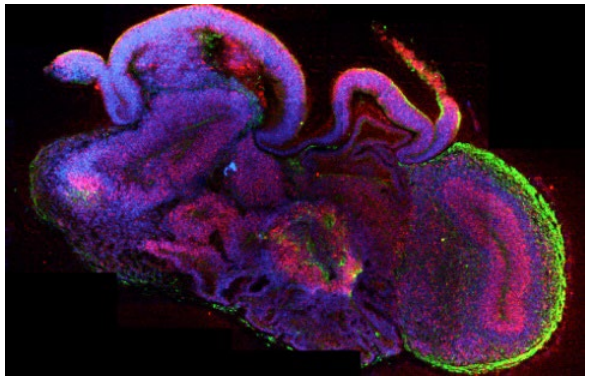
Modelling Parkinson's disease with midbrain organoids

Javier Jarazo

Co-founder and CSO

6/11/2023

Organoids news



Lancaster et al., *Nature*, 2013

The Guardian

Alok Jha, *science correspondent*

Wed 28 Aug 2013 19.00 CEST

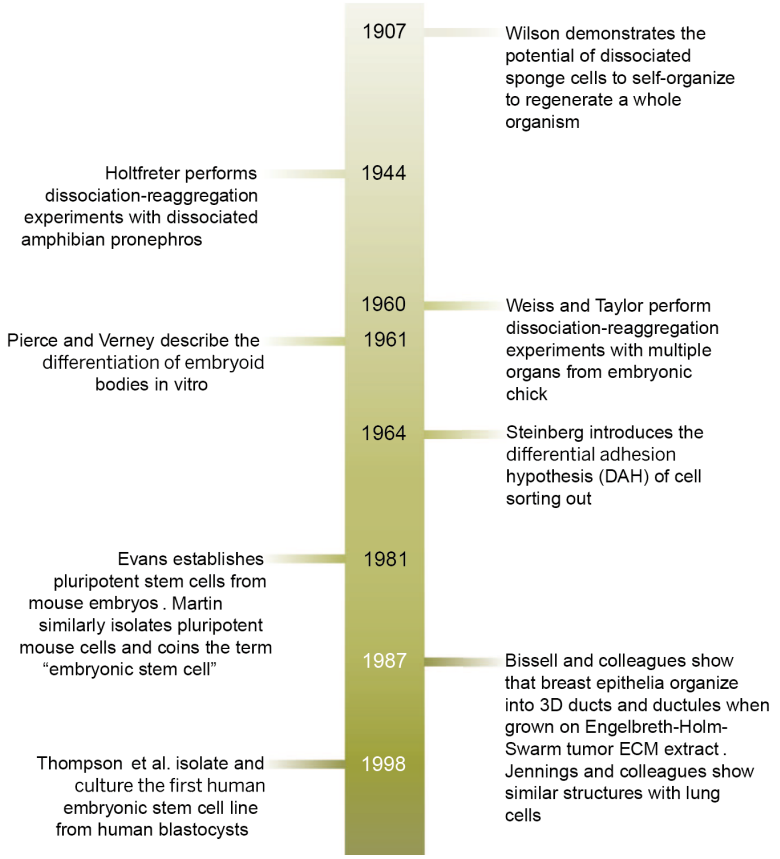
Miniature brains grown in test tubes – a new path for neuroscience?

Lab-grown 'organoids' resembling embryo brains could be used for modelling diseases and testing drugs

BBC Health NEWS

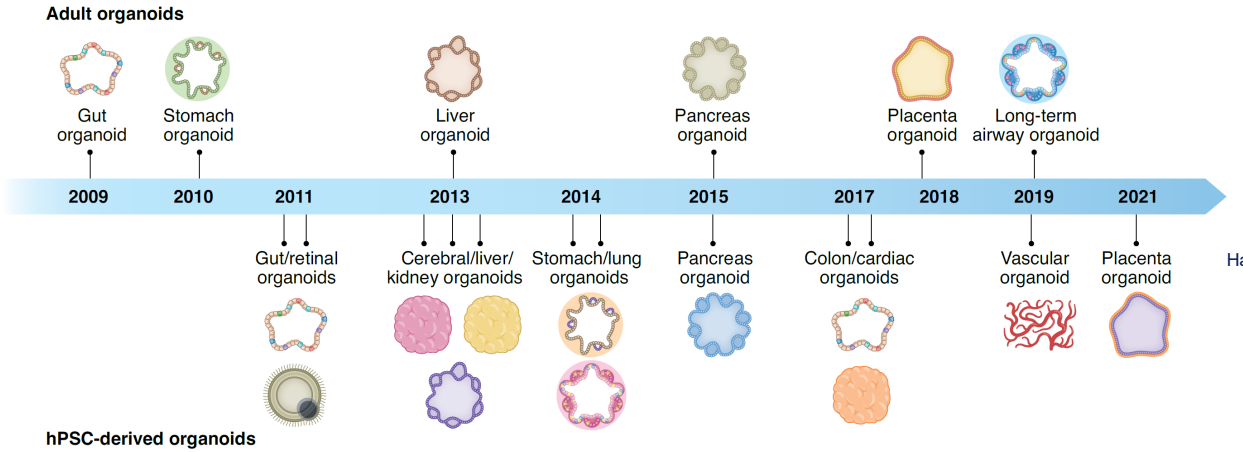
Miniature 'human brain' grown in lab

28 August 2013

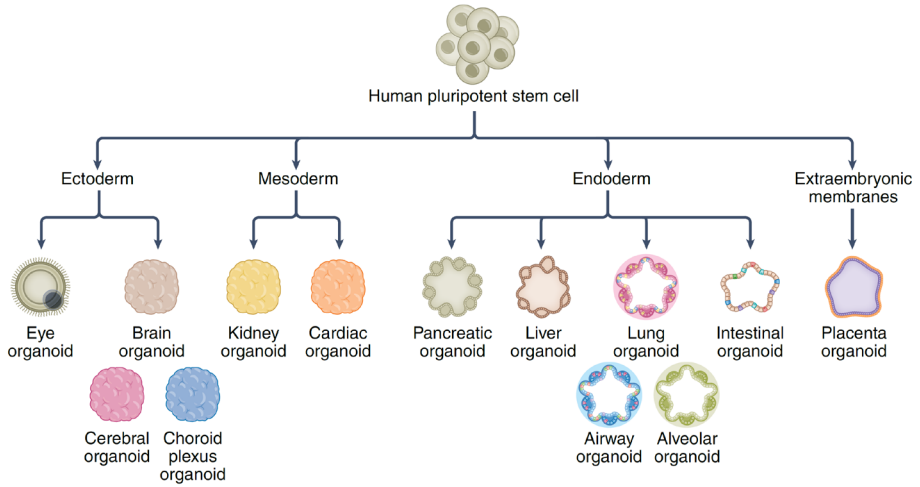


Lancaster and Knoblich., *Science*, 2014

Organoids history



Han et al., *Nature Methods*, 2022



Han et al., *Nature Methods*, 2022

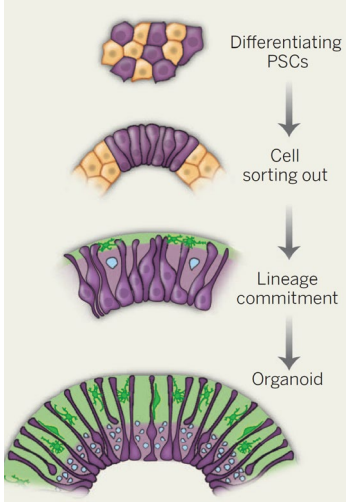
In vitro models

Organoid *n.* Resembling an organ.

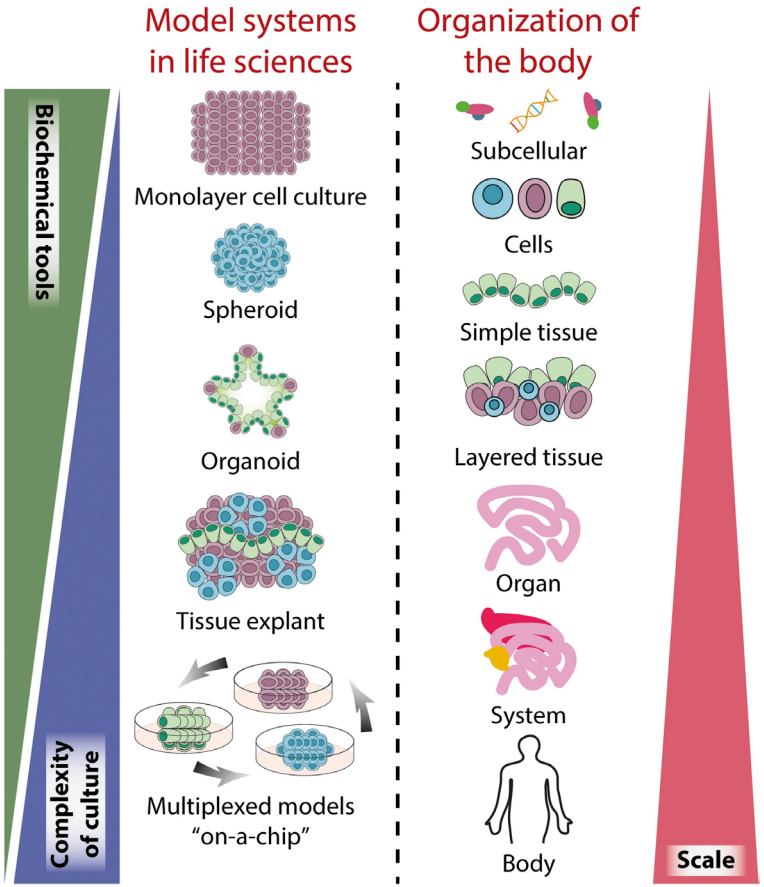
This implies:

1. Multiple organ-specific cell types
2. Capable of recapitulating some specific function of the organ (eg. excretion, filtration, neural activity, contraction)
3. Grouped together and spatially organized similar to an organ

Organoid formation recapitulates both major processes of self-organization during development: cell sorting out and spatially restricted lineage commitment

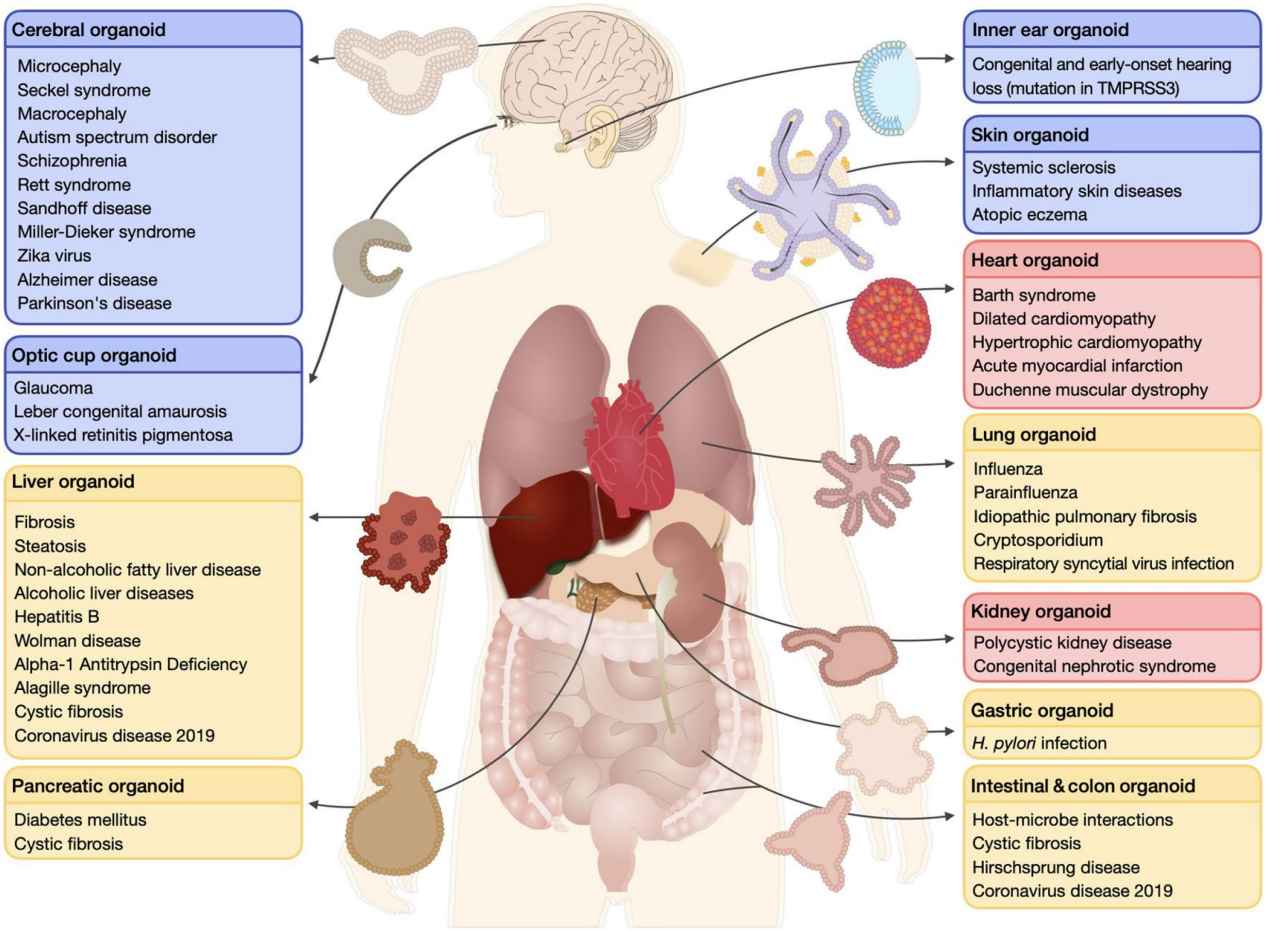


Lancaster and Knoblich., *Science*, 2014



Yin et al., *Cell Stem Cell*, 2016

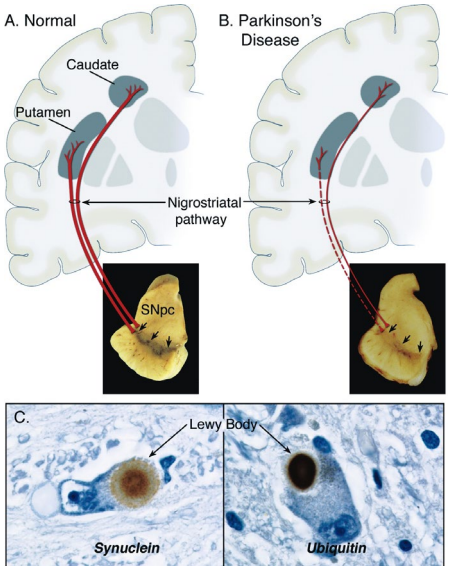
Organoid application



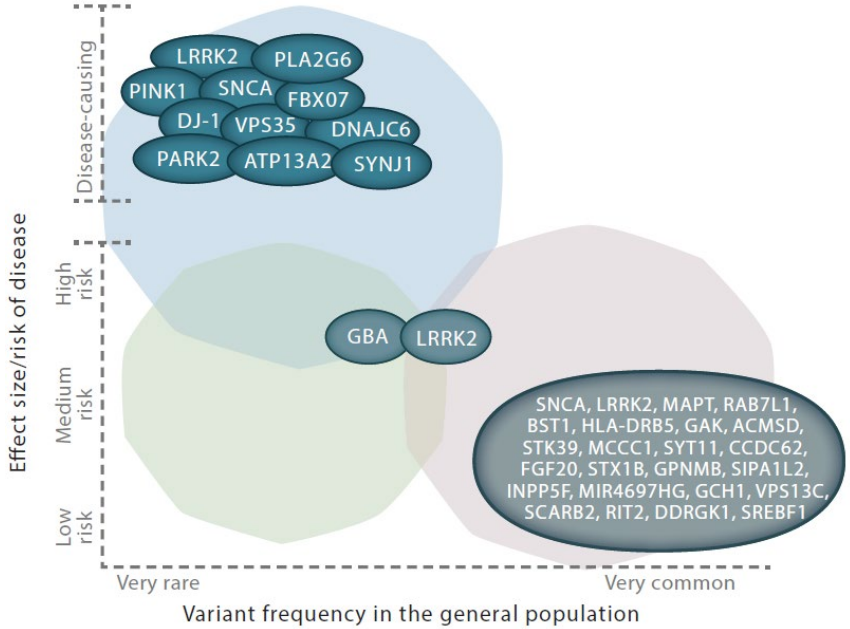
Heydari et al., *Bio-Design and Manufacturing*, 2021

Parkinson's disease

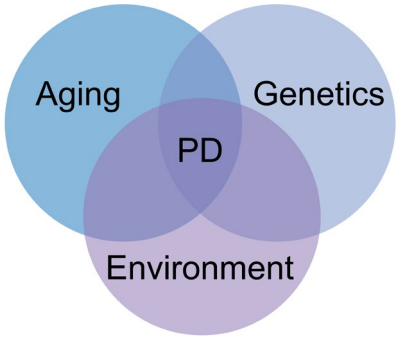
W. R. Gowers: A manual of diseases of the nervous system (1886)

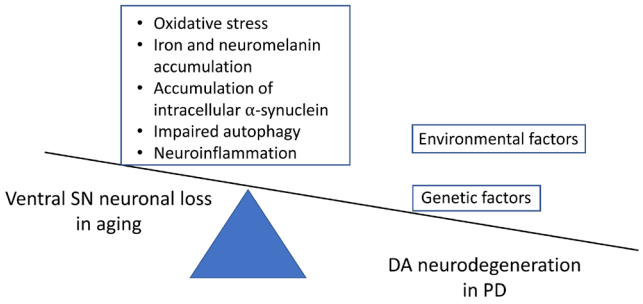


Dauer and Przedborski, *Neuron*, 2003



Bras et al., *Cell*, 2015

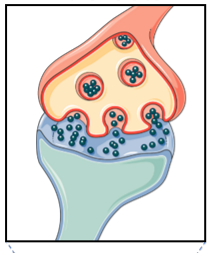


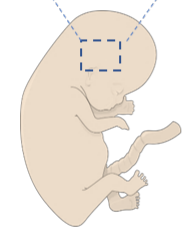


Pang et al., *Translational neurodegeneration*, 2019

Multiple hit hypothesis

Neurodevelopmental defects





First "hit"

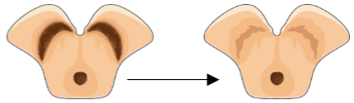
Mutations in PD associated genes

SNCA
PINK1
LRRK2
DJ-1
GBA

Neuronal Death

Second "hit"

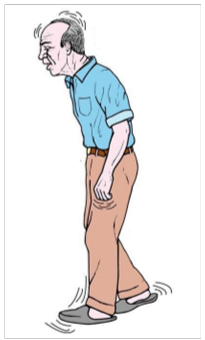
- Environment
- Brain injury
- Age



40-60% DA neuronal loss in SNc

Non motor symptoms

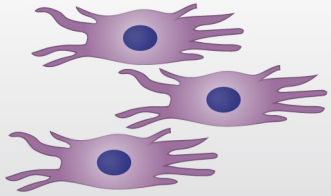
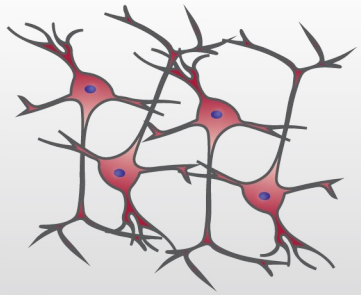
(Depression, Dementia, Sleep Disorder…)



Motor symptoms

(Bradikynesia, Rigidity, Tremor…)

PD: Previous models

Animal models	Human post mortem tissue	Human primary cells	Human DANs
			
Advantages: - Whole organism - 3D environment - Behavioral testing - Gene editing **Disadvantages:** - Ethical concerns - Poor translation to humans - Low-throughput	**Advantages:** - Human origin - Whole brain - 3D environment - Patient-specific **Disadvantages:** - Possibly poor tissue quality - Limited availability - Model end-stage disease - tissue confounds of aging and drug use - Low-throughput	**Advantages:** - Human origin - Patient-specific - Easily accessible **Disadvantages:** - Cannot model neuron-specific pathogenesis - Slow growth, few material - Hayflick limit	**Advantages:** - Human origin - Patient-specific - iPSC-derived - Gene editing - High-throughput **Disadvantages:** - Immaturity - 2D environment not physiological - Lacks brain cytoarchitecture - Largely homogeneous cultures

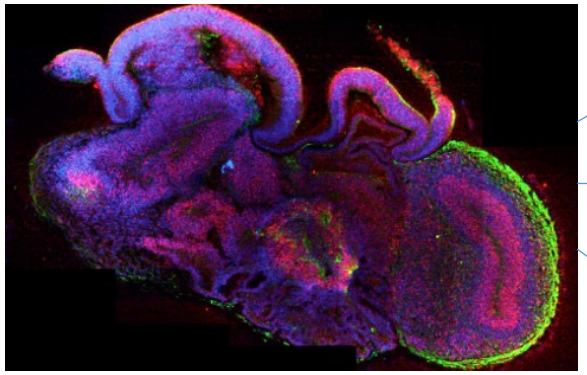
Cerebral organoids

ARTICLE

doi:10.1038/nature12517

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]



Lancaster et al., *Nature*, 2013

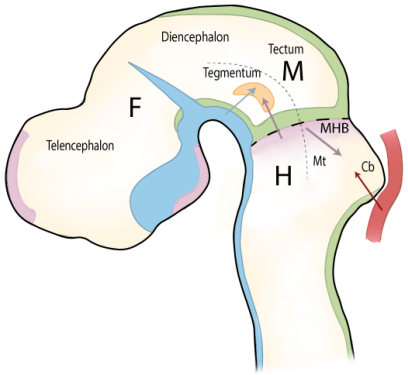
Microcephaly, autism,…

ZIKV infection

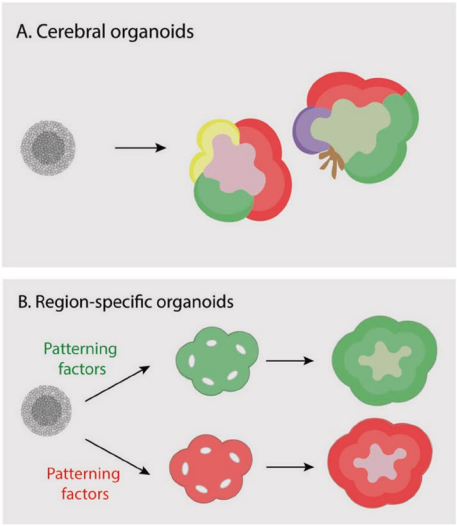
Human brain evolution

- Mostly cortical development
- High batch to batch variability
- Low abundance of mDANs (0-5%)

Not suitable to model PD

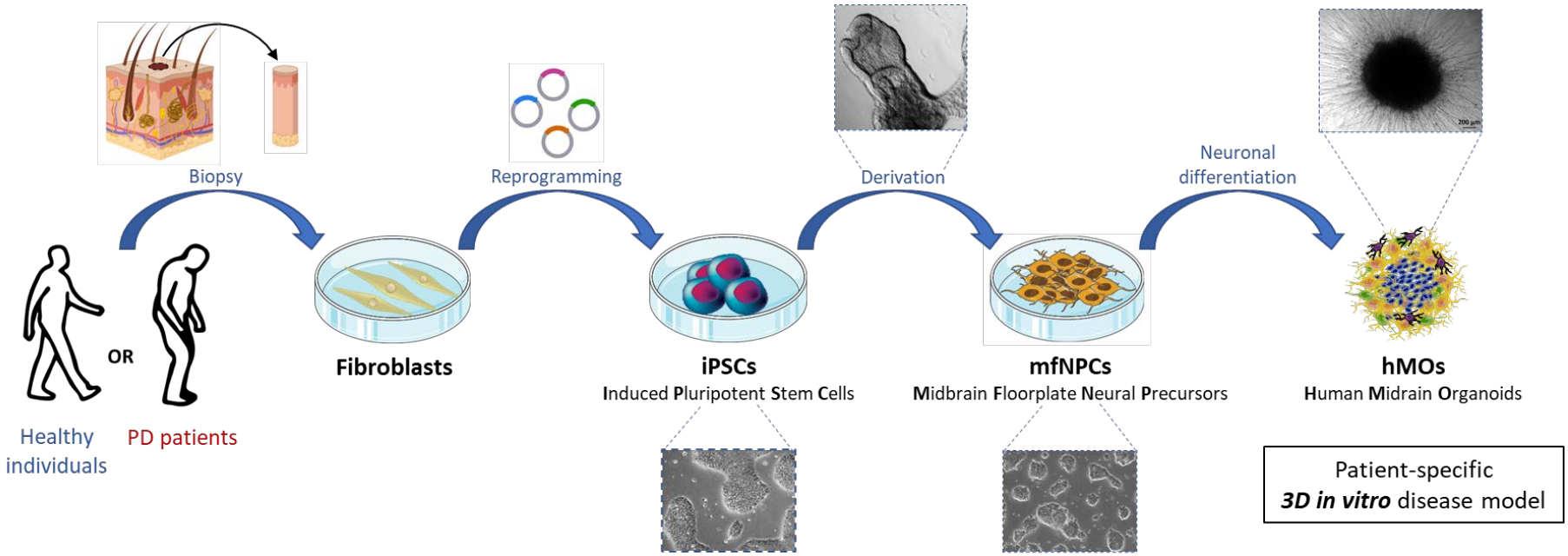


Wurst and Bally-Cuif, *Nat Rev Neurosc*, 2001



Sidhaye and Knoblich, *Cell Death & Differentiation*, 2021

Midbrain organoid



Organoid generation

Stem Cell Reports
Report
OPEN ACCESS

Derivation of Human Midbrain-Specific Organoids from Neuroepithelial Stem Cells

Anna S. Monzel,[1,4] Lisa M. Smits,[1,4] Kathrin Hemmer,[1,4] Siham Hachi,[2] Edinson Lucumi Moreno,[2] Thea van Wuellen,[1] Javier Jarazo,[1] Jonas Walter,[1] Inga Brüggemann,[1] Ibrahim Boussaad,[3] Emanuel Berger,[1] Ronan M.T. Fleming,[2] Silvia Bolognin,[1] and Jens C. Schwamborn[1,*]

[1]Developmental and Cellular Biology, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, 7, avenue des Hauts-Fourneaux, 4362 Esch-sur-Alzette, Luxembourg
[2]Systems Biochemistry
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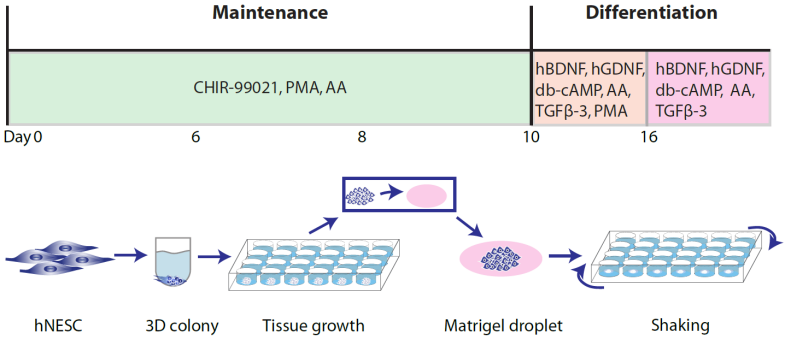
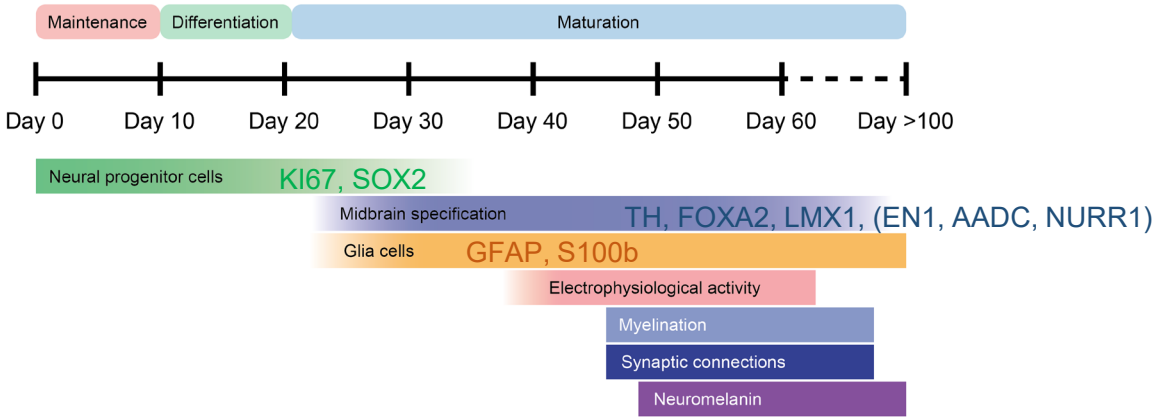
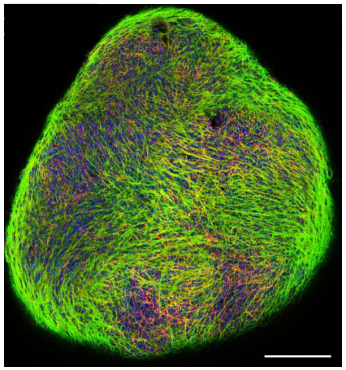
Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, 4362 Esch-sur-Alzette, Luxembourg
[4]Co-first author
*Correspondence: jens.schwamborn@uni.lu
http://dx.doi.org/10.1016/j.stemcr.2017.03.010





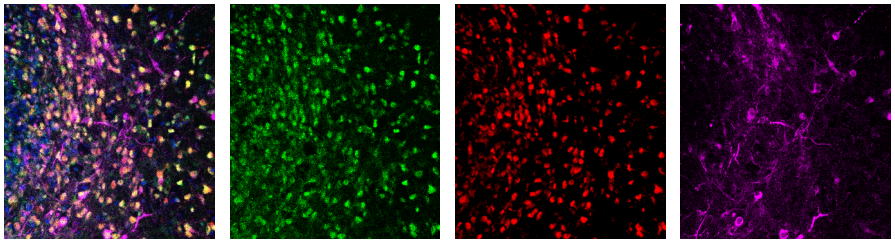
Midbrain organoids

TUBB3 TH DNA

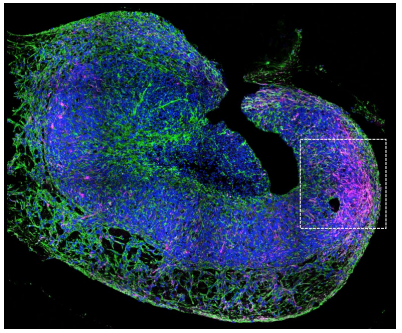


Midbrain identity

MERGED FOXA2 LMX1A TH

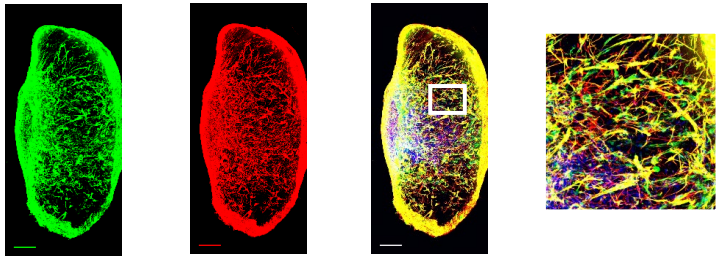


Self organization

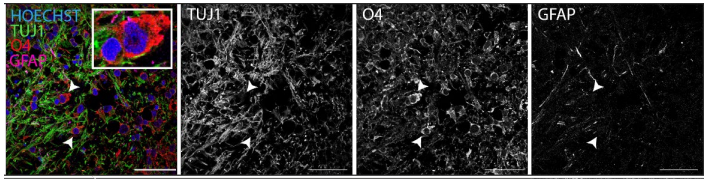


Astrocytes

S100b GFAP S100b GFAP DNA



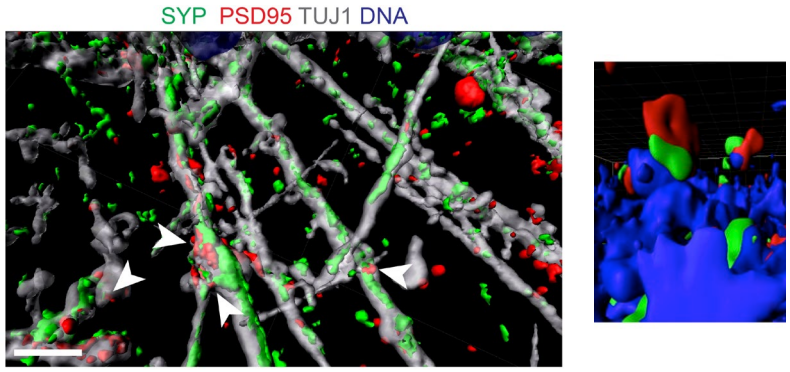
Oligodendrocytes



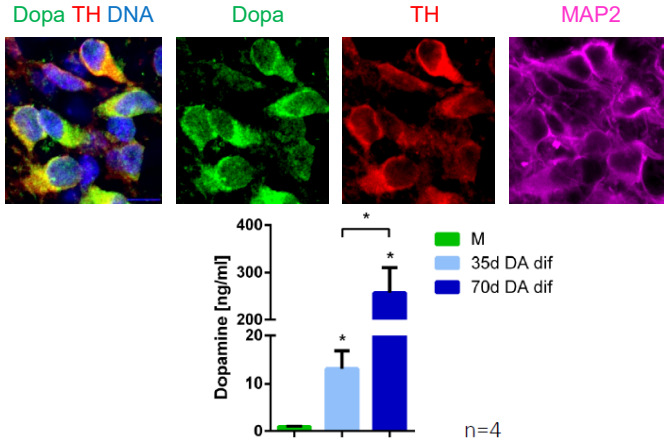
Monzel et al., *Stem Cells Reports*, 2017

Midbrain organoids

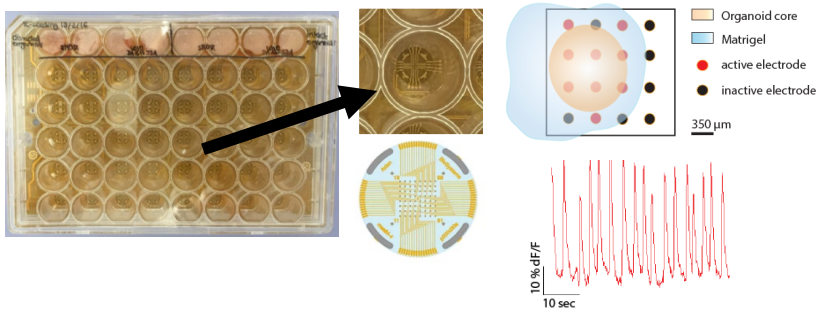
Synapses formation



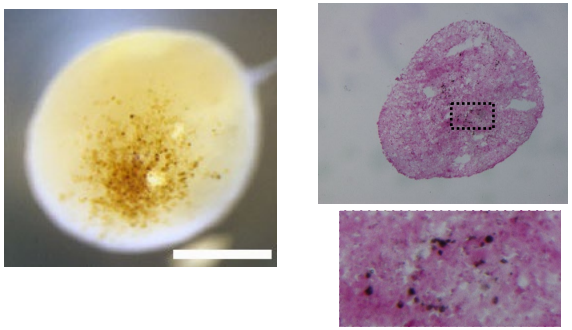
Dopamine production and release



Electrophysiological activity



Neuromelanin formation

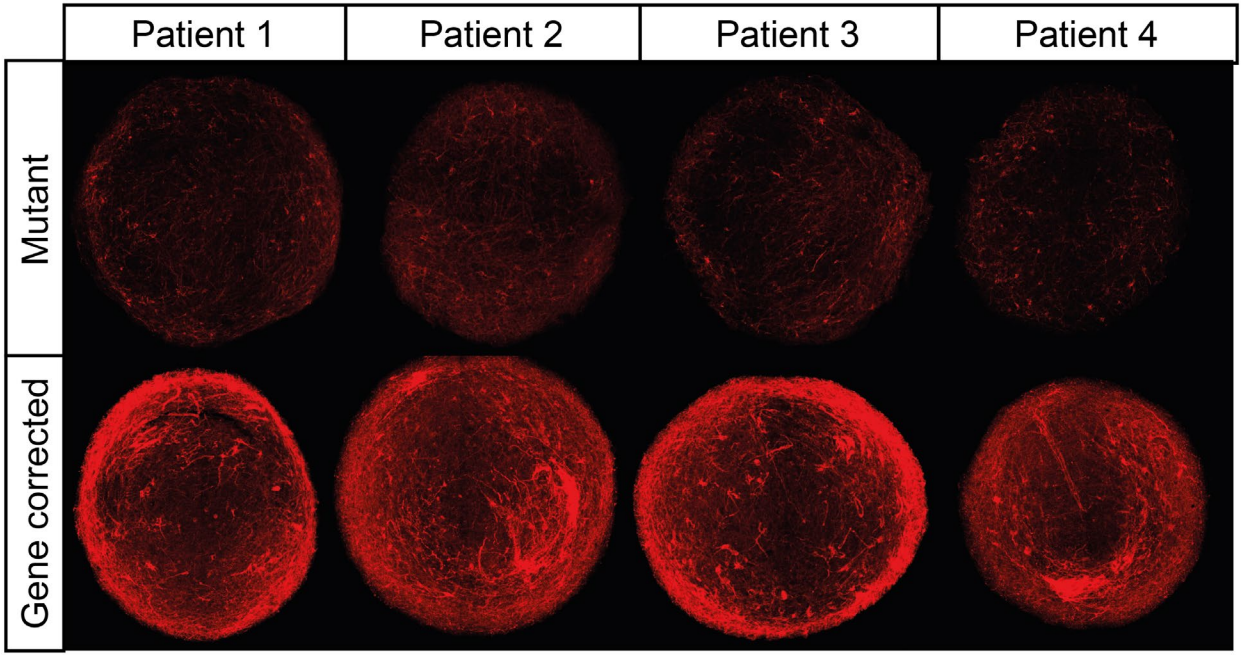


Monzel et al., *Stem Cells Reports*, 2017

Disease recapitulation

PD key characteristics:

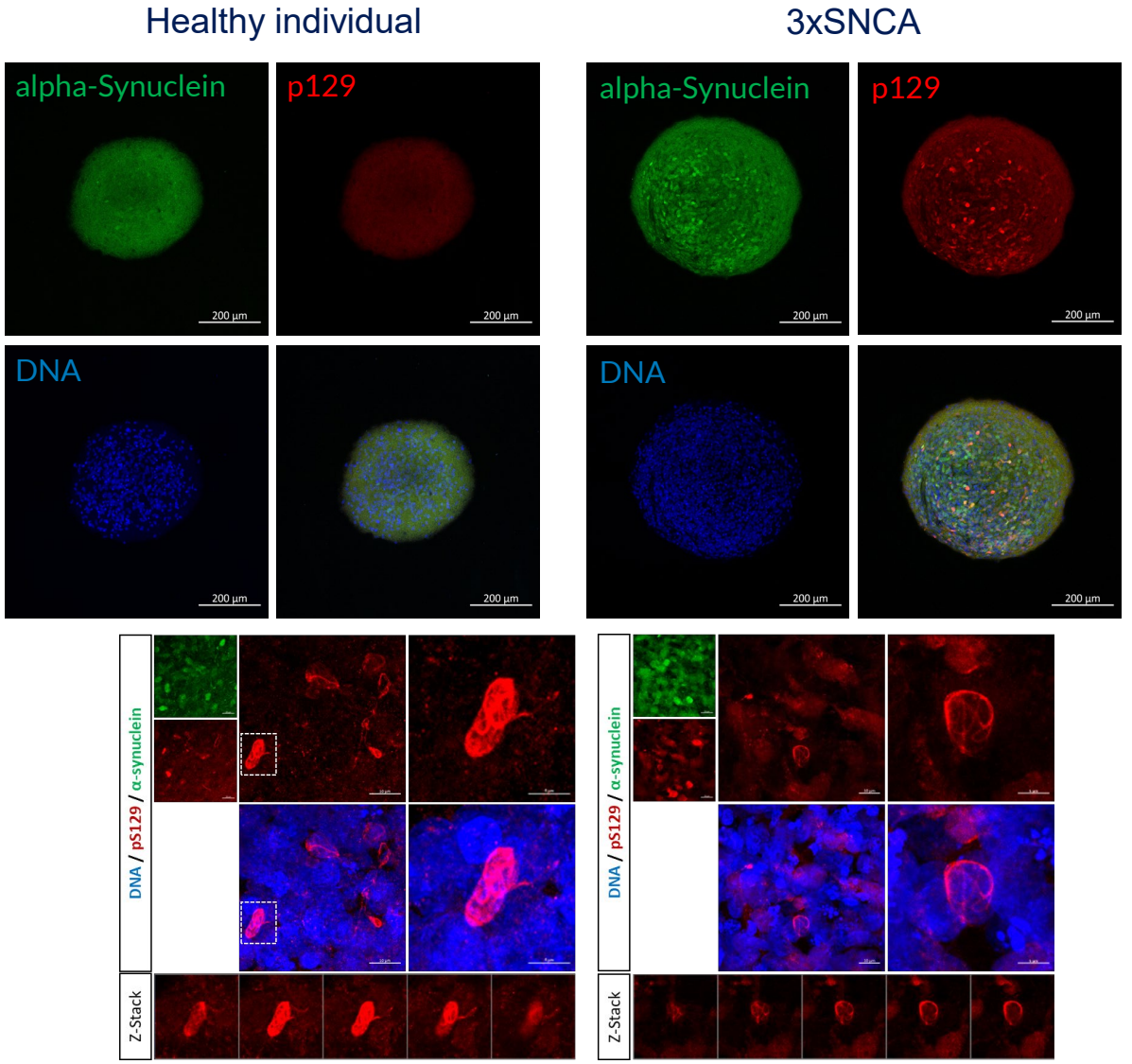
Loss of dopaminergic neurons



Disease recapitulation

PD key characteristics:

- Loss of dopaminergic neurons
- a-synuclein aggregates



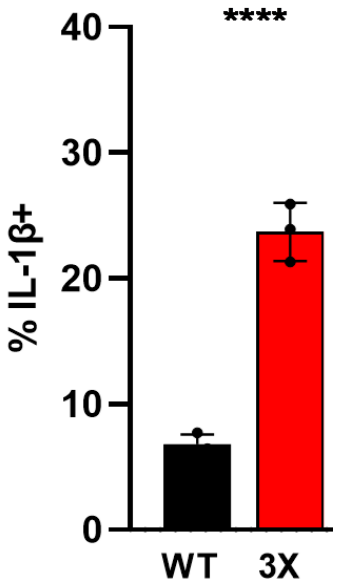
Disease recapitulation

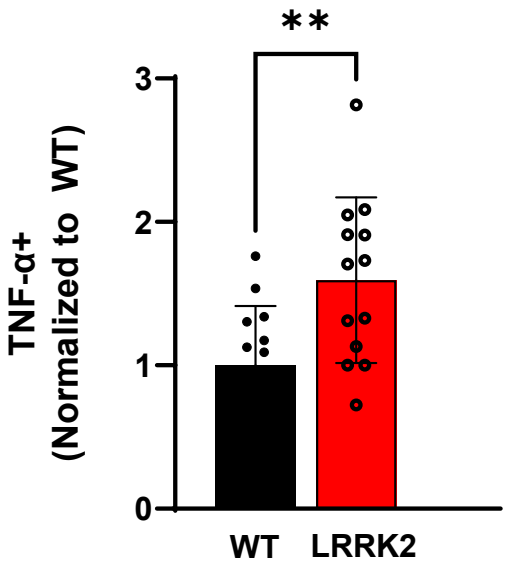
PD key characteristics:

Loss of dopaminergic neurons

a-synuclein aggregates

Neuroinflammation





Validation data

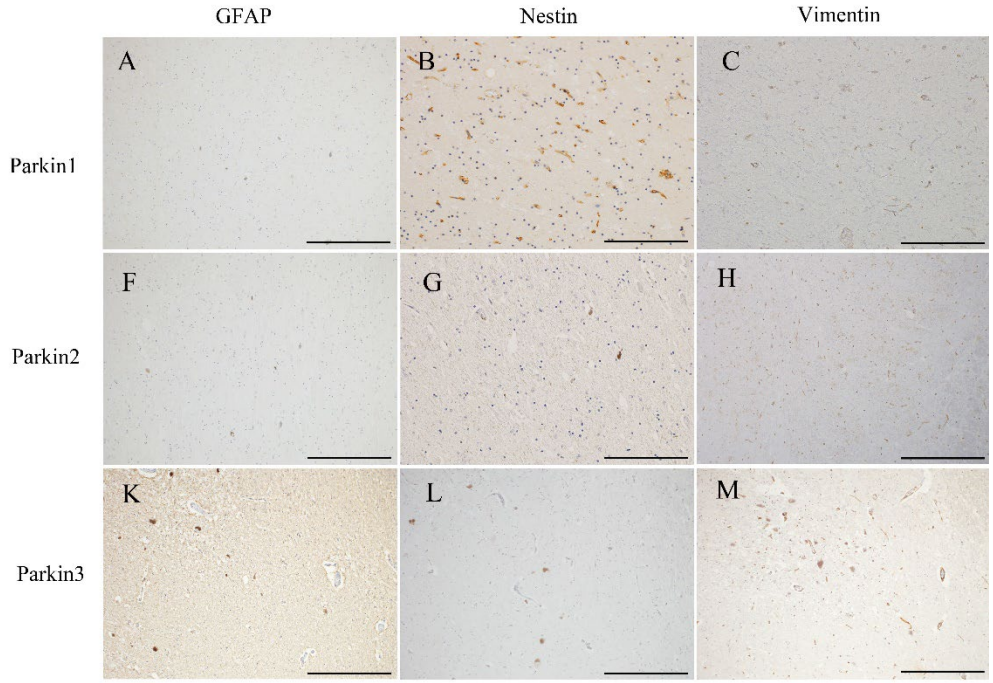
Collaboration with Prof. Nobutaka Hattori, Juntendo

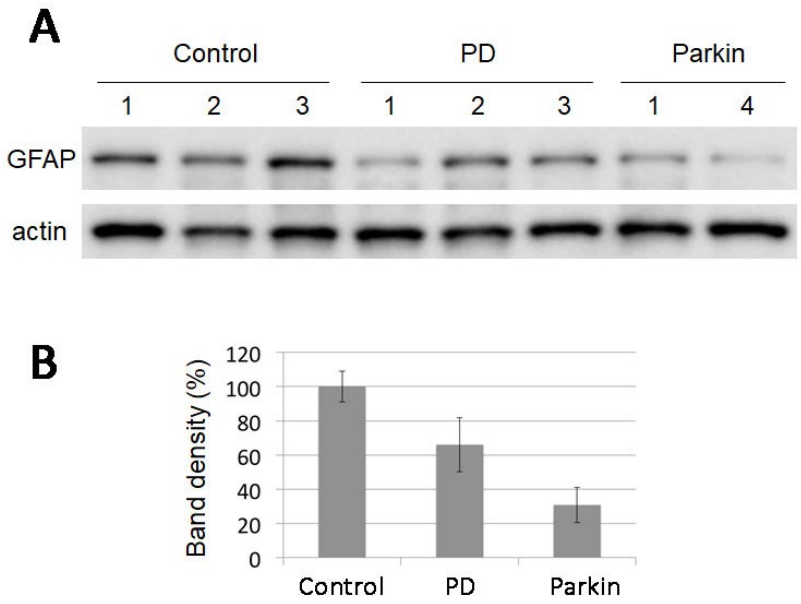
ARTICLE OPEN

npj | Parkinson's Disease

Reduced astrocytic reactivity in human brains and midbrain organoids with *PRKN* mutations

Masayoshi Kano[1], Masashi Takanashi[1✉], Genko Oyama[1], Asako Yoritaka[2], Taku Hatano[1], Kahori Shiba-Fukushima[3], Makiko Nagai[4], Kazutoshi Nishiyama[4], Kazuko Hasegawa[5], Tsuyoshi Inoshita[6], Kei-ichi Ishikawa[1,7], Wado Akamatsu[7], Yuzuru Imai[1,8], Silvia Bolognin[9,10], Jens Christian Schwamborn[9,10] and Nobutaka Hattori[1✉]

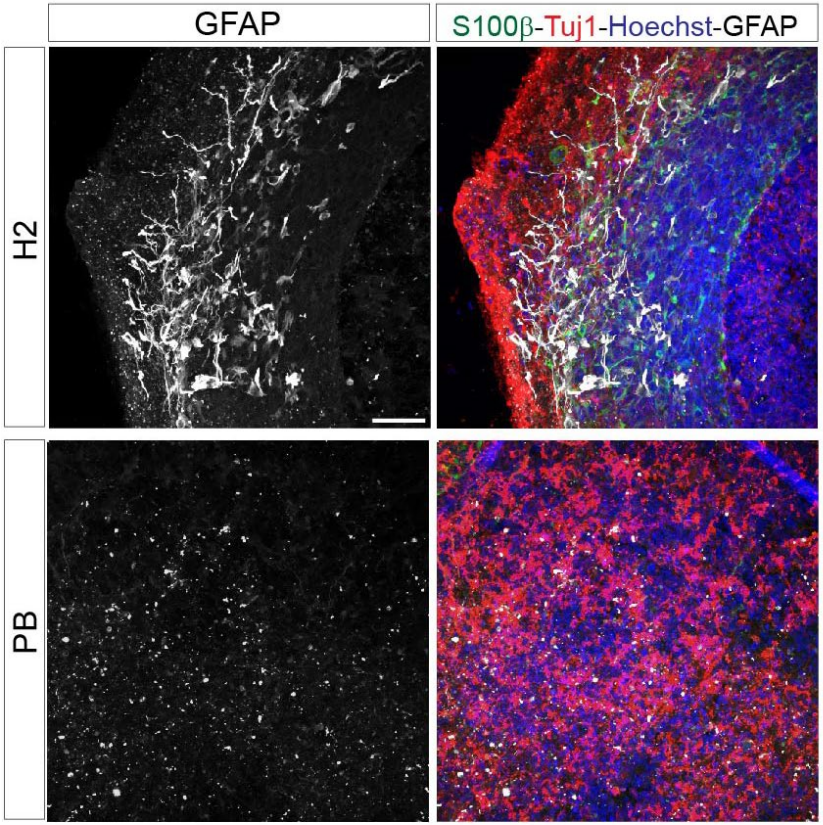


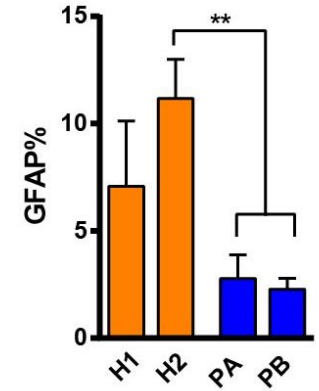


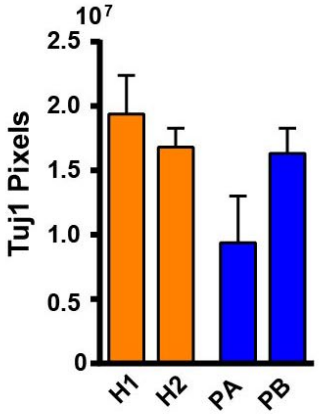
Kano et al., *npj Parkinson's Disease*, 2020

Validation data

Collaboration with Prof. Nobutaka Hattori, Juntendo







Kano et al., *npj Parkinson's Disease*, 2020

Use cases

Disease phenotyping

BRIEF COMMUNICATION OPEN

npj | Parkinson's Disease

Modeling Parkinson's disease in midbrain-like organoids

Lisa M. Smits[1], Lydia Reinhardt[2,3], Peter Reinhardt[2,3,6], Michael Glatza[2,3], Anna S. Monzel[1], Nancy Stanslowsky[4], Marcelo D. Rosato-Siri[5], Alessandra Zanon[5], Paul M. Antony[1], Jessica Bellmann[2], Sarah M. Nicklas[1], Kathrin Hemmer[1], Xiaobing Qing[1], Emanuel Berger[1], Norman Kalmbach[4], Marc Ehrlich[3], Silvia Bolognin[1], Andrew A. Hicks[5], Florian Wegner[4], Jared L. Sterneckert[2,3] and Jens C. Schwamborn[1]

Cell and Tissue Research (2020) 382:463–476
https://doi.org/10.1007/s00441-020-03249-y

REGULAR ARTICLE

Check for updates

Single-cell transcriptomics reveals multiple neuronal cell types in human midbrain-specific organoids

Lisa M. Smits[1] · Stefano Magni[1] · Kaoru Kinugawa[2] · Kamil Grzyb[1] · Joachim Luginbühl[3] · Sonia Sabate-Soler[1] · Silvia Bolognin[1] · Jay W. Shin[3] · Eiichiro Mori[2] · Alexander Skupin[1,4] · Jens C. Schwamborn[1]

Stem Cell Research 46 (2020) 101870
Contents lists available at ScienceDirect
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journal homepage: www.elsevier.com/locate/scr

Reproducible generation of human midbrain organoids for *in vitro* modeling of Parkinson's disease

Sarah Louise Nickels[a,b], Jennifer Modamio[a], Bárbara Mendes-Pinheiro[a,c,d], Anna Sophia Monzel[a], Fay Betsou[b], Jens Christian Schwamborn[a,*]

Parkinsonism and Related Disorders 75 (2020) 105–109
Contents lists available at ScienceDirect
Parkinsonism and Related Disorders
journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Machine learning-assisted neurotoxicity prediction in human midbrain organoids

Anna S. Monzel[a], Kathrin Hemmer[a], Tony Kaoma[b], Lisa M. Smits[a], Silvia Bolognin[a], Philippe Lucarelli[a], Isabel Rosety[a], Alise Zagare[a], Paul Antony[a], Sarah L. Nickels[a], Rejko Krueger[c,d,e], Francisco Azuaje[b,f], Jens C. Schwamborn[a,*]

scientific reports

PINK1 deficiency impairs adult neurogenesis of dopaminergic neurons

Sarah J. Brown[1,2,3,13], Ibrahim Boussaad[5,6,13], Javier Jarazo[7,8,13], Julia C. Fitzgerald[9], Paul Antony[5], Marcus Keatinge[1,3,4], Janna Blechman[10], Jens C. Schwamborn[7,8], Rejko Krüger[5,11,12], Marysia Placzek[1,2,13] & Oliver Bandmann[1,3,13]✉

AJHG ARTICLE

Midbrain organoids mimic early embryonic neurodevelopment and recapitulate LRRK2-p.Gly2019Ser-associated gene expression

Alise Zagare,[1,2] Kyriaki Barmpa,[1,2] Semra Smajic,[1] Lisa M. Smits,[1] Kamil Grzyb,[1] Anne Grünewald,[1] Alexander Skupin,[1] Sarah L. Nickels,[1,*] and Jens C. Schwamborn[1,*]

Drug testing

RESEARCH ARTICLE

Parkinson's Disease Phenotypes in Patient Neuronal Cultures and Brain Organoids Improved by 2-Hydroxypropyl-β-Cyclodextrin Treatment

Javier Jarazo, PhD,[1,2] Kyriaki Barmpa, MSc,[1] Jennifer Modamio, PhD,[1] Cláudia Saraiva, PhD,[1] Sònia Sabaté-Soler, MSc,[1] Isabel Rosety, MSc,[1] Anne Griesbeck, PhD,[3] Florian Skwirblies, BSc,[3] Gaia Zaffaroni, PhD,[4] Lisa M. Smits, PhD,[1] Jihui Su, BSc,[5] Jonathan Arias-Fuenzalida, PhD,[1] Jonas Walter, PhD,[1] Gemma Gomez-Giro, PhD,[1] Anna S. Monzel, PhD,[1] Xiaobing Qing, PhD,[1] Armelle Vitali, MSc,[6] Gerald Cruciani, MSc,[6,7] Ibrahim Boussaad, PhD,[6,7] Francesco Brunelli, PhD,[8] Christian Jäger, PhD,[9] Aleksandar Rakovic, PhD,[10] Wen Li, PhD,[5] Lin Yuan, PhD,[5] Emanuel Berger, PhD,[1] Giuseppe Arena, PhD,[6] Silvia Bolognin, PhD,[1] Ronny Schmidt, PhD,[3] Christoph Schröder, PhD,[3] Paul M.A. Antony, PhD,[6] Christine Klein, MD,[10] Rejko Krüger, MD,[6,11,12] Philip Seibler, PhD,[10] and Jens C. Schwamborn, PhD[1*]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

A patient-based model of RNA mis-splicing uncovers treatment targets in Parkinson's disease

Ibrahim Boussaad[1]*, Carolin D. Obermaier[1,2]*, Zoé Hanss[1], Dheeraj R. Bobbili[1], Silvia Bolognin[1], Enrico Glaab[1], Katarzyna Wołyńska[3], Nicole Weisschuh[4], Laura De Conti[5], Caroline May[6], Florian Giesert[7,8,9], Dajana Grossmann[1], Annika Lambert[1], Susanne Kirchen[1], Maria Biryukov[1], Lena F. Burbulla[10], Francois Massart[1], Jill Bohler[1], Gérald Cruciani[1], Benjamin Schmid[2], Annerose Kurz-Drexler[7], Patrick May[1], Stefano Duga[11,12], Christine Klein[13], Jens C. Schwamborn[1], Katrin Marcus[6], Dirk Woitalla[14], Daniela M. Vogt Weisenhorn[7,9], Wolfgang Wurst[7,8,9,15], Marco Baralle[5], Dimitri Krainc[10], Thomas Gasser[2,16], Bernd Wissinger[4], Rejko Krüger[1,2,17,18†]

Science AAAS

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ANIMAL RESEARCH

FDA no longer has to require animal testing for new drugs

Agency can rely on animal-free alternatives before human trials

Drug development

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

A patient-based model of RNA mis-splicing uncovers treatment targets in Parkinson's disease

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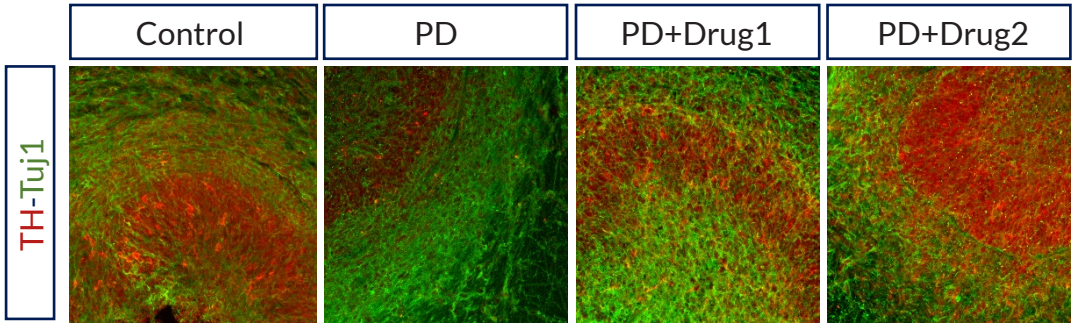
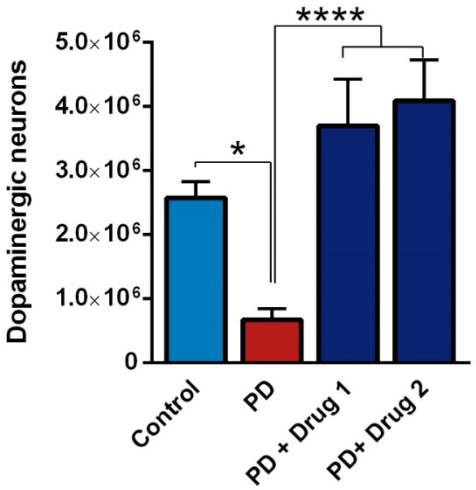


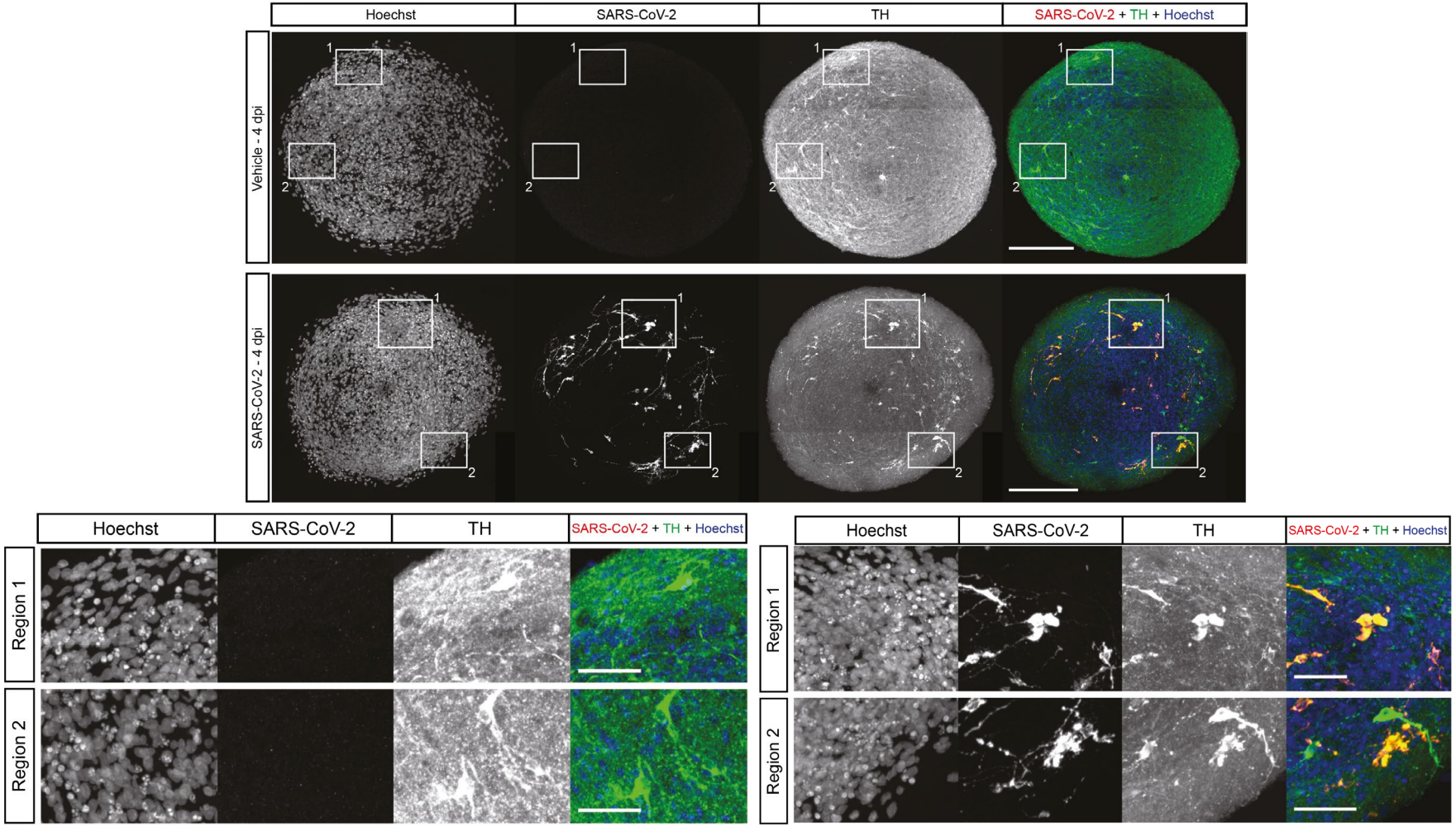
25 days of treatment with two drugs rescued the dopaminergic neuron loss in organoids derived from a PD patient



Boussad et al., *Science Translational Medicine*, 2020

Use cases

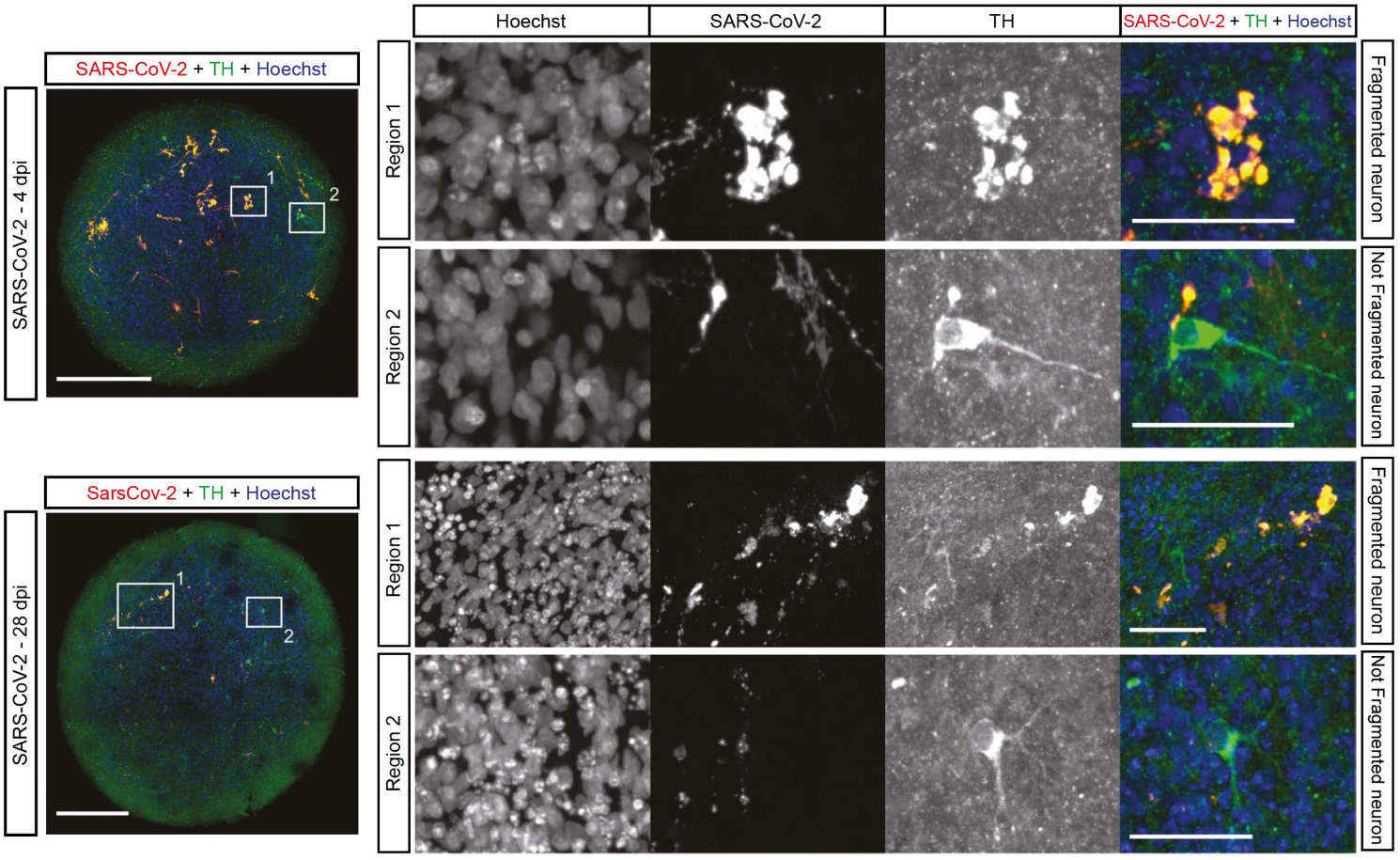
SARS-CoV-2 infection



Jarazo et al., *biorxiv*, 2023

Use cases

SARS-CoV-2 infection



Jarazo et al., *biorxiv*, 2023

Use cases

Collaboration with:

Klinikum rechts der Isar
Technische Universität München

Clinical trial for treatment of PD patients with Fasudil.

OrganoTherapeutics will generate brain organoids from 25 patients & treat with Fasudil.

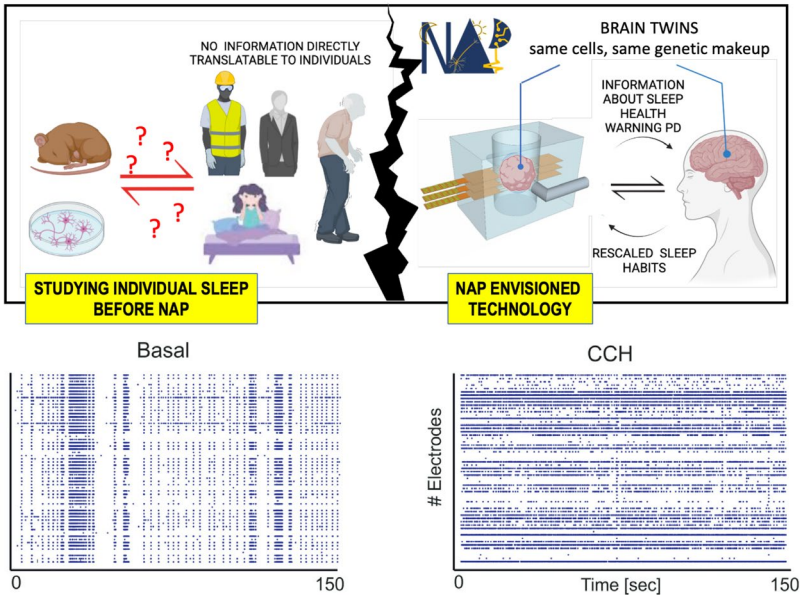
Correlation of clinical data with brain organoid data.

↓

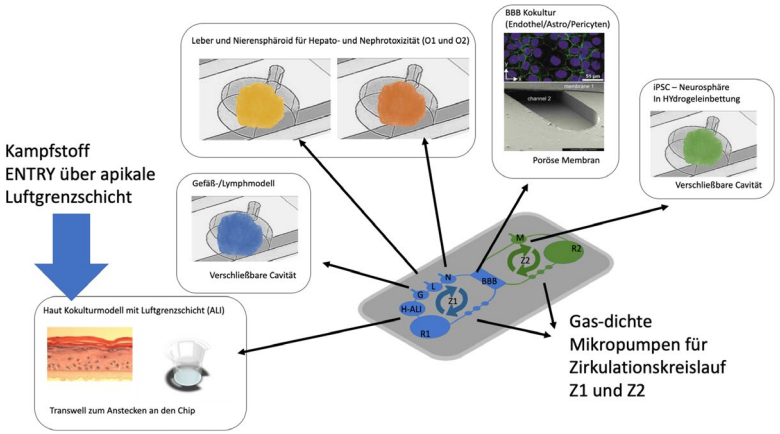
Decision support for treatment options.
Entry into true personalized medicine for PD.

Use cases

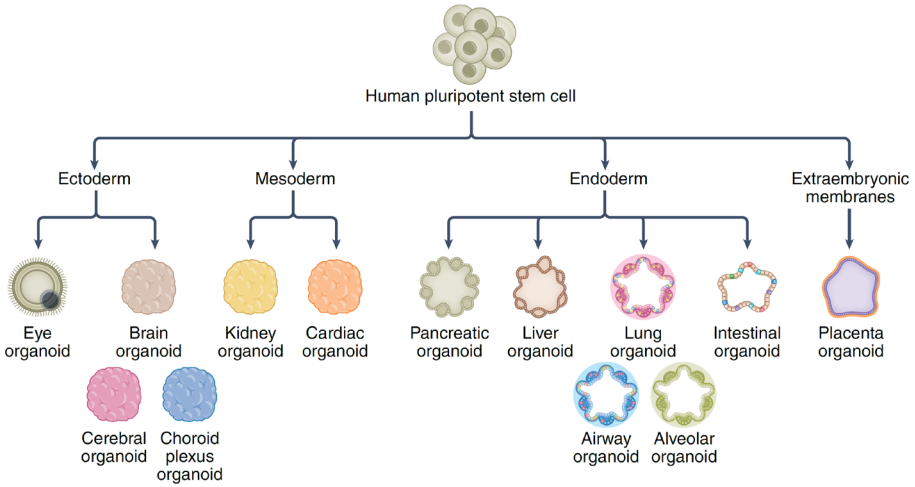
European Innovation Council



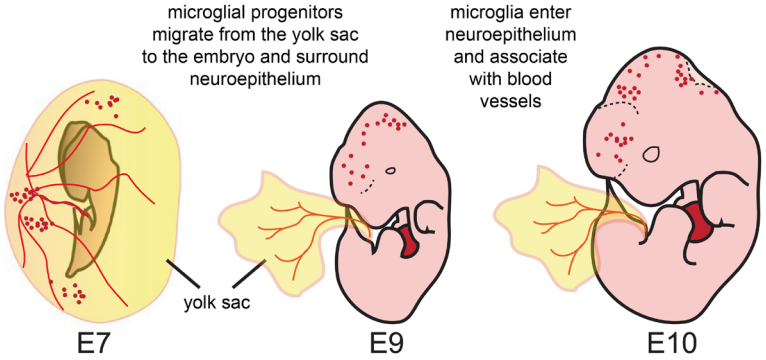
BodyTox



Model improvement



Han et al., *Nature Methods*, 2022



Arnold and Betsholtz., *Vascular Cell*, 2013

Microglia incorporation

Received: 21 January 2022 | Revised: 25 February 2022 | Accepted: 28 February 2022
DOI: 10.1002/glia.24167

GLIA
WILEY

RESEARCH ARTICLE

Microglia integration into human midbrain organoids leads to increased neuronal maturation and functionality

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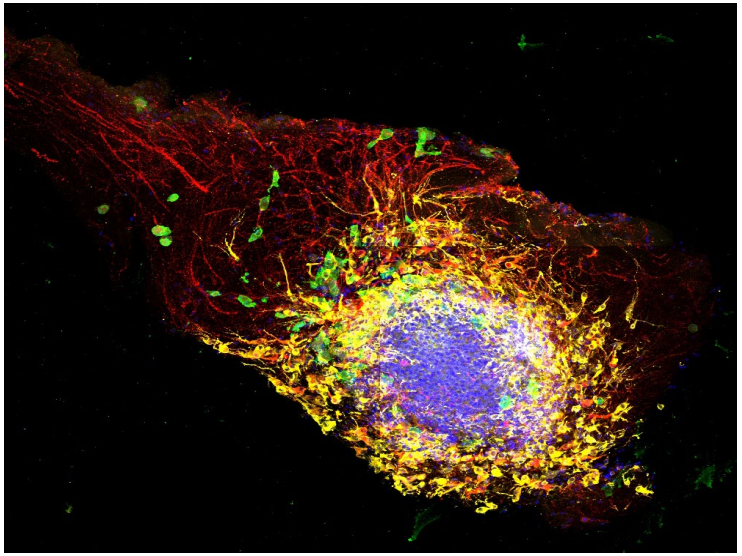
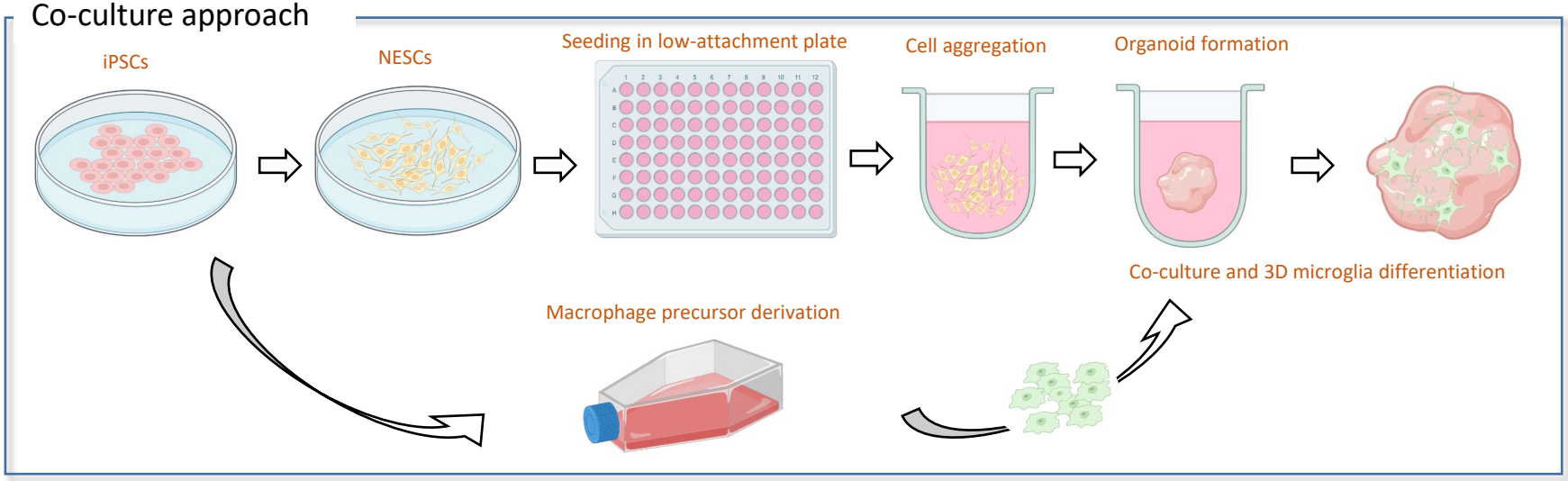
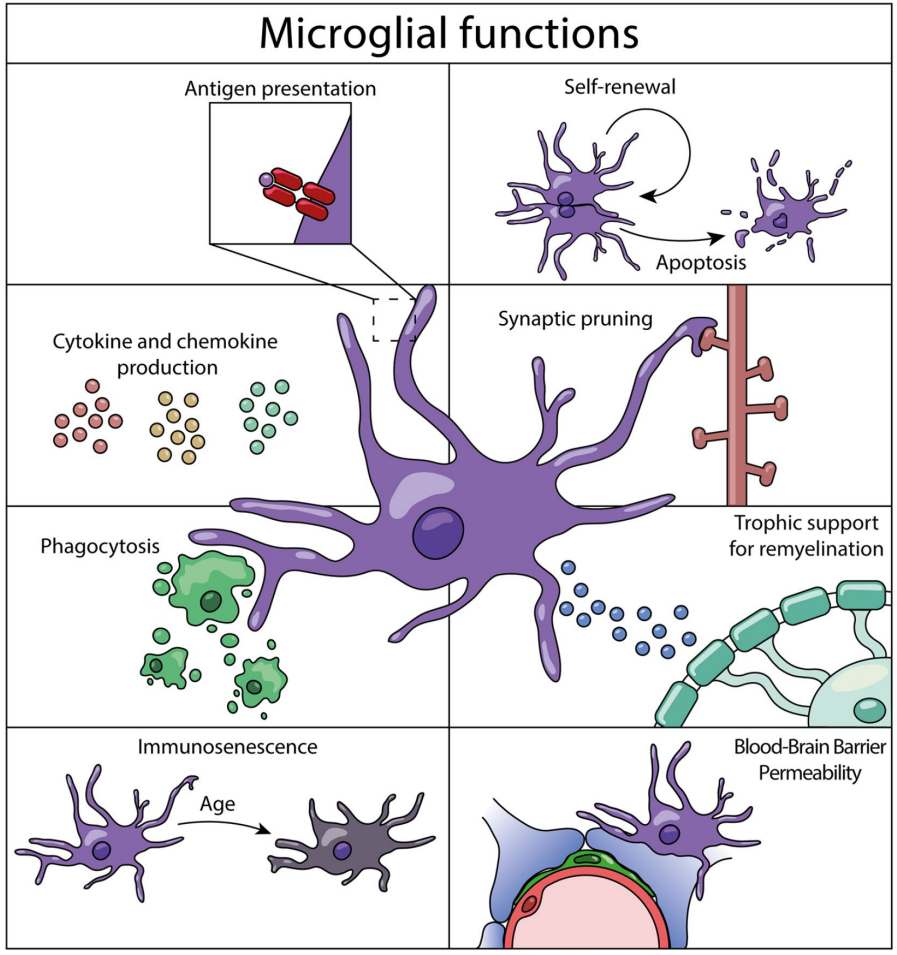


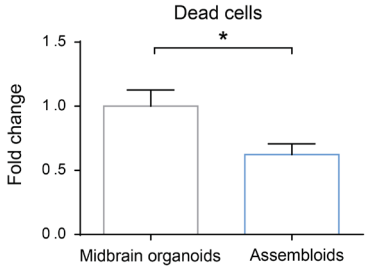


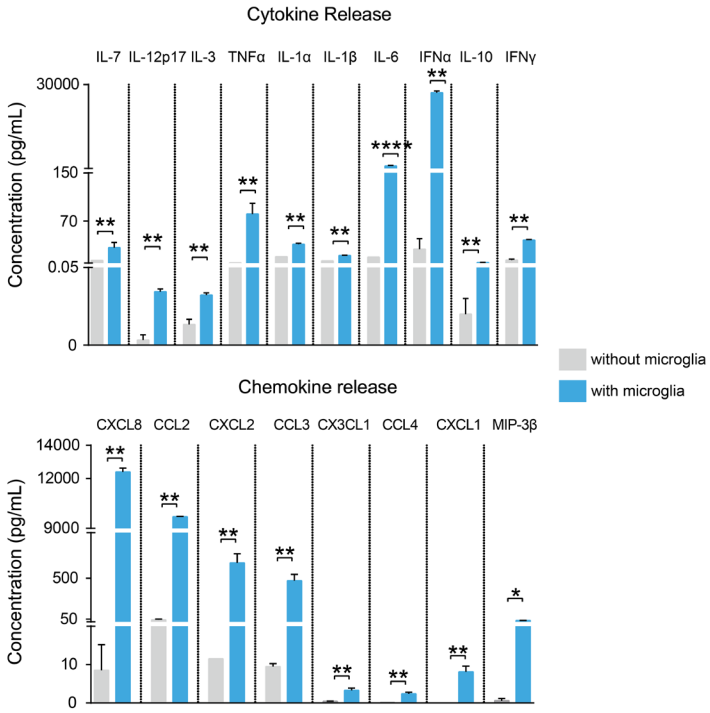
Microglia incorporation



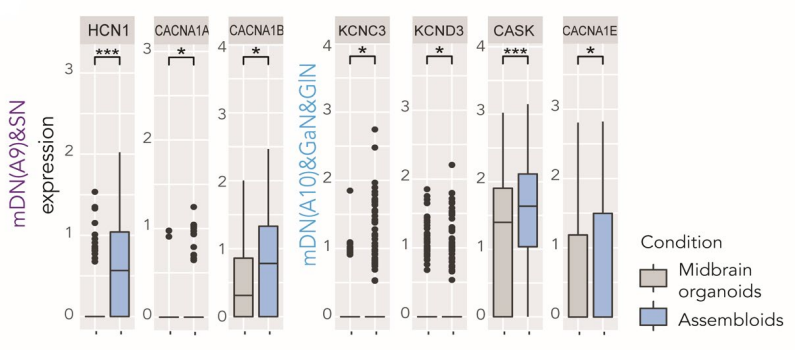
Amor et al., *Acta Neuropathologica*, 2022

Microglia incorporation

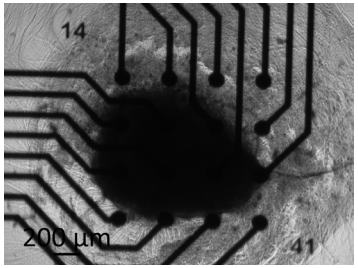


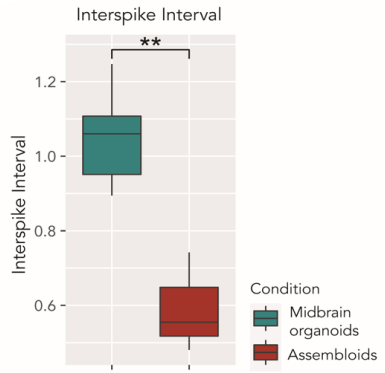


Synapse functionality



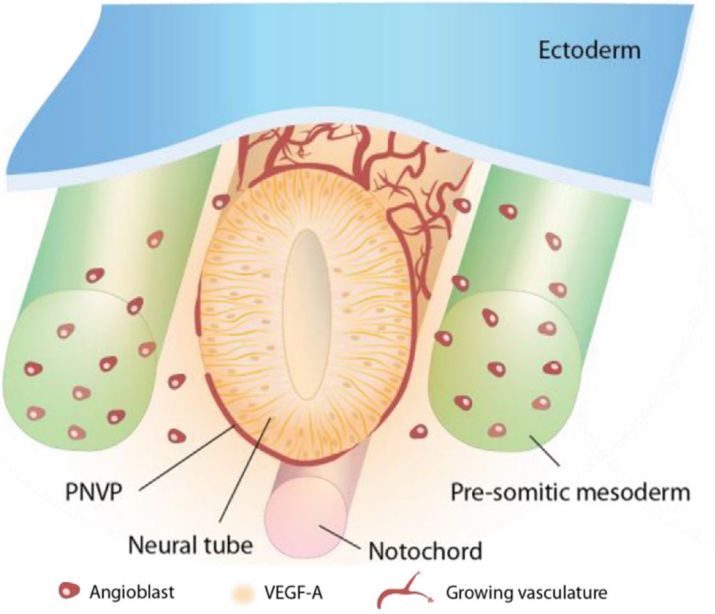
Multi-electrode array (MEA)





Sabate-Soler et al., *Glia*, 2022

Vasculature incorporation



Paguera et al., *Curr. Op. Neurobiology*, 2021

LETTER

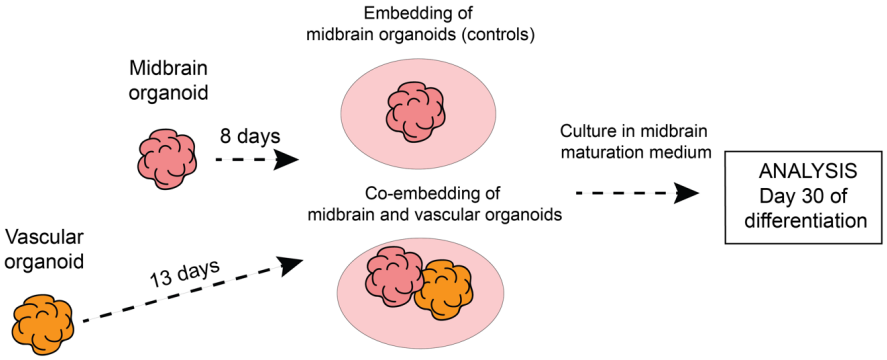
https://doi.org/10.1038/s41586-018-0858-8

Human blood vessel organoids as a model of diabetic vasculopathy

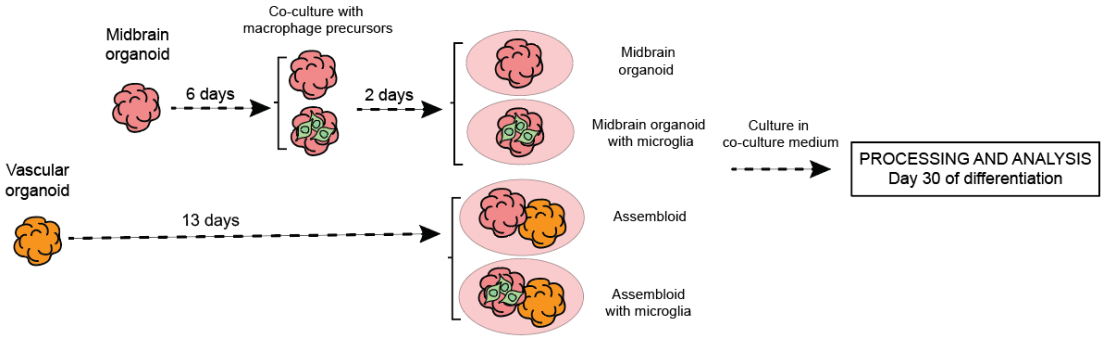
Reiner A. Wimmer[1]*, Alexandra Leopoldi[1], Martin Aichinger[2], Nikolaus Wick[3], Brigitte Hantusch[3], Maria Novatchkova[1], Jasmin Taubenschmid[1], Monika Hämmerle[3], Christopher Esk[1], Joshua A. Bagley[1], Dominik Lindenhofer[1], Guibin Chen[4], Manfred Boehm[4], Chukwuma A. Agu[1], Fengtang Yang[5], Beiyuan Fu[5], Johannes Zuber[2], Juergen A. Knoblich[1], Dontscho Kerjaschki[3] & Josef M. Penninger[1,6]*

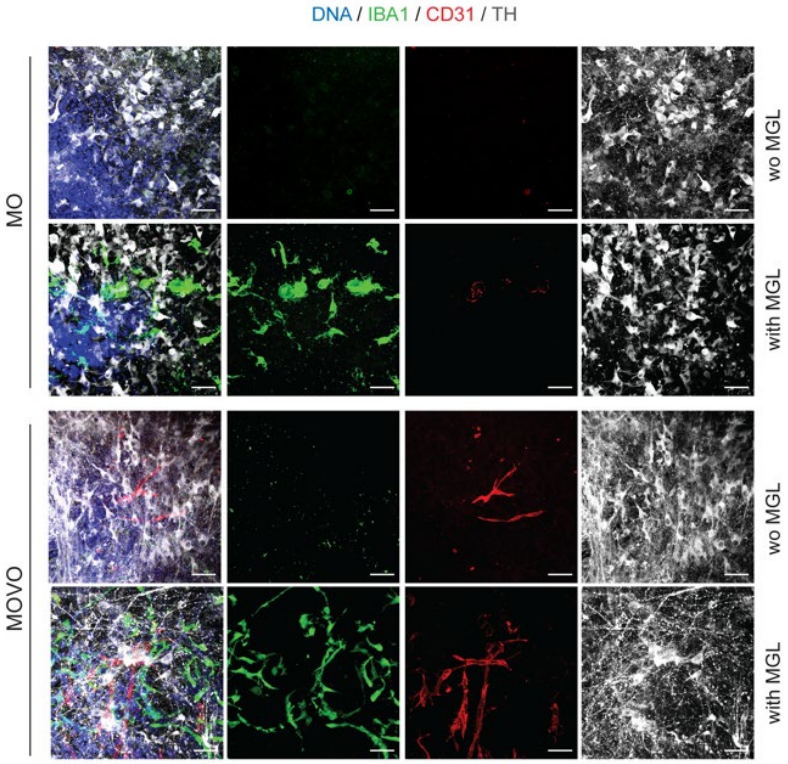
Development:

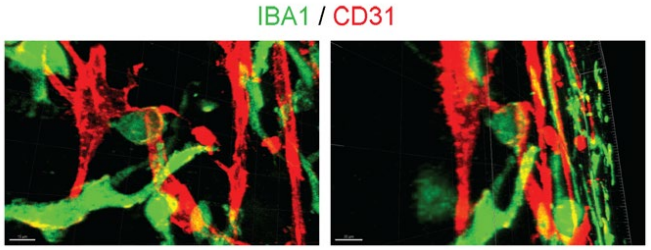
- Endothelial cell precursors from the somites (angioblasts) establish the peri-neural vascular plexus (PNVP).
- Cells form the PNVP follow proangiogenic molecular queues, mainly VEGF-A.
- Endothelial cells will form close contacts via tight and adherens junctions, forming the BBB.

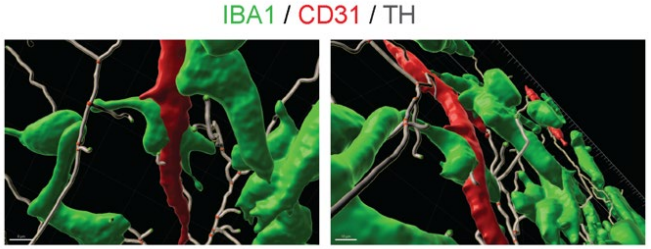


Vasculature incorporation



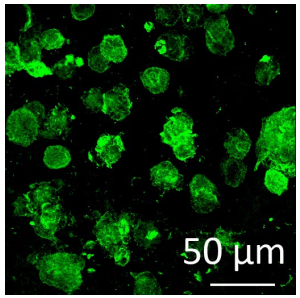


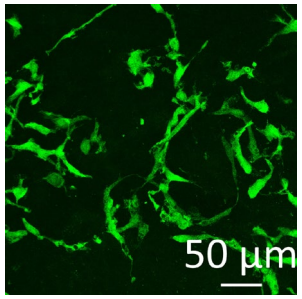




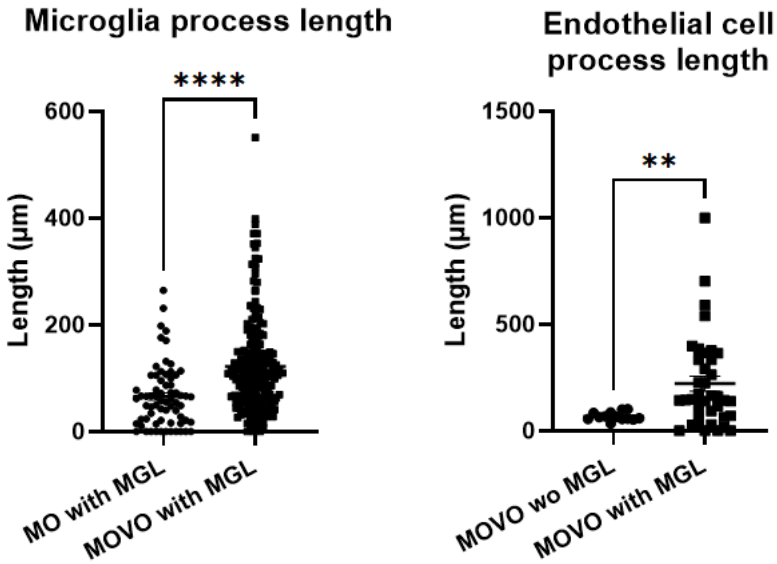
Vasculature incorporation

IBA1

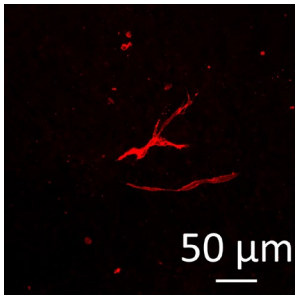


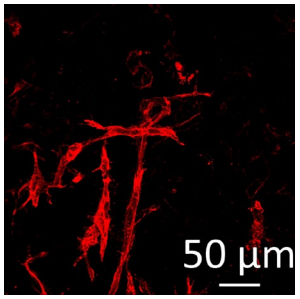


Morphological complexity



CD31

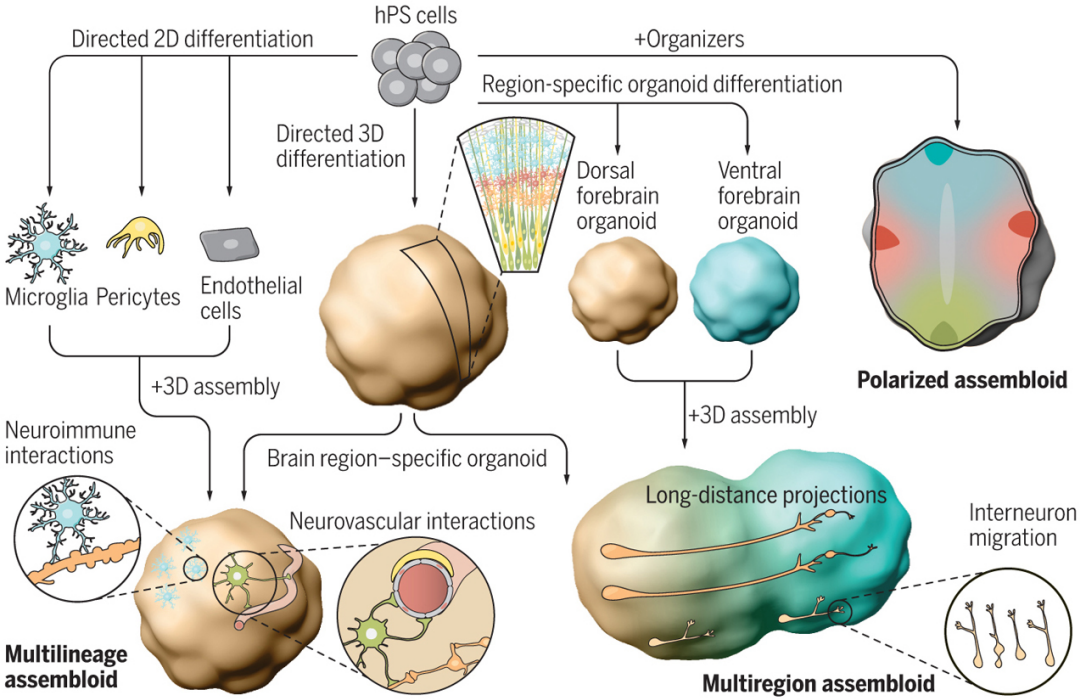




Assembloids

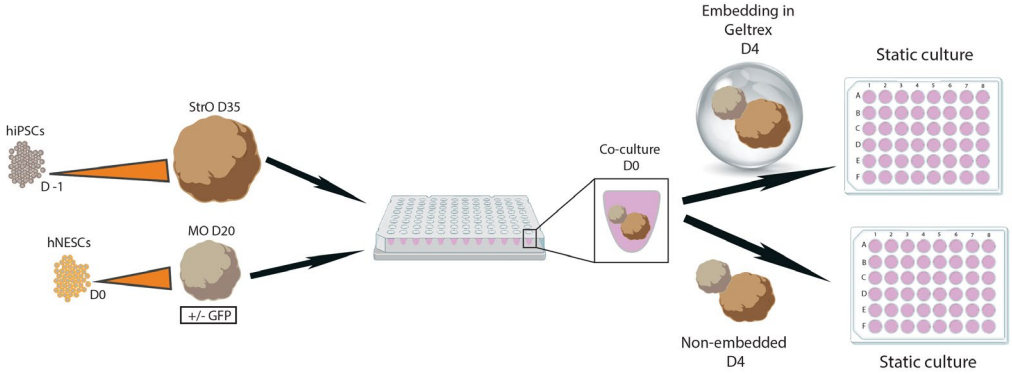
Generating assembloids

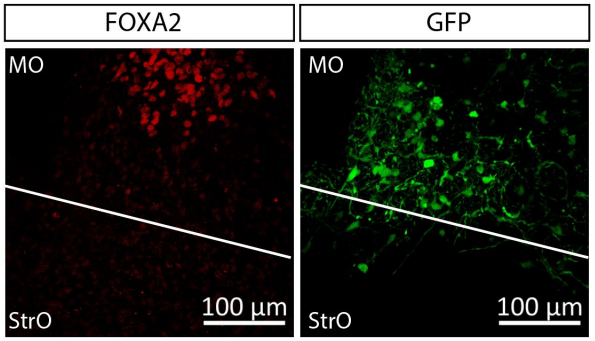
Brain region–specific organoids are generated from human pluripotent stem (hPS) cells and can be assembled with other cell types (multilineage assembloids), with other organoids (multiregion assembloids), or with morphogens or organizer-like cells (polarized assembloids). Brain organoids and assembloids can be used to model complex cell-cell interactions and neural circuit formation in the human nervous system.

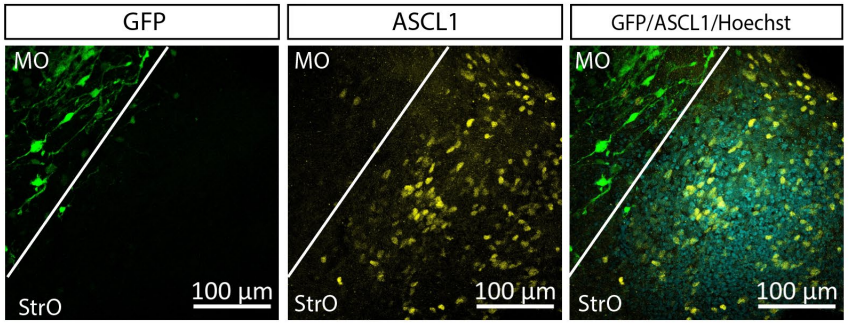


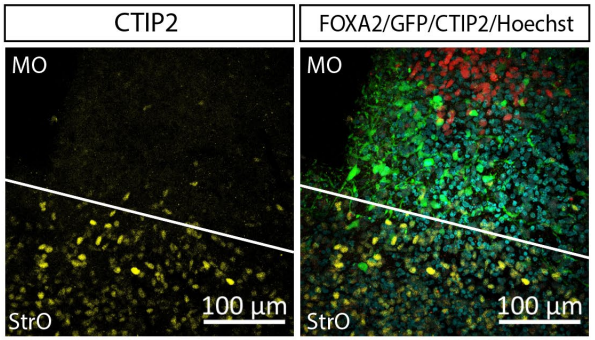
Pasca, *Science*, 2019

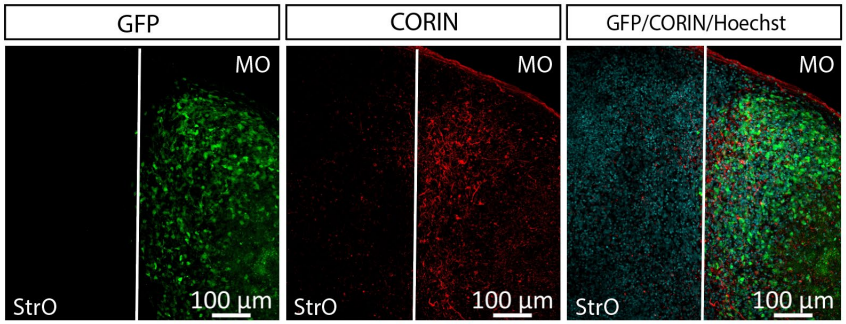
Midbrain-Striatum assembloid







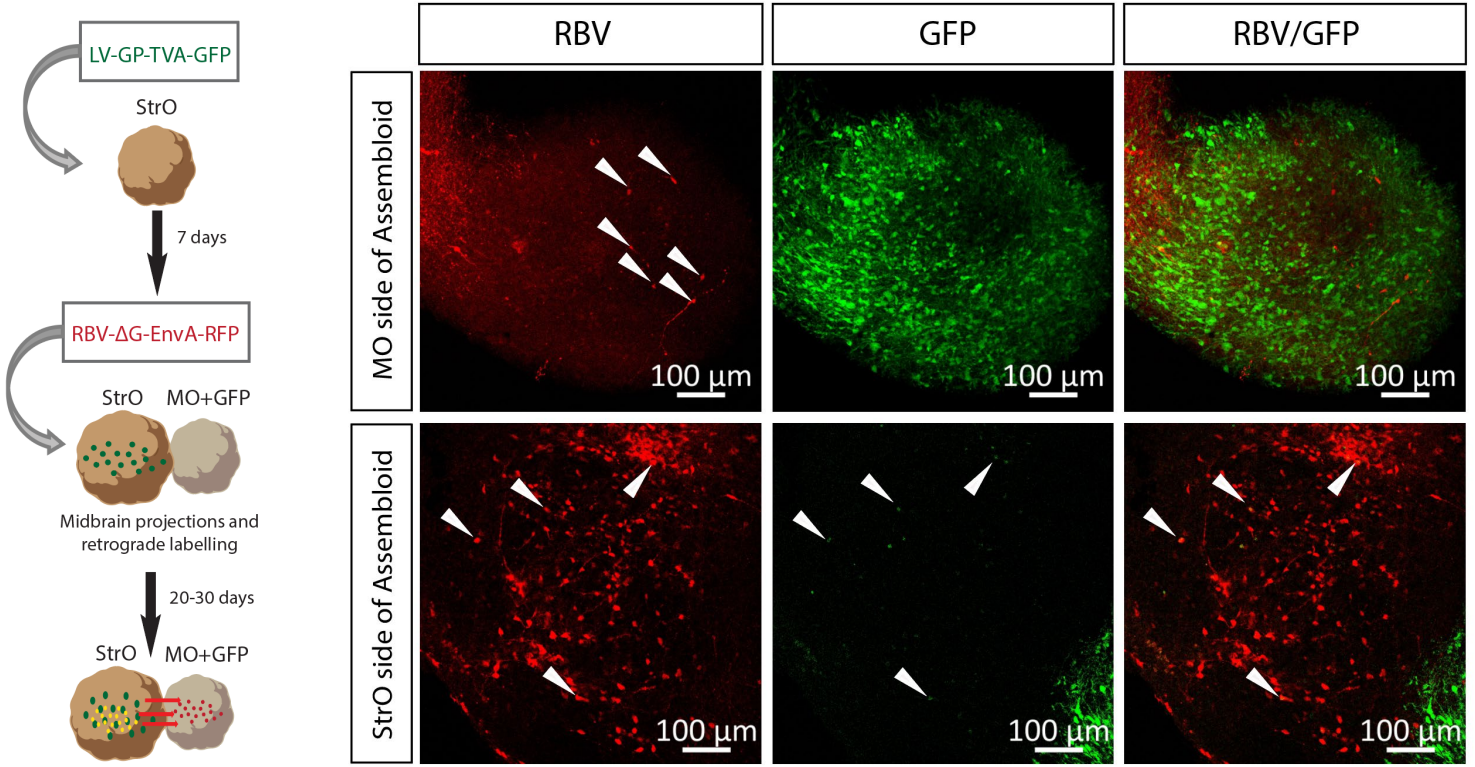




Barmpa et al., *biorxiv*, 2023

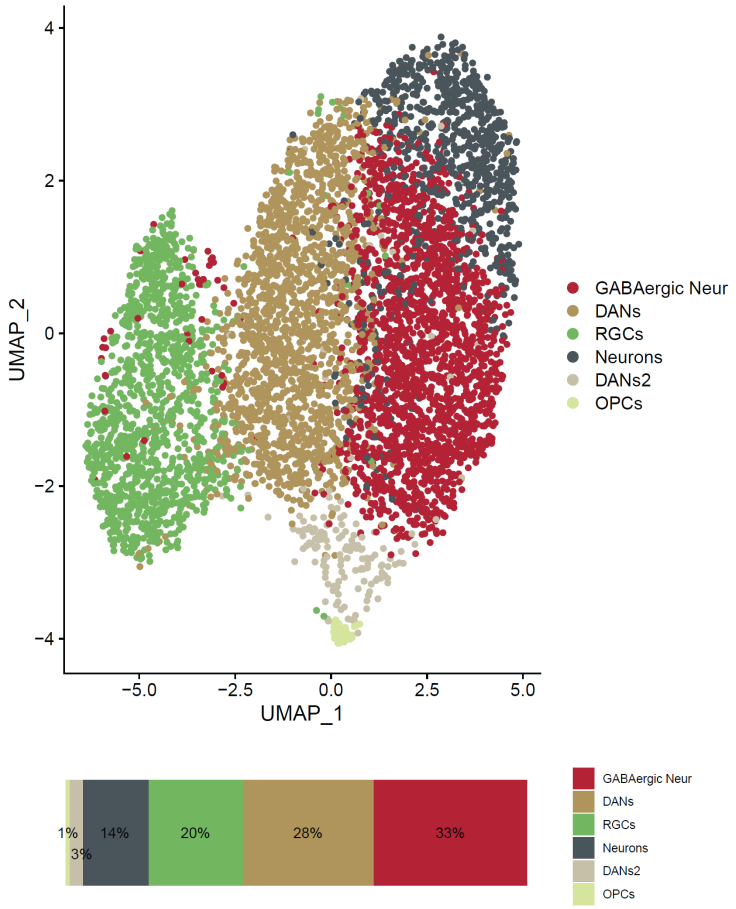
Midbrain-Striatum assembloid

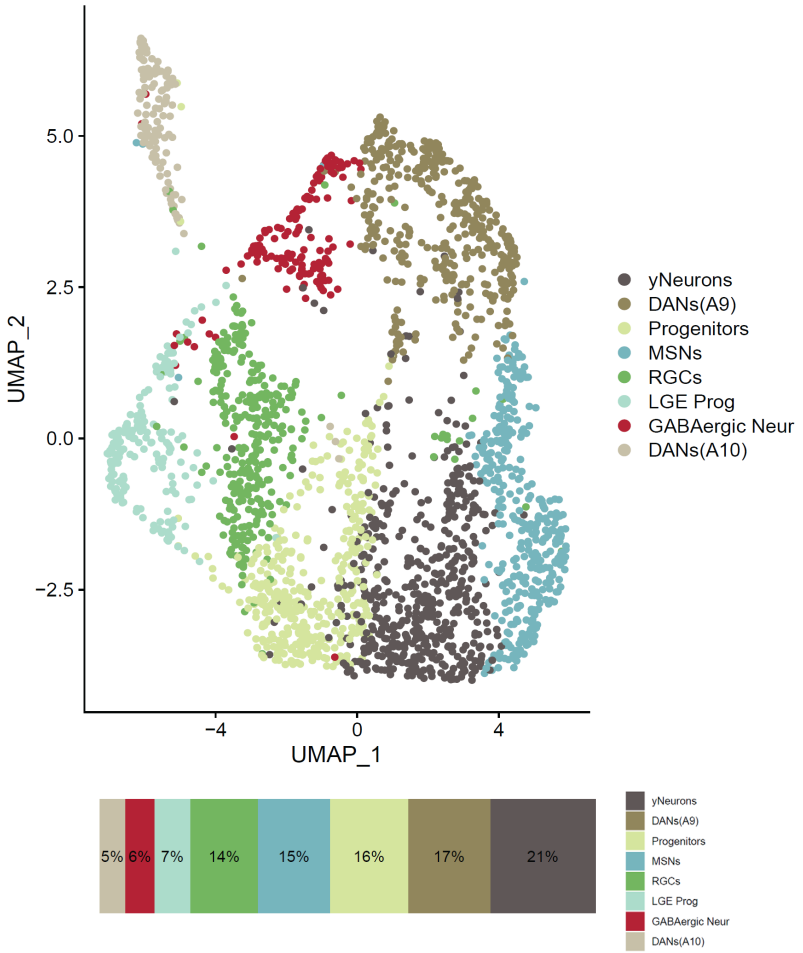
Retrograde monosynaptic tracing



Barmpa et al., *biorxiv*, 2023

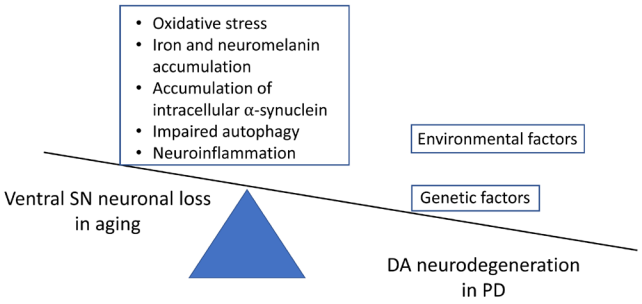
Midbrain-Striatum assembloid



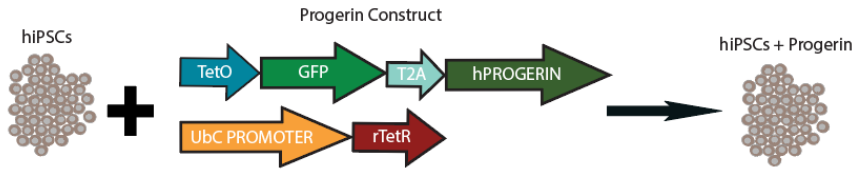


Barmpa et al., *biorxiv*, 2023

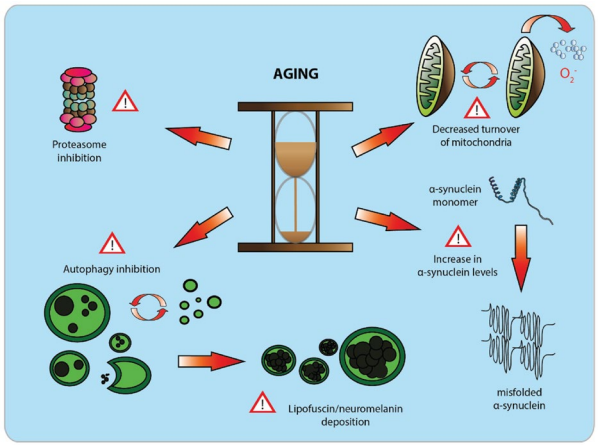
Aging



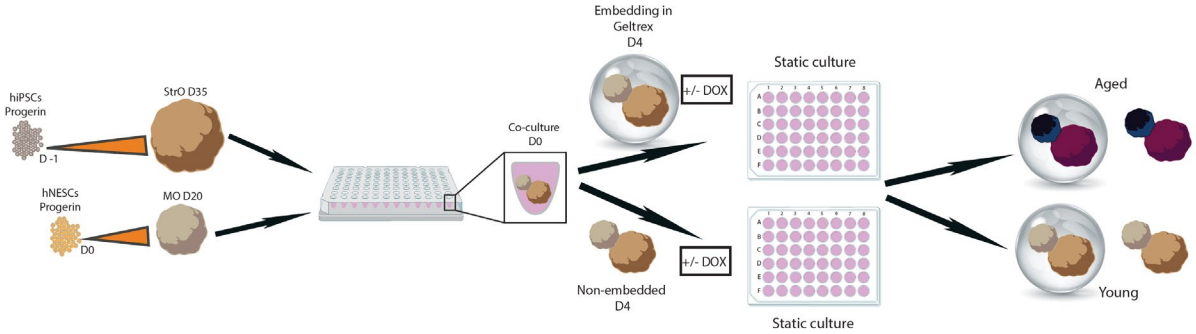
Pang et al., *Translational neurodegeneration*, 2019



Molecular changes in DA neurons

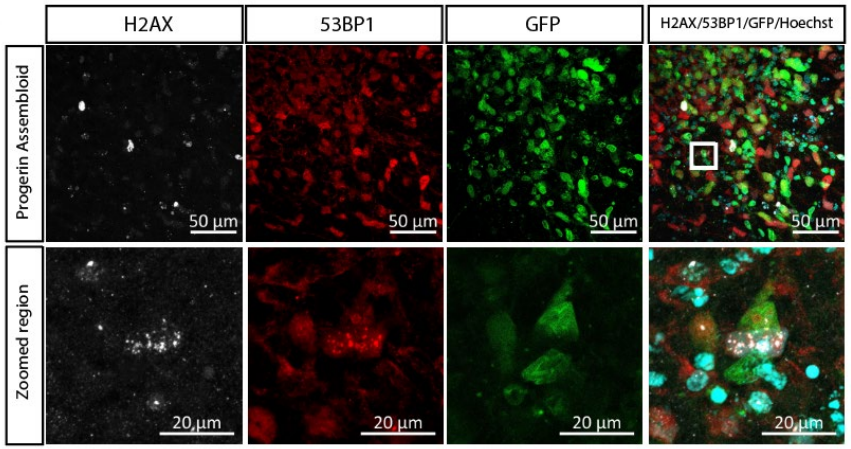


Bobela et al., *Biomolecules*, 2015

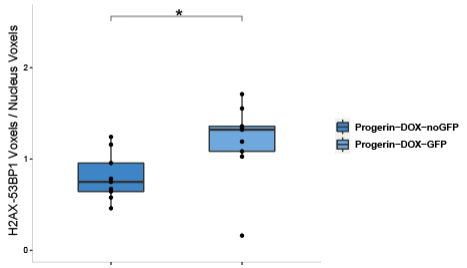


Barmpa et al., *biorxiv*, 2023

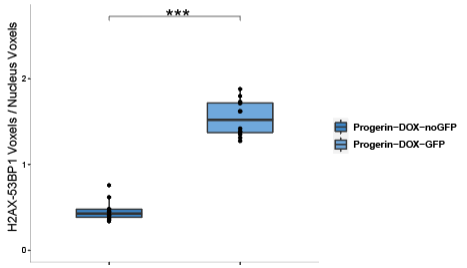
Aging

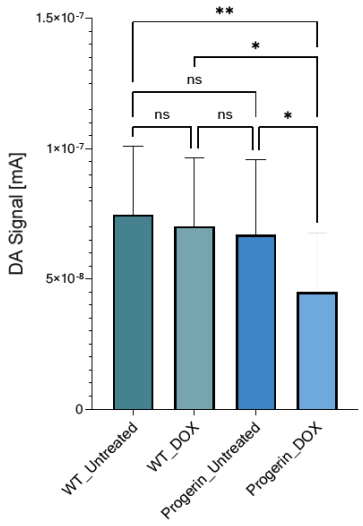


D30 Assembloids

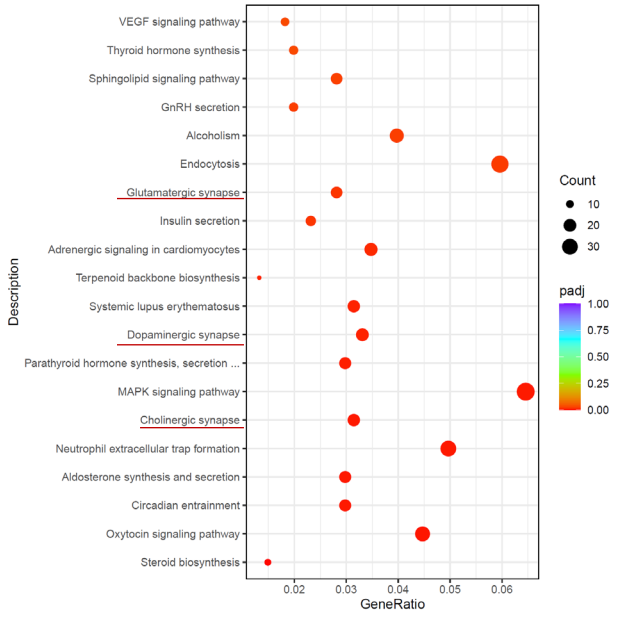


D60 Assembloids

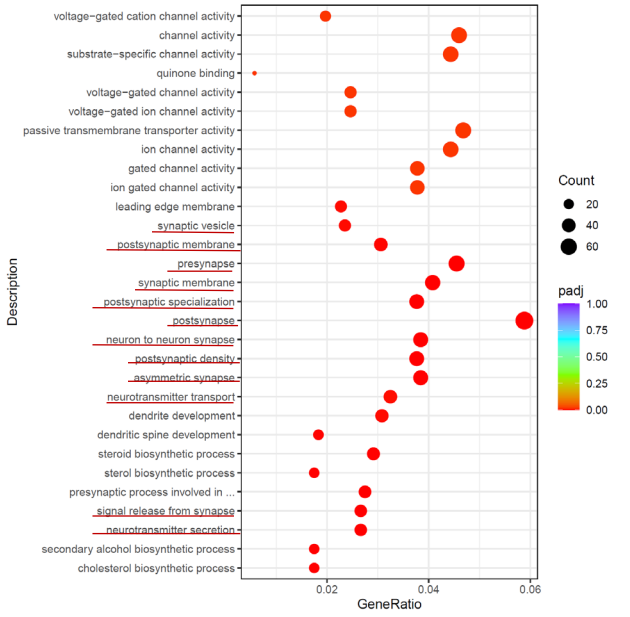




KEGG pathways



GO pathways



Barmpa et al., *biorxiv*, 2023

Summary

- Development of organoid model for most organs and several diseases
- Midbrain specific organoids can be used for Parkinson's disease phenotyping and drug development
- Increasing the complexity of the organoids improves the recapitulation of normal physiology

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Thank you for your attention