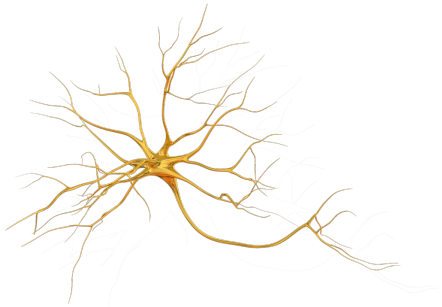
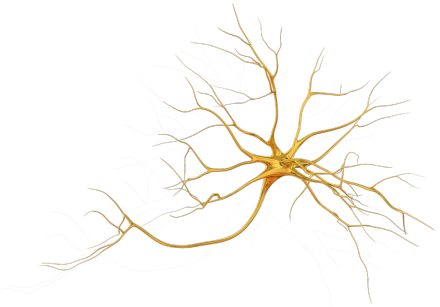
RCCN Workshop: Multidisciplinary Research in Aging/Team Science

Human Cell Models for Brain Aging

Exploring multidisciplinary approaches for using organoids in early translational applications.

May 20-21, 2026 | Bethesda, MD





Jerome Mertens, PhD
Associate Professor
Department of Neurosciences
UC San Diego

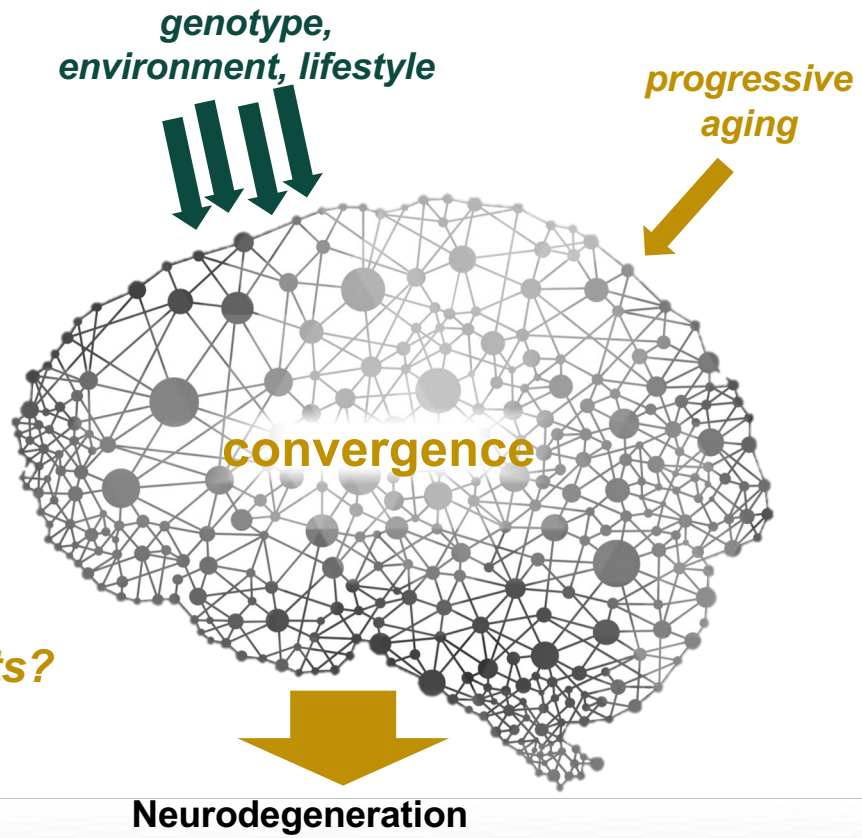
Aging and neurodegeneration

UC San Diego School of Medicine

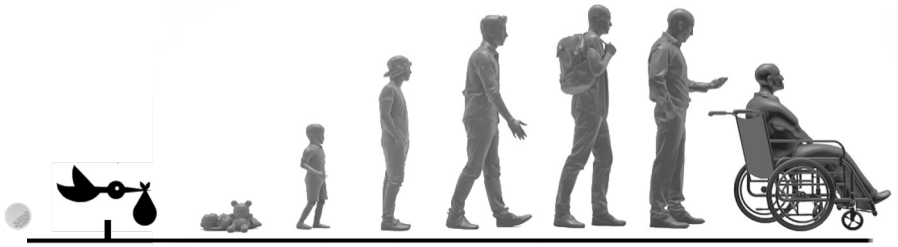
- Alzheimer's disease is critically age-dependent
- ~95-98% of cases are sporadic, no transgenic models
- familial (inherited) AD is rare, and age-dependent
- no unifying age-dependent disease etiology known; no cure

Human aging biology is a central determinant of disease vulnerability
→ Model choice matters!

Aging biology of the available cellular ingredients?



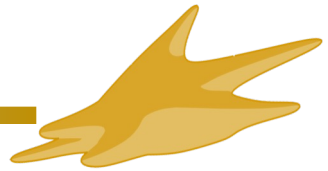
Rejuvenated versus age-equivalent human neuronal models





iPSCs

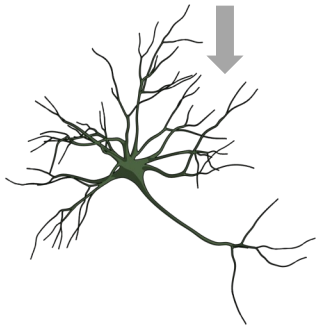
rejuvenation



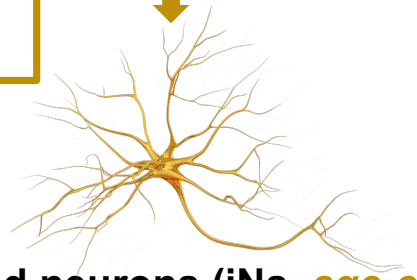
fibroblasts

Age-equivalency:
- Ontogenic identity of adult neurons
- Biological age of donors

TF-based direct conversion



iPSC-neurons, etc… (*rejuvenated*)



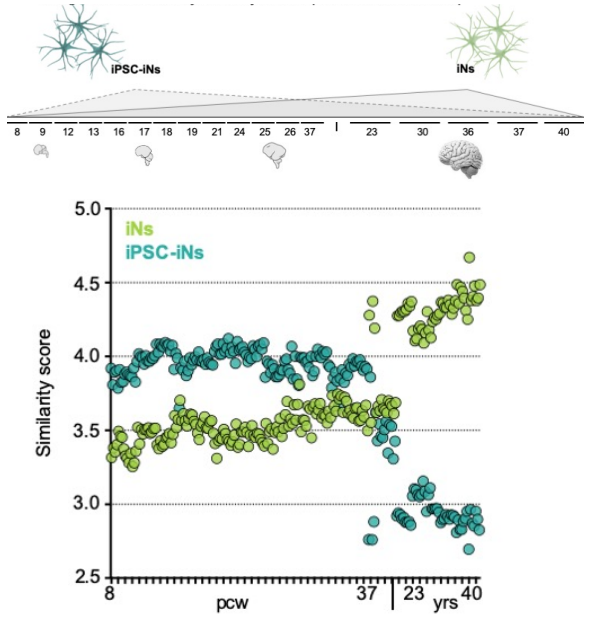
induced neurons (iNs, *age-equivalent*)

Traxler L et al. FEBS letters 2019; Böhnke L et al. Drug Discovery Today 2018

Age-equivalency: Ontogenic identity and biological age of iNs

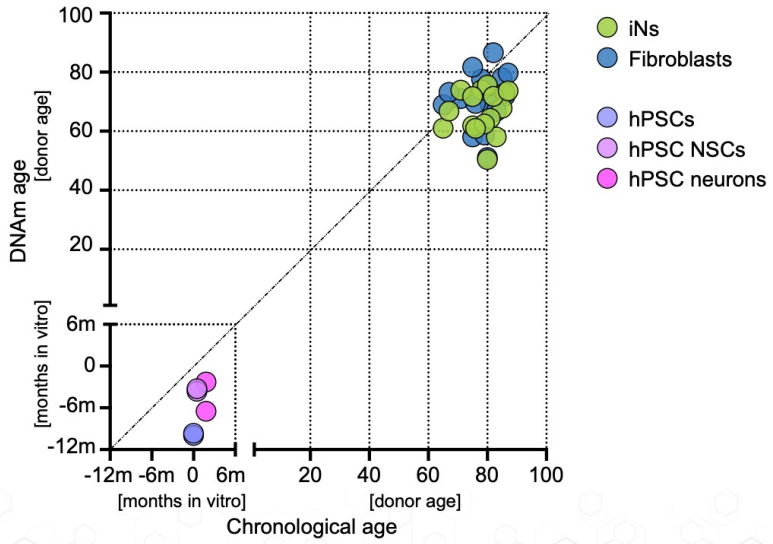
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Transcriptome correlation with adult fetal or adult brain



- iPSC neurons resemble fetal stages
- iNs resemble adult stages

Epigenetic (DNA methylation) clock



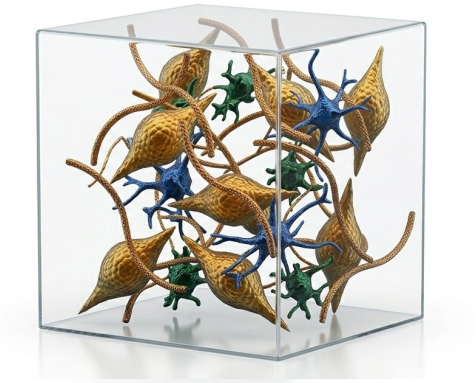
- iPSC neurons have *pre-birth* ages
- iNs reflect individual donor ages

Mertens J et al. Cell Stem Cell 2015 & Cell Stem Cell 2021
Herdy J et al. eLife 2019 & Herdy J et al. Cell Stem Cell 2022

Why 3D and multicellular human brain models?



2D



3D

Advantages of 3D cultures / MPS:

- Tissue architecture and spatial organization
- Cell-cell and cell-ECM interactions
- Biomechanical stiffness and more realistic microenvironments
- Multicellular complexity/connectivity
- Stable long-term maturation;

Aging phenotypes are not only cell-autonomous:

- Senescence (SASP) bystander effects
- Aging ECM and biomechanics
- Metabolic cell-cell interactions (*also with glia*)
- etc… → all shape tissue-level vulnerability

Current 3D route 1: iPSC-derived organoid systems



iPSCs ***Embryoid bodies*** ***Brain organoids***

Strong fit for genetic, developmental and multicellular questions

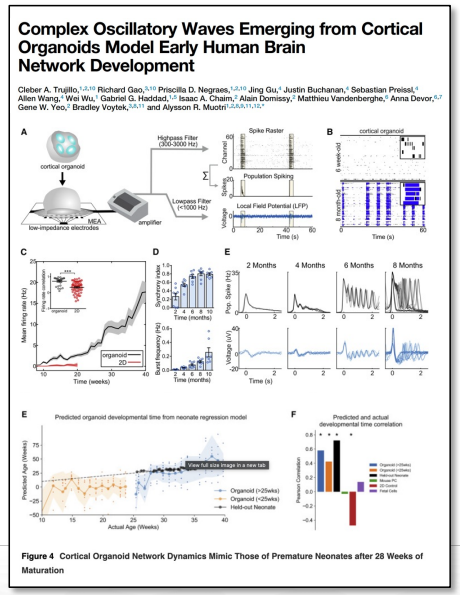
Advantages	Challenges	Emerging directions
• Intrinsic self-organization and multicellular patterning • Engineerable stem cell source • Virtually unlimited cell numbers	• Embryo-like developmental state • Rejuvenation resets donor-age state • Inter-line and -organoid variability • Experimental accessibility (hyper-dense tissue) • Lack of vasculature	• Improved differentiation protocols and QC/benchmarks • Genetic “progeroid” iPSC lines • Age-induction (stressors to accelerate aging phenotypes) • Assembloids • Transplantation and in vivo maturation

Current 3D route 1: iPSC-derived organoid systems

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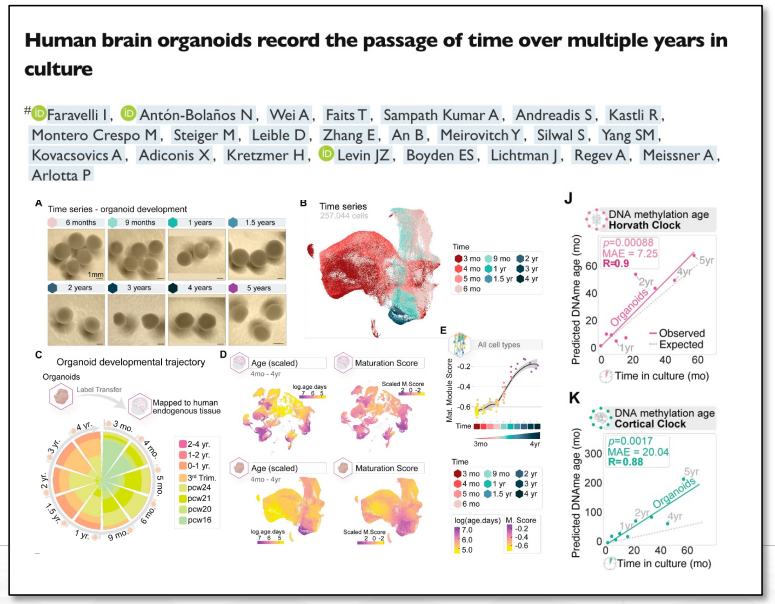
iPSCs → *Embryoid bodies* → *Brain organoids*



Complex Oscillatory Waves Emerging from Cortical Organoids Model Early Human Brain Network Development

Cleber A. Trujillo, Richard Gao, Priscilla D. Negraes, Jing Gu, Justin Buchanan, Sebastian Preissl, Allen Wang, Wei Wu, Gabriel G. Haddad, Isaac A. Chaim, Alain Domissy, Matthieu Vandenberghe, Anna Devor, Gene W. Yeo, Bradley Voytek, Alysson R. Muotri

Figure 4 Cortical Organoid Network Dynamics Mimic Those of Premature Neonates after 28 Weeks of Maturation



Human brain organoids record the passage of time over multiple years in culture

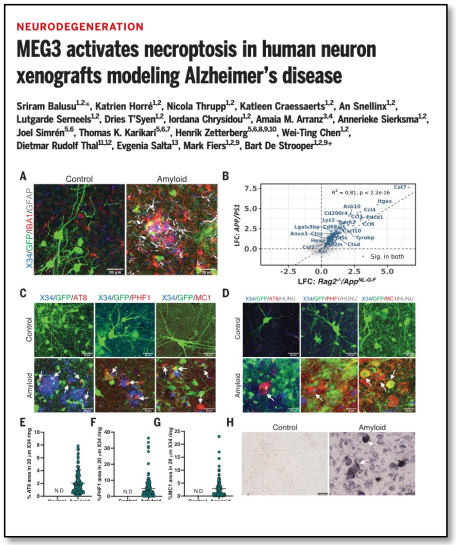
Faravelli I, Antón-Bolaños N, Wei A, Faits T, Sampath Kumar A, Andreadis S, Kastli R, Montero Crespo M, Steiger M, Leible D, Zhang E, An B, Meirovitch Y, Silwal S, Yang SM, Kovacsovics A, Adiconis X, Kretzmer H, Levin JZ, Boyden ES, Lichtman J, Regev A, Meissner A, Arlotta P

Current 3D route 1: iPSC-derived organoid systems

UC San Diego SCHOOL OF MEDICINE



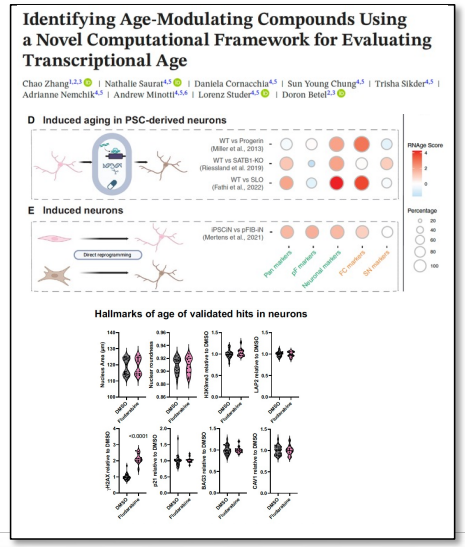
iPSCs → *Embryoid bodies* → *Brain organoids*



NEURODEGENERATION

MEG3 activates necroptosis in human neuron xenografts modeling Alzheimer's disease

Sriram Balusu[1,2,*], Katrien Horré[1,2], Nicola Thrupp[1,2], Katleen Craessaerts[1,2], An Snellinx[1,2], Lutgarde Serneels[1,2], Dries T'Syen[1,2], Iordana Chrysidou[1,2], Amaia M. Arranz[3,4], Annerieke Sierksma[1,2], Joel Simrén[5,6], Thomas K. Karikari[5,6,7], Henrik Zetterberg[5,6,8,9,10], Wei-Ting Chen[1,2], Dietmar Rudolf Thal[11,12], Evgenia Salta[13], Mark Fiers[1,2,9], Bart De Strooper[1,2,9,*]



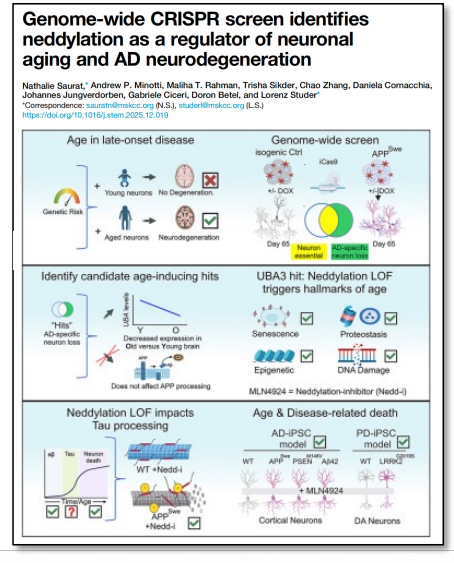
Identifying Age-Modulating Compounds Using a Novel Computational Framework for Evaluating Transcriptional Age

Chao Zhang[1,2,3] | Nathalie Saurat[4,5] | Daniela Cornacchia[4,5] | Sun Young Chung[4,5] | Trisha Sikder[4,5] | Adrianne Nemchik[4,5] | Andrew Minotti[4,5,6] | Lorenz Studer[4,5] | Doron Betel[2,3]

D Induced aging in PSC-derived neurons

E Induced neurons

Hallmarks of age of validated hits in neurons

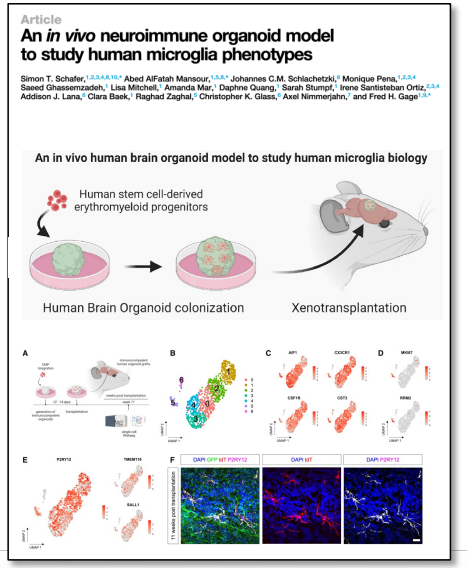


Genome-wide CRISPR screen identifies neddylation as a regulator of neuronal aging and AD neurodegeneration

Nathalie Saurat,[*] Andrew P. Minotti, Maliha T. Rahman, Trisha Sikder, Chao Zhang, Daniela Cornacchia, Johannes Jungverdorben, Gabriele Ciceri, Doron Betel, and Lorenz Studer[*]

[*]Correspondence: sauratn@mskcc.org (N.S.), studerl@mskcc.org (L.S.)

https://doi.org/10.1016/j.stem.2025.12.019



Article

An *in vivo* neuroimmune organoid model to study human microglia phenotypes

Simon T. Schafer,[1,2,3,4,8,10,*] Abed AlFatah Mansour,[1,5,8,*] Johannes C.M. Schlachetzki,[6] Monique Pena,[1,4,7,8] Saeed Ghassemzadeh,[1] Lisa Mitchell,[1] Amanda Mar,[1] Daphne Quang,[1] Sarah Stumpf,[1] Irene Santisteban Ortiz,[2,3,4] Addison J. Lana,[9] Clara Baek,[1] Raghad Zaghal,[1] Christopher K. Glass,[4] Axel Nimmerjahn,[7] and Fred H. Gage[1,8,*]

An in vivo human brain organoid model to study human microglia biology

Human stem cell-derived erythromyeloid progenitors

Human Brain Organoid colonization

Xenotransplantation

Current 3D route 2: direct-conversion-based engineered systems



Fibroblasts ***pure iNs*** ***3D iN spheres or constructs***

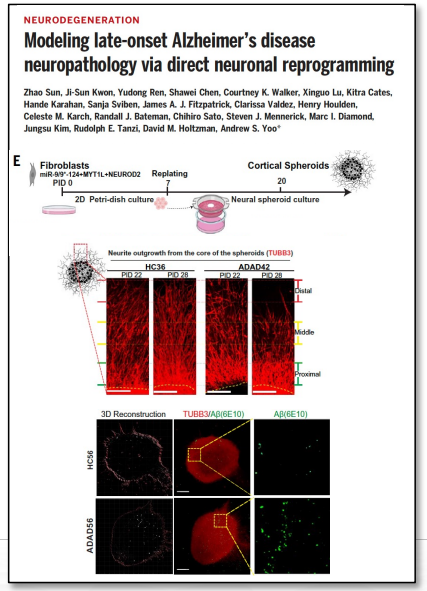
Strong fit for age-dependent and sporadic disease questions and 'flag post' phenotypes

Advantages	Challenges	Emerging directions
• Adult neuronal identity • Donor-specific age retention • Endogenous age-linked disease-relevant • Controlled assembly of defined cell combinations • Rejuvenation and heterochronic study designs possible	• Stepwise assembly laborious • Limited material and scalability • No self-organized tissue architecture (e.g. layering) • Experimental accessibility • Complex multicellular 3D constructs are very early stage	• Engineered scaffolds • Controllable microenvironments and cell density • Low-input omics and single-cell readouts • Neuron-Glia co-cultures • Transplantation and in vivo maturation

Current 3D route 2: direct-conversion-based engineered systems



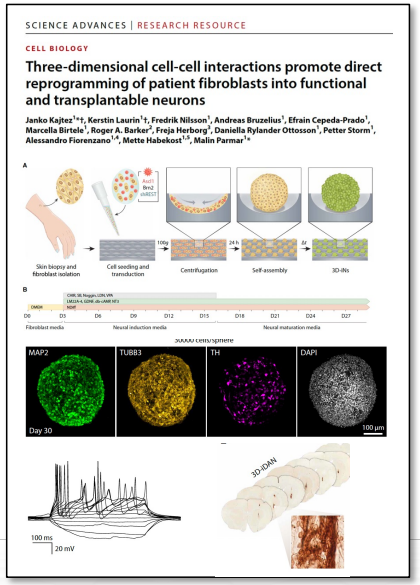
Fibroblasts ***pure iNs*** ***3D iN spheres or constructs***



NEURODEGENERATION

Modeling late-onset Alzheimer's disease neuropathology via direct neuronal reprogramming

Zhao Sun, Ji-Sun Kwon, Yudong Ren, Shawei Chen, Courtney K. Walker, Xinguo Lu, Kitra Cates, Hande Karahan, Sanja Sviben, James A. J. Fitzpatrick, Clarissa Valdez, Henry Houlden, Celeste M. Karch, Randall J. Bateman, Chihiro Sato, Steven J. Mennerick, Marc I. Diamond, Jungsu Kim, Rudolph E. Tanzi, David M. Holtzman, Andrew S. Yoo*



SCIENCE ADVANCES | RESEARCH RESOURCE

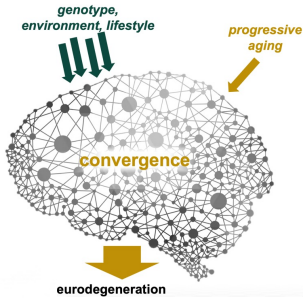
CELL BIOLOGY

Three-dimensional cell-cell interactions promote direct reprogramming of patient fibroblasts into functional and transplantable neurons

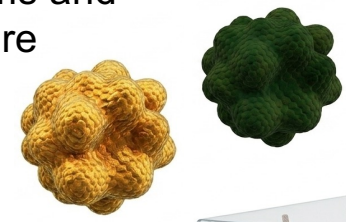
Janko Kajtez[1*†], Kerstin Laurin[1†], Fredrik Nilsson[1], Andreas Bruzelius[1], Efrain Cepeda-Prado[1], Marcella Birtele[1], Roger A. Barker[2], Freja Herborg[3], Daniella Rylander Ottosson[1], Petter Storm[1], Alessandro Fiorenzano[1,4], Mette Habekost[1,5], Malin Parmar[1*]

Conclusions and Acknowledgement

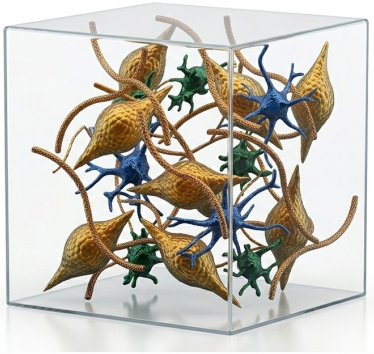
- Aging biology is a core determinant of neuronal vulnerability that matters in AD etc.



- iPSC-derived organoid systems and direct iN conversion models are complementary and evolving



- Human 3D brain models that combine defined multicellular complexity with age-retaining cells is next frontier



Mertens lab
Lucia Zhou-Yang
Larissa Traxler
Oliver Borgogno
Lukas Karbacher
Jessica Lagerwall
Sophie Eichhorner
Ismail Özcan
Cat Siler
Gerdo Wagner-Swanepoel
Mario Medina
Kylie Champion

Cardiff University
Ben Newland

Thank you!