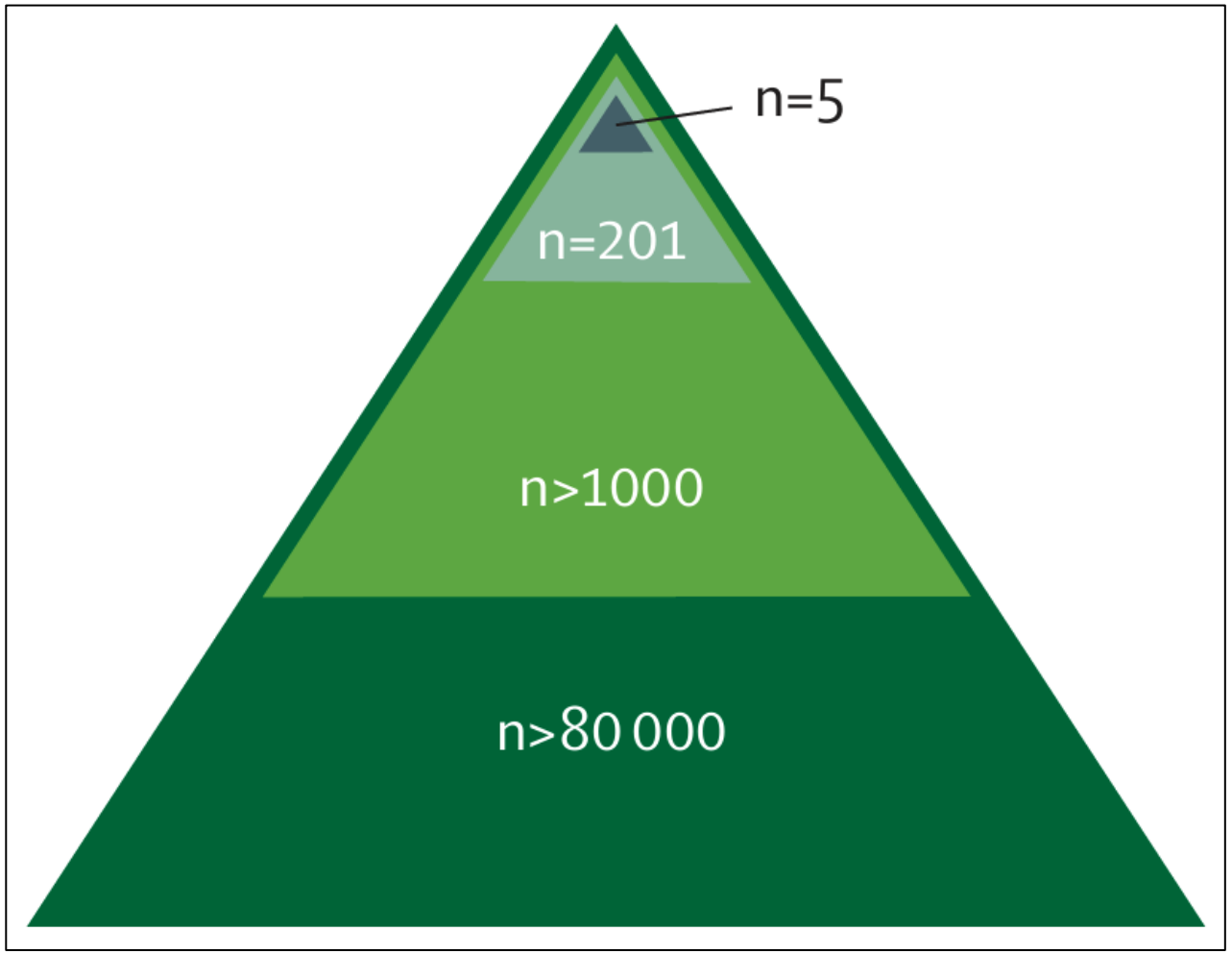
Steady State



Constant Flux

Adapted from Smirnova et al. (2014)

Classified DNToxicants in 2006: 5



Chemicals known to be toxic to human neurodevelopment

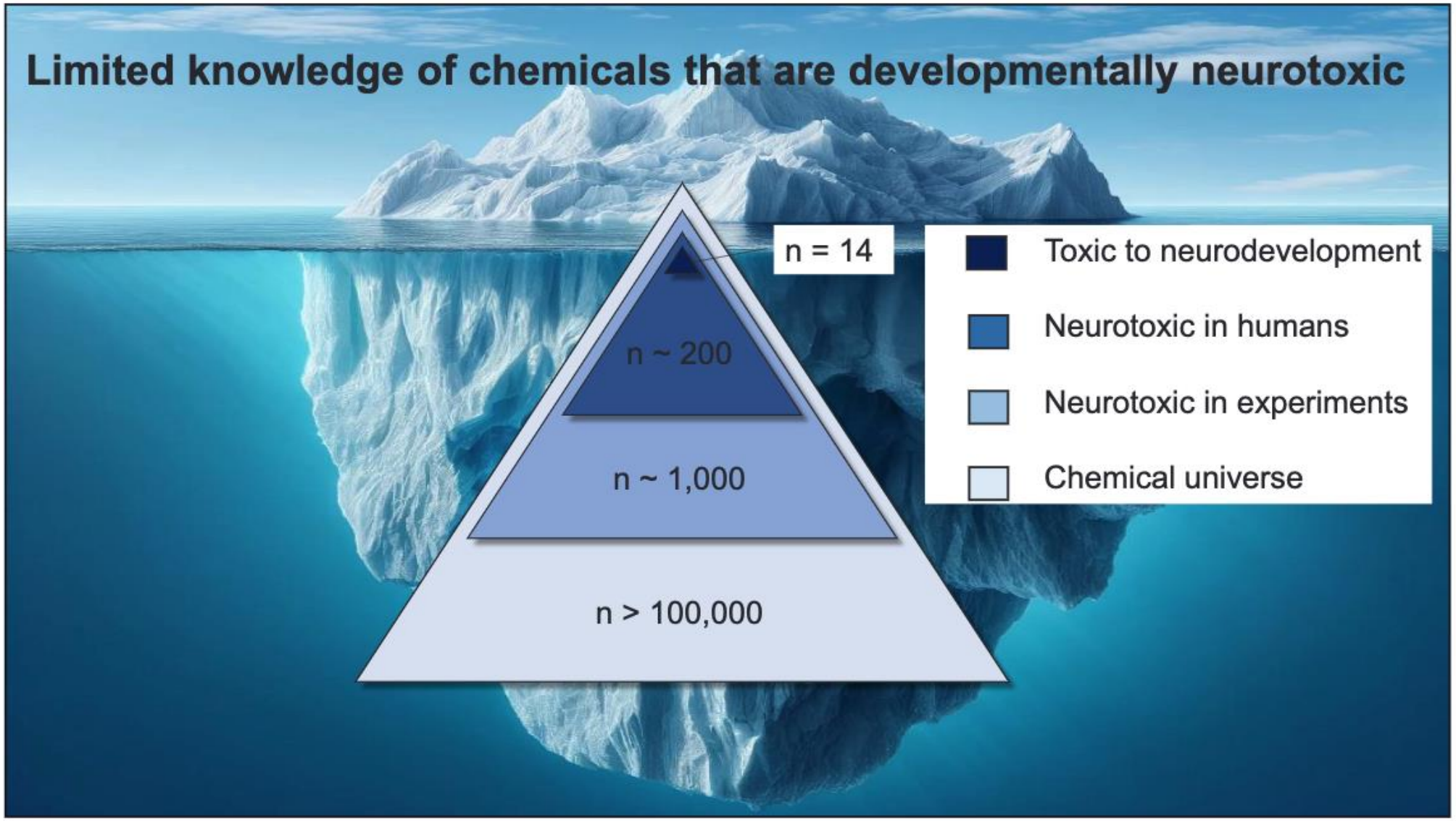
Chemicals known to be neurotoxic in human beings

Chemicals known to be neurotoxic in experiments

Chemical universe

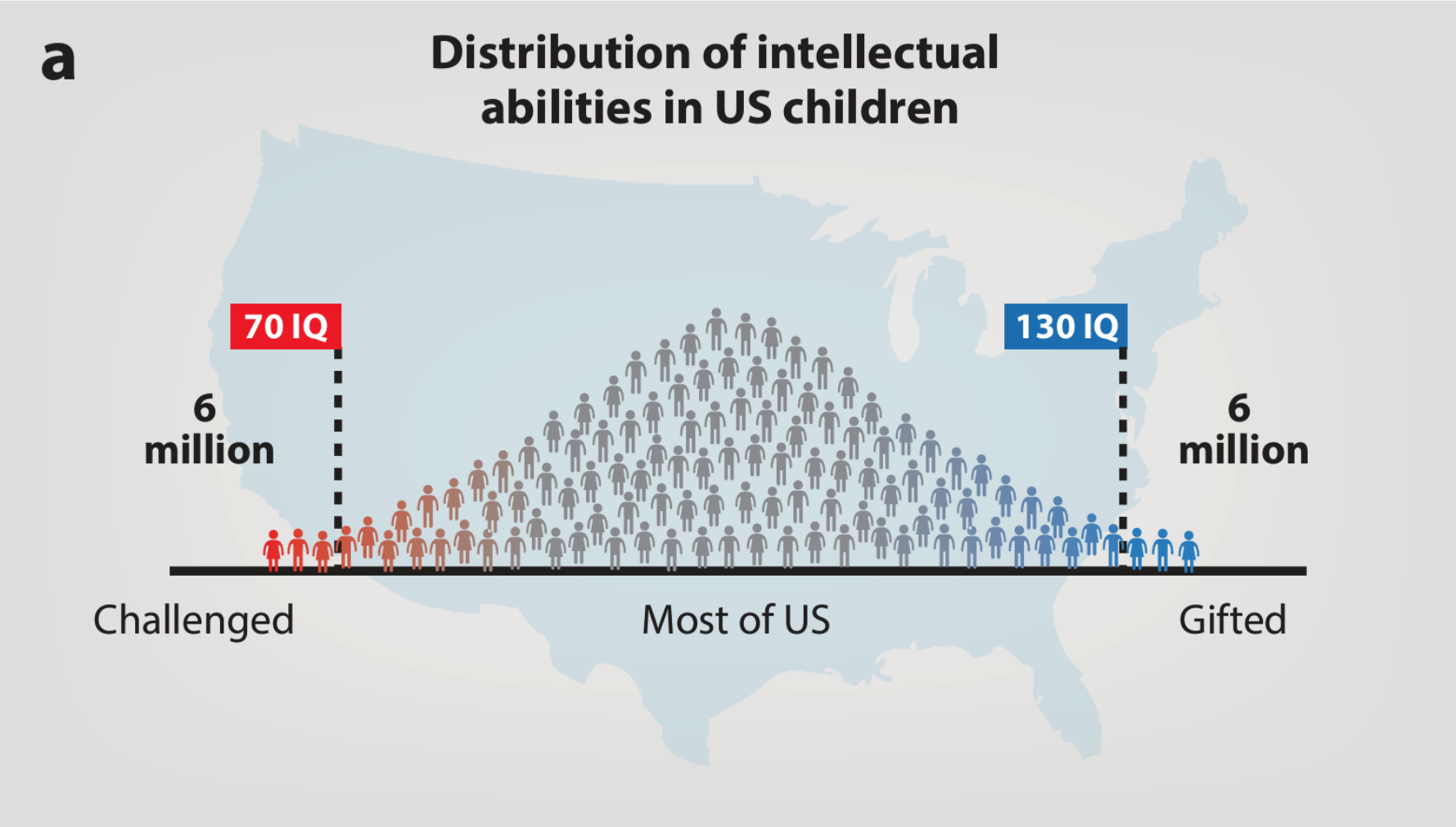
Grandjean et al. (2006)

Classified DNToxicants in 2025: 14



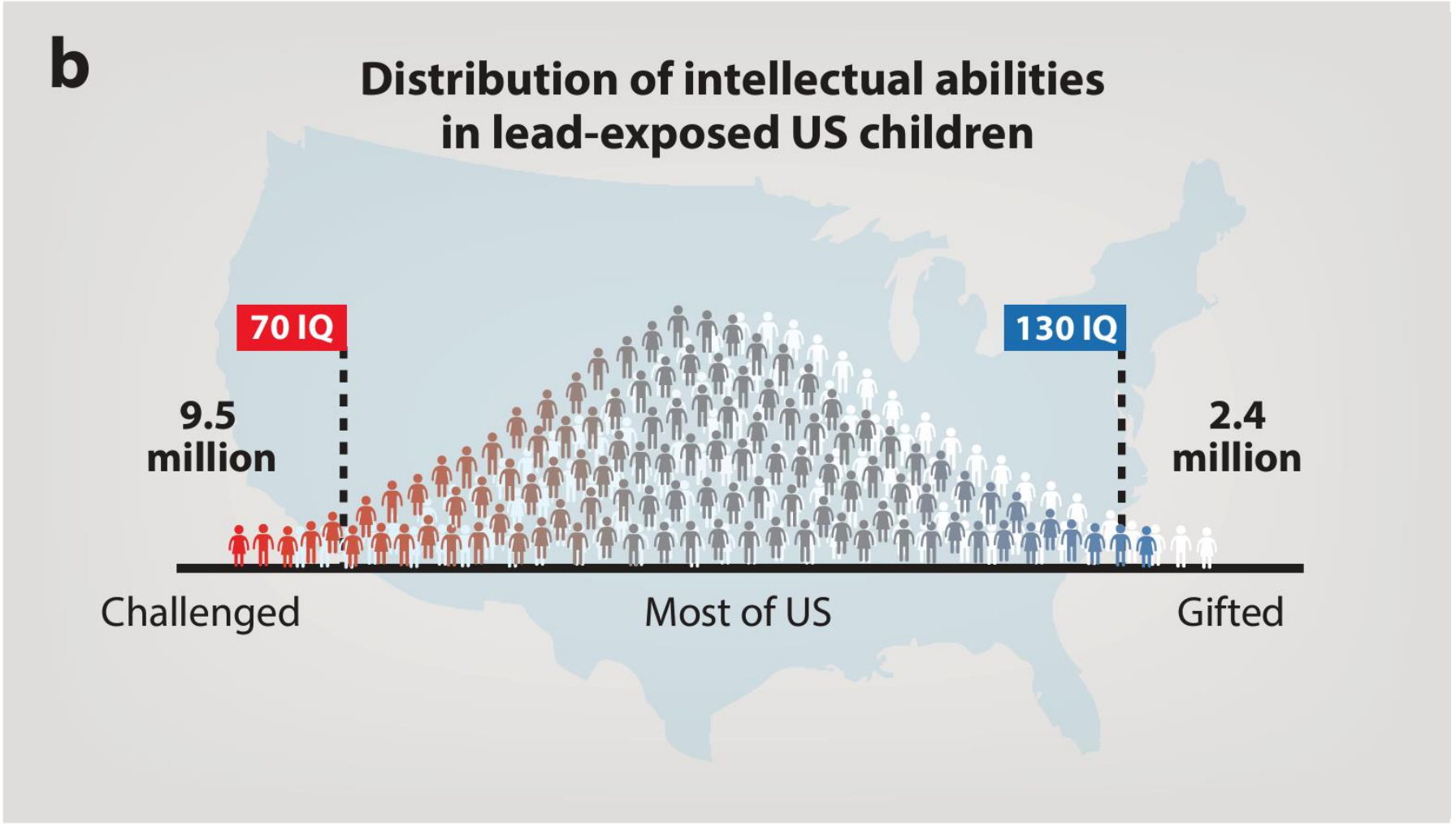
Smirnova et al. (2024)

Superfund Chemical: *Pb* (Lead)



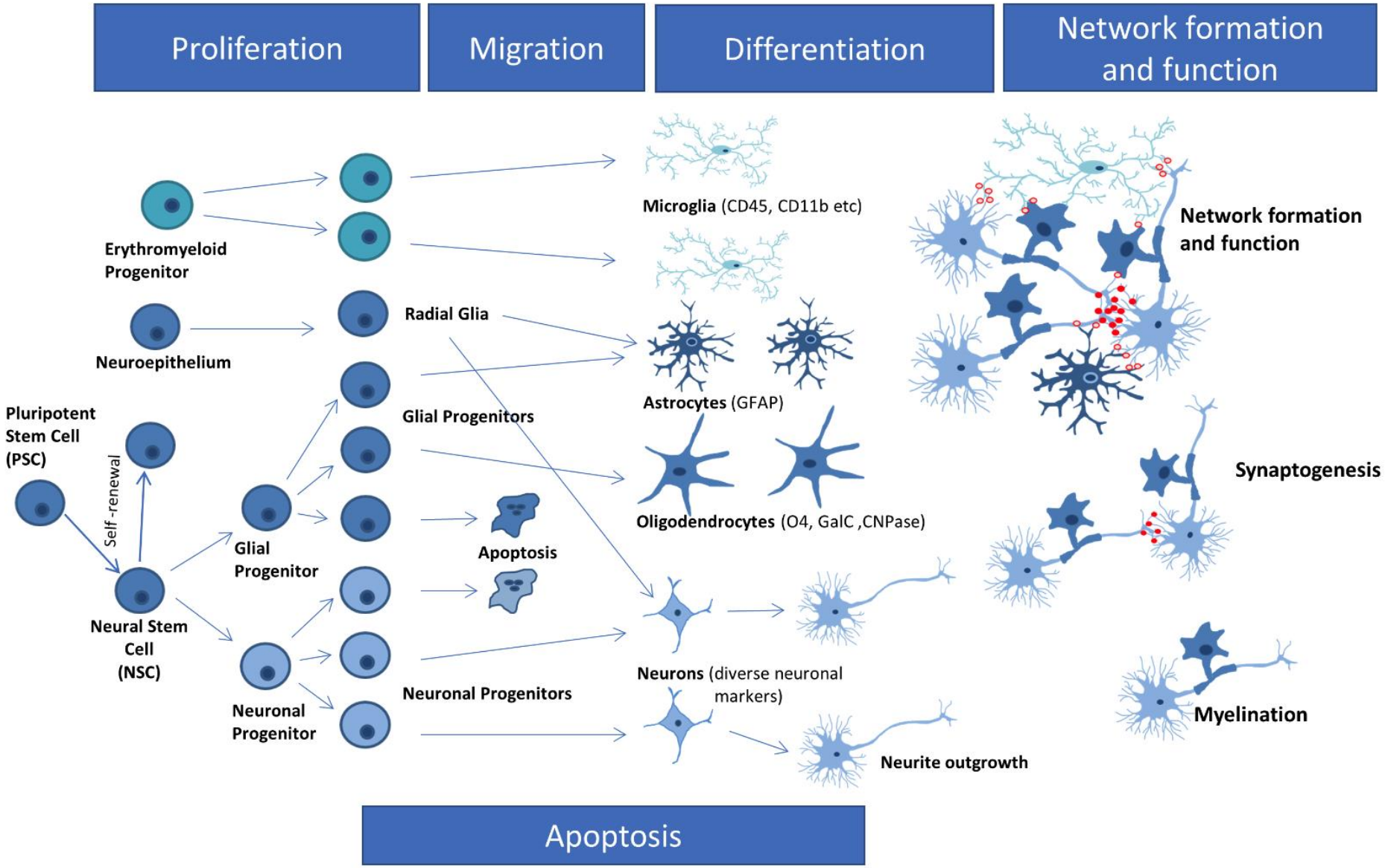
Lanphear et al. (2015)

Superfund Chemical: *Pb* (Lead)

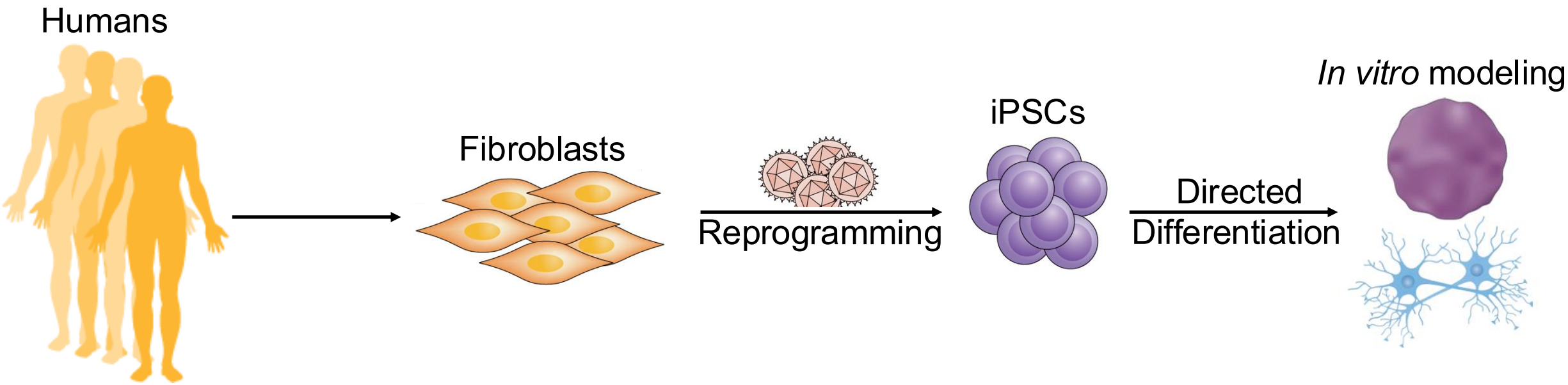


Lanphear et al. (2015)

Fundamental neurodevelopmental processes



Leveraging hiPSCs for human relevance

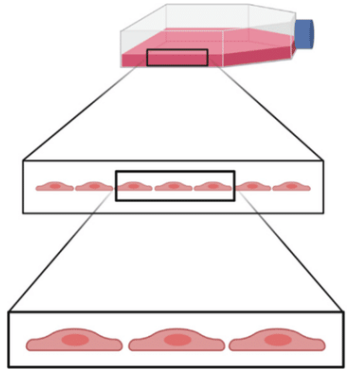


- human derived induced pluripotent cells (hiPSCs) can mature into most cell types
- A powerful tool to study a wide range of biological systems and responses

Adapted from di val Cervo et al. (2021)

2D vs 3D Modeling

2D Cell Cultures

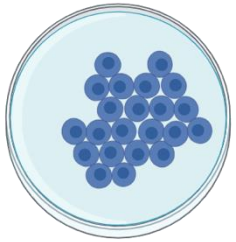


ADVANTAGES

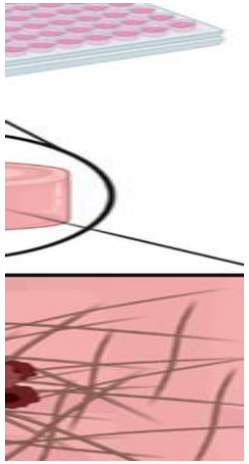
- ❖ Scalable & Homogenous
- ❖ Cell type specific effects

DISADVANTAGES

- ❖ Lowered physiological relevance



3D Cell Cultures

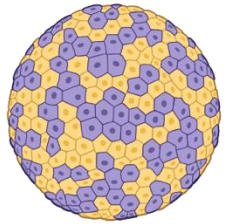


ADVANTAGES

- ❖ Interactions b/w cell types
- ❖ Self organization

DISADVANTAGES

- ❖ Limited vascularization
- ❖ Reproducibility



Research Article

A Human Brain Microphysiological System Derived from Induced Pluripotent Stem Cells to Study Neurological Diseases and Toxicity

David Pamies [1#], Paula Barreras [2,3#], Katharina Block [1], Georgia Makri [2,4], Anupama Kumar [2,3], Daphne Wiersma [1], Lena Smirnova [1], Ce Zhang [2,4], Joseph Bressler [5], Kimberly M. Christian [2,4], Georgina Harris [1], Guo-li Ming [2,4,6], Cindy J. Berlinicke [7], Kelly Kyro [8], Hongjun Song [2,4,6], Carlos A. Pardo [2,3], Thomas Hartung [1,9] and Helena T. Hogberg [1]

Cerebral organoids model human brain development and microcephaly

Madeline A. Lancaster[1], Magdalena Renner[1], Carol-Anne Martin[2], Daniel Wenzel[1], Louise S. Bicknell[2], Matthew E. Hurles[3], Tessa Homfray[4], Josef M. Penninger[1], Andrew P. Jackson[2] & Juergen A. Knoblich[1]

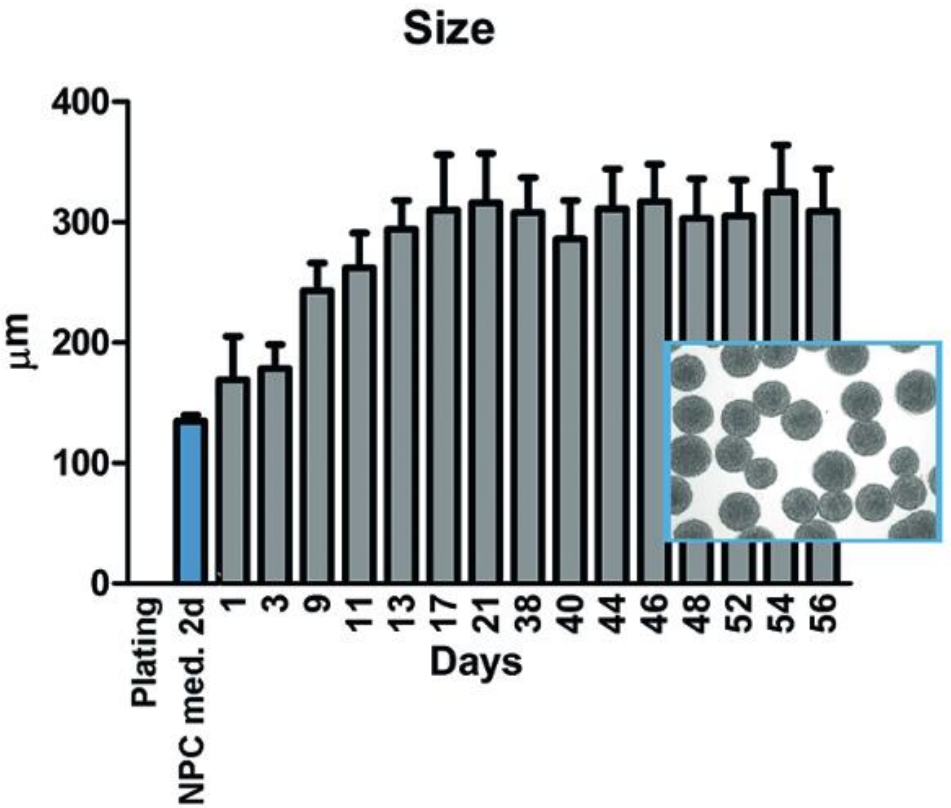
Multi-Region Brain Organoids Integrating Cerebral, Mid-Hindbrain, and Endothelial Systems

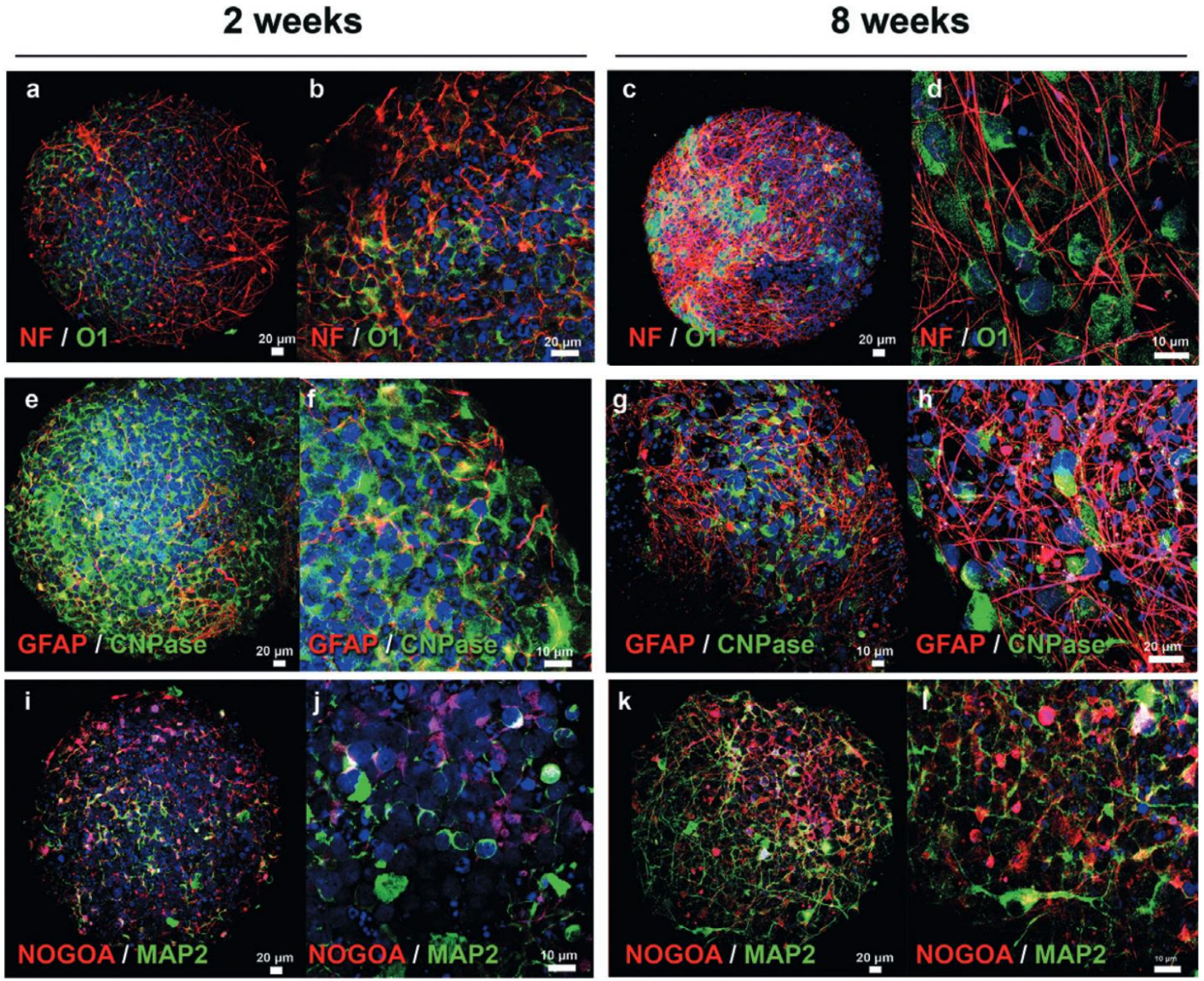
Anatsakanyan, Sai Kulkarni, John Guo, Kai Cheng, ra, Ram Sagar, Vasiliki Mahairaki, Christian E Badr,

Human cerebral organoids recapitulate gene expression programs of fetal neocortex development

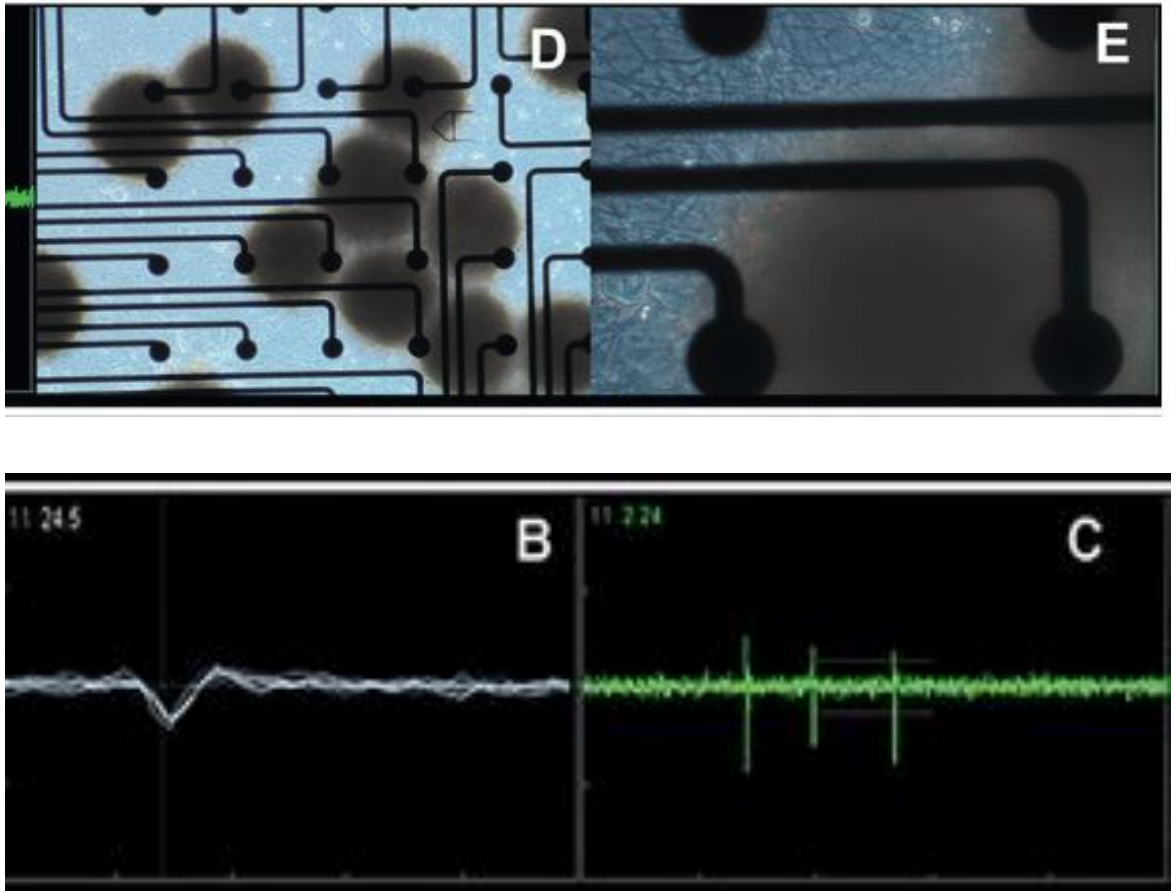
J. Gray Camp[a,1], Farhath Badsha[b,1], Marta Florio[b], Sabina Kanton[a], Tobias Gerber[a], Michaela Wilsch-Bräuninger[b], Eric Lewitus[c], Alex Sykes[b], Wulf Hevers[a], Madeline Lancaster[d,e], Juergen A. Knoblich[e], Robert Lachmann[f], Svante Pääbo[a,2], Wieland B. Huttner[b,2], and Barbara Treutlein[a,b,2]

Uniform sizes, numbers and multiple cell types



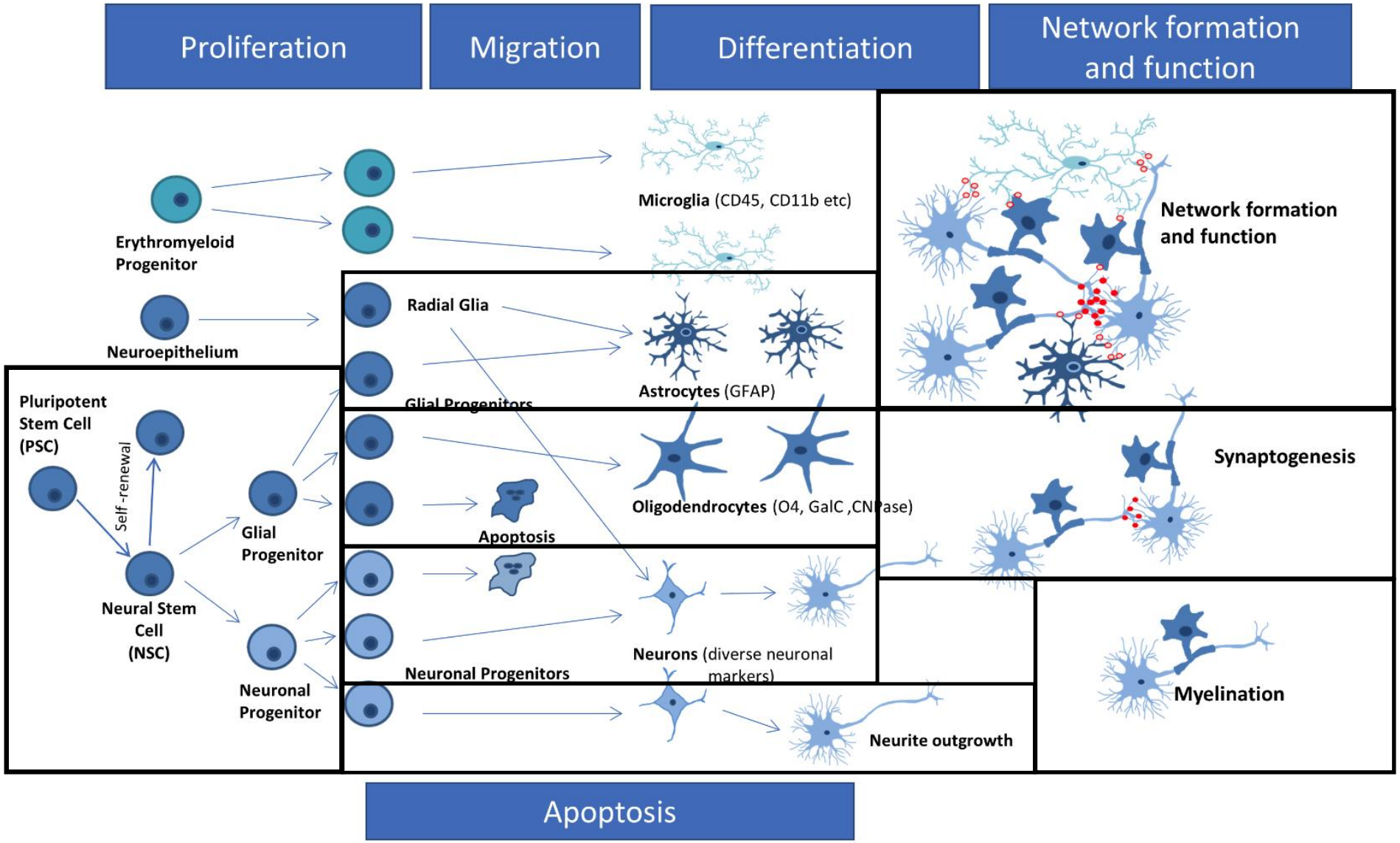


Electrically active, network formation, memory



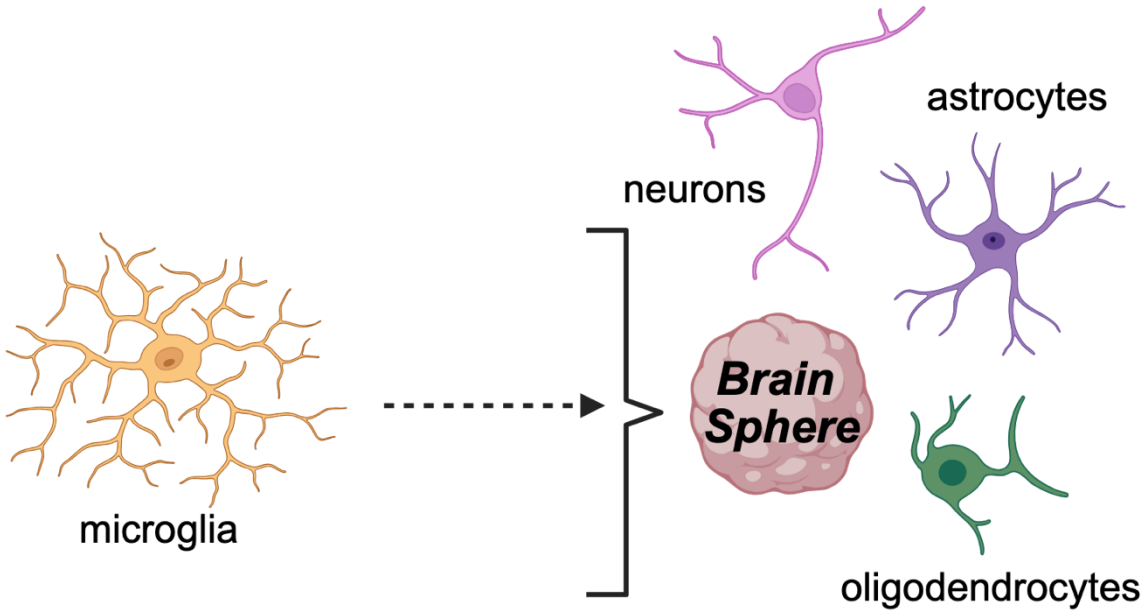
Adapted from Pamies et al. (2017)

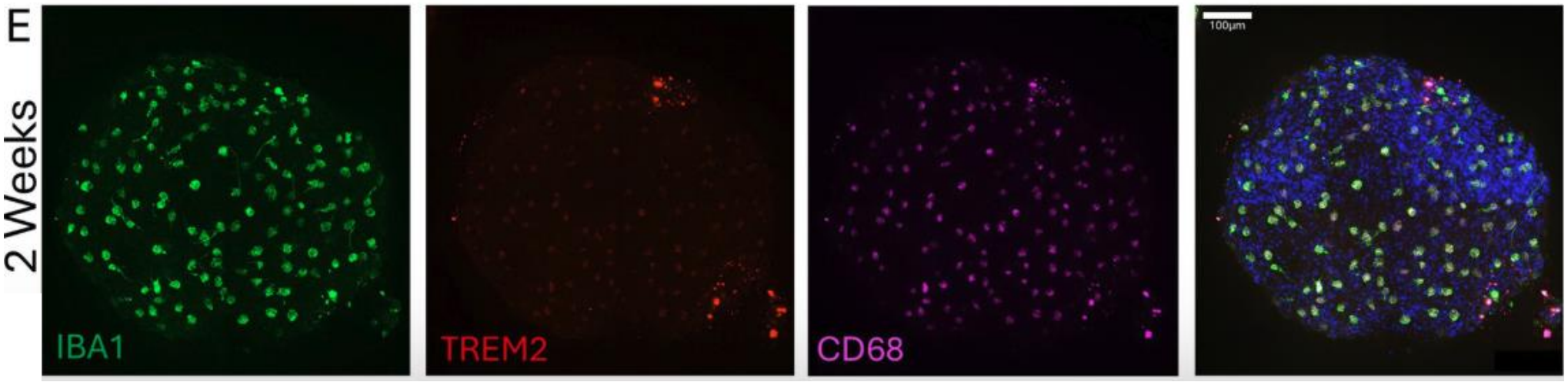
Fundamental neurodevelopmental processes



Adapted from Bal-Price et al. (2018)

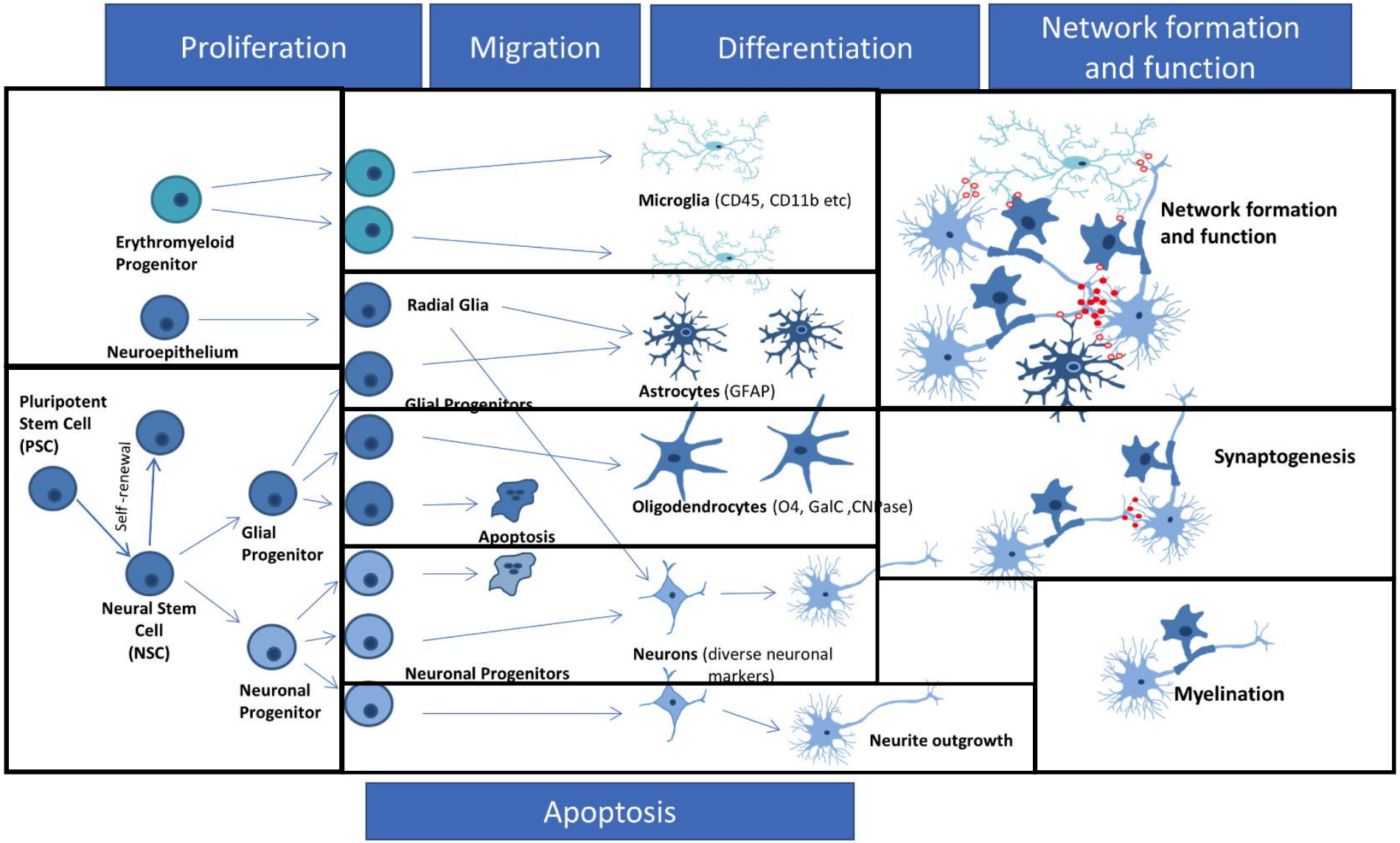
Incorporation of Microglia





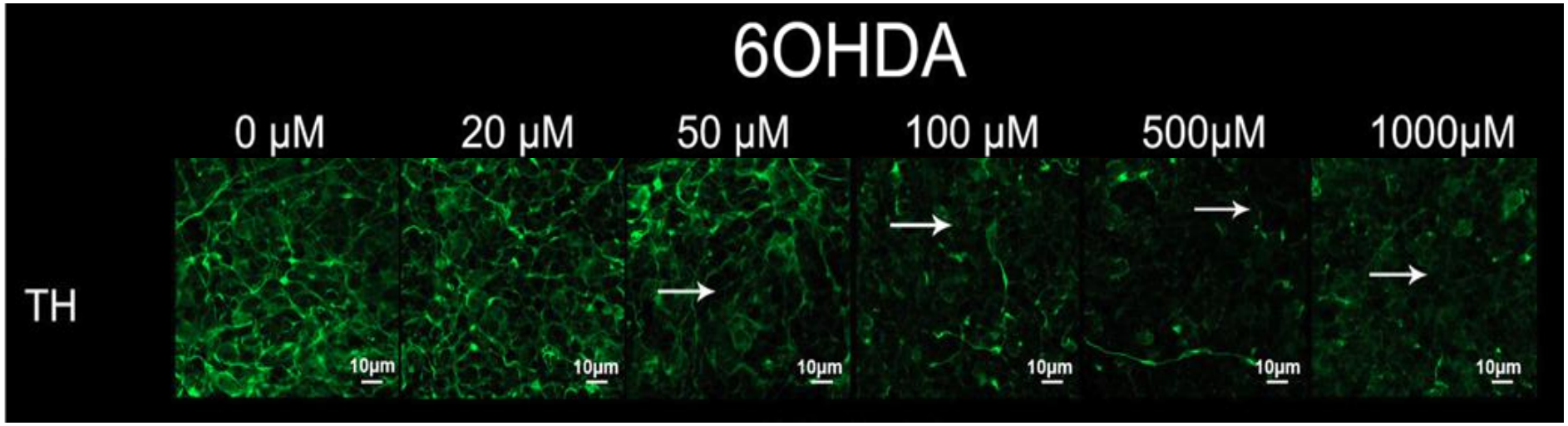
Adapted from Rittenhouse et al. (2025)

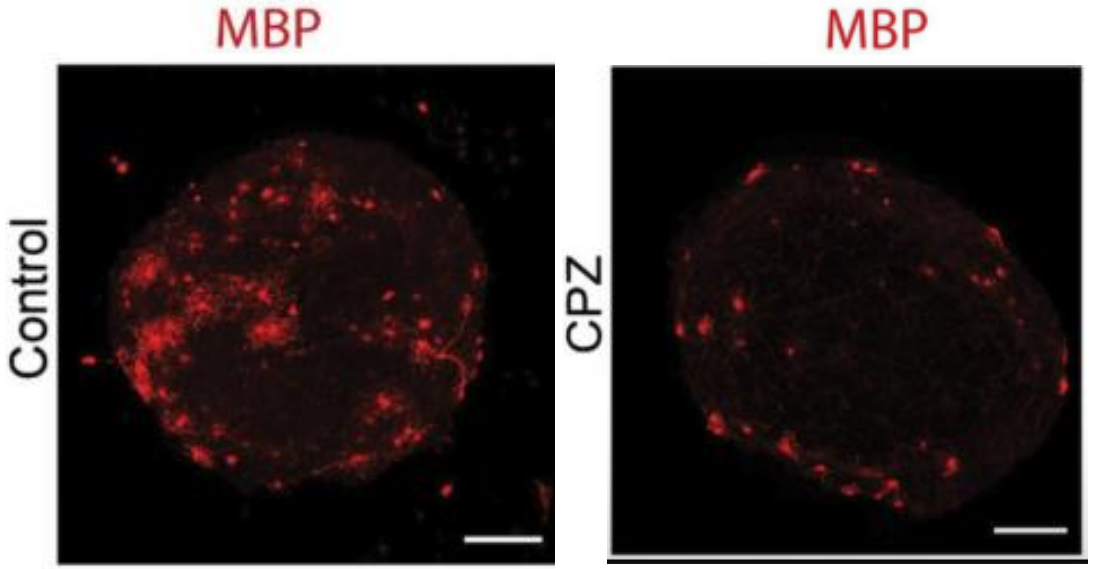
Fundamental neurodevelopmental processes



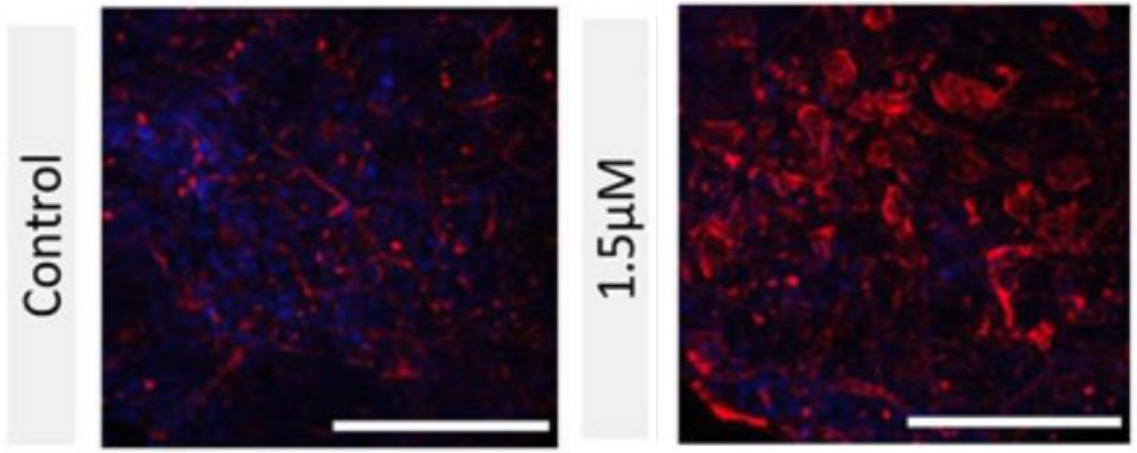
Adapted from Bal-Price et al. (2018)

Brain Spheres capture cell-type specific effects





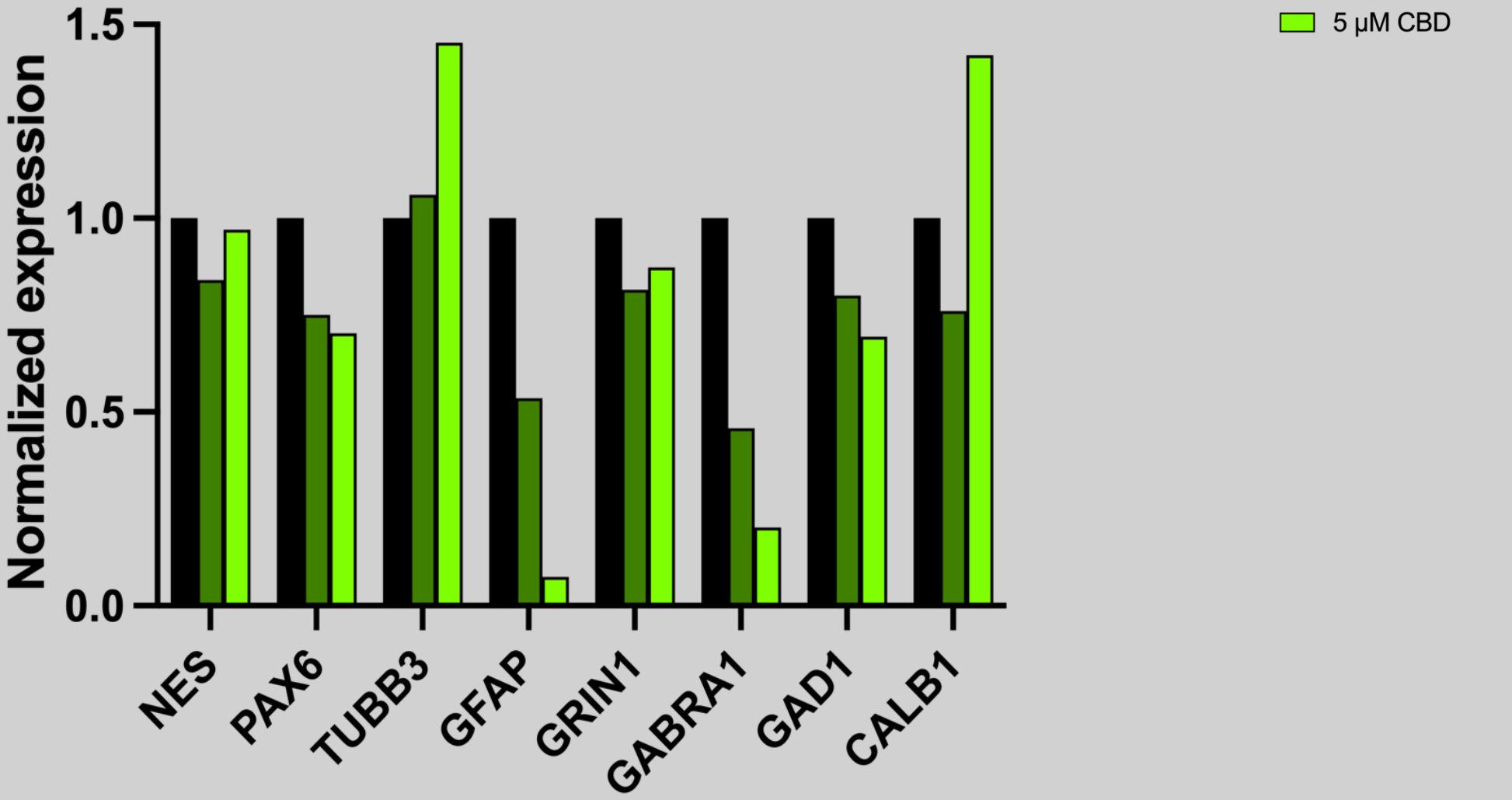
Amiodarone



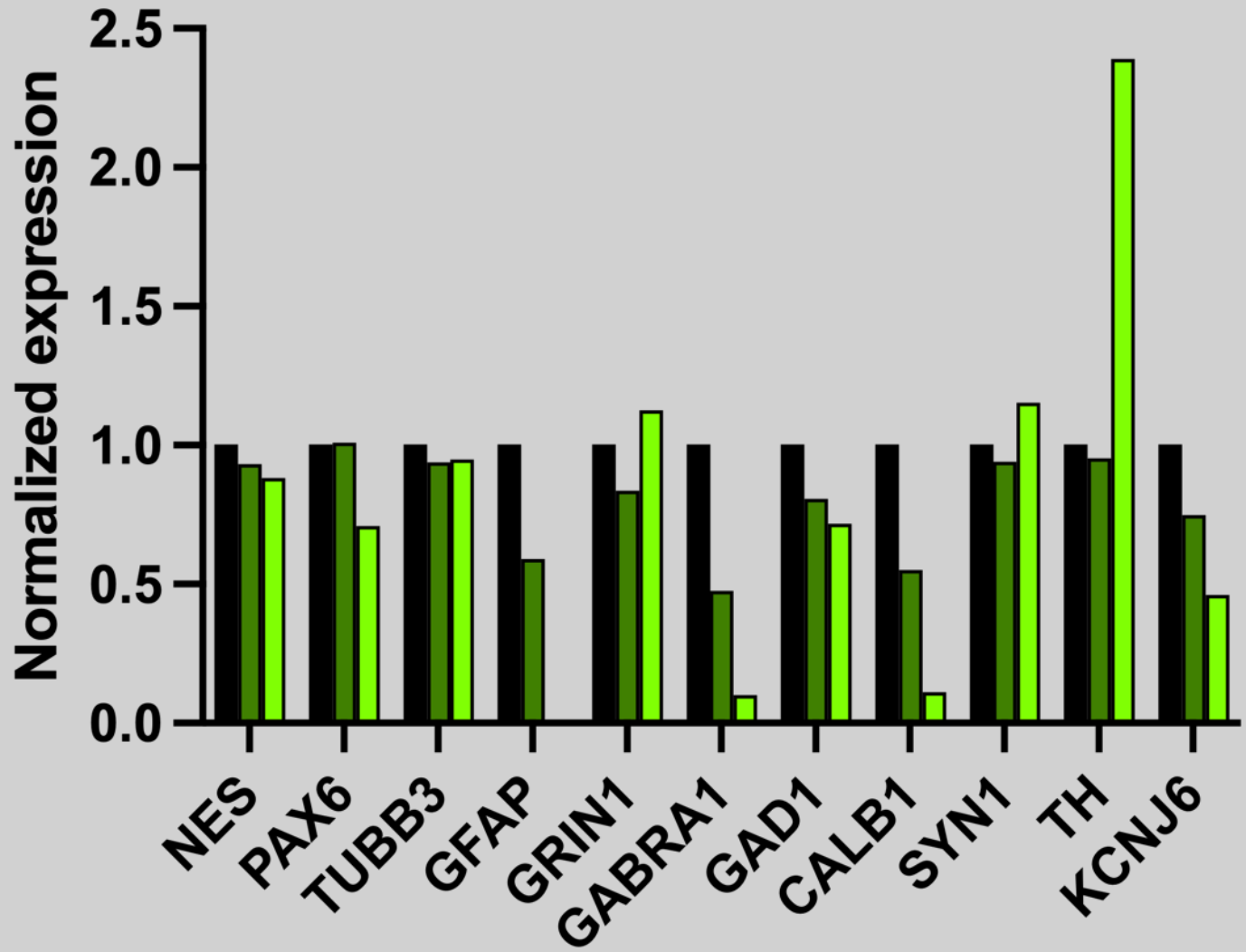
S100B Expression

Adapted from Pamies et al. (2018), Nunes et al. (2023) and Romero et al. (2023)

Modeling temporal effects



Modeling temporal effects



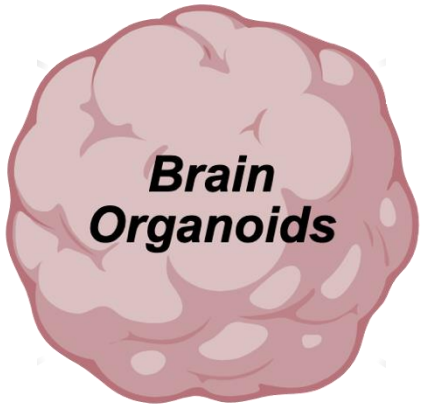
Conclusions and Ongoing Work

- Human brain development is an **incredibly complex process**, hence making **DNT** hard to model.

- Brain organoids generated from hiPSCs provide a **powerful** tool to capture **neurodevelopment's** intricacy in a **human-relevant** manner.

- Now, at the Duke Superfund Research Center, we're currently modeling **physiologically relevant** exposures to **heavy metals and PAHs.**

Overall Purpose/Use?



Acknowledgements

Duke Obstetrics & Gynecology
Duke University School of Medicine

Duke UNIVERSITY | SUPERFUND Research Center
early life exposures, later life consequences

Murphy Lab

NIH National Institute of Environmental Health Sciences
Superfund Research Program

Dr. Susan Murphy
Carole Grenier
Dr. Joel Meyer
Dr. Ed Levin
Duke Superfund Research Center

Questions?