



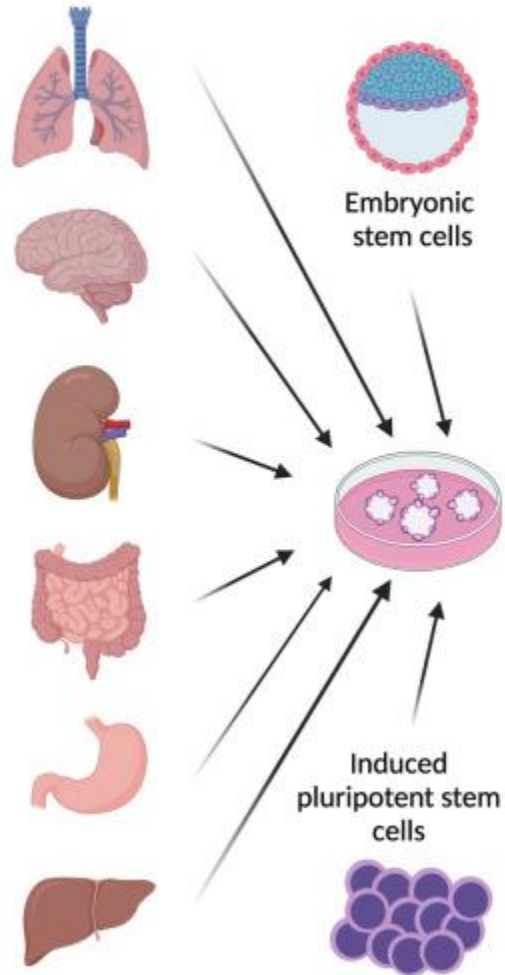
How faithfully can organoids recapitulate real organs?

from cell identity to morphodynamics

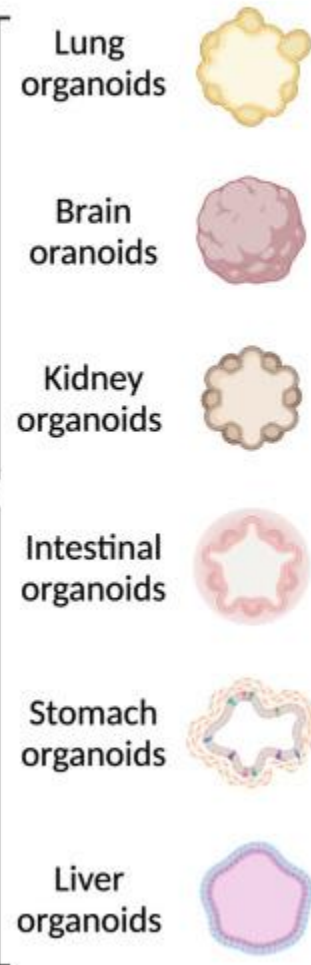
**Dan YU
3/4/2026**

What organoids are?

A. Tissue sources for organoids

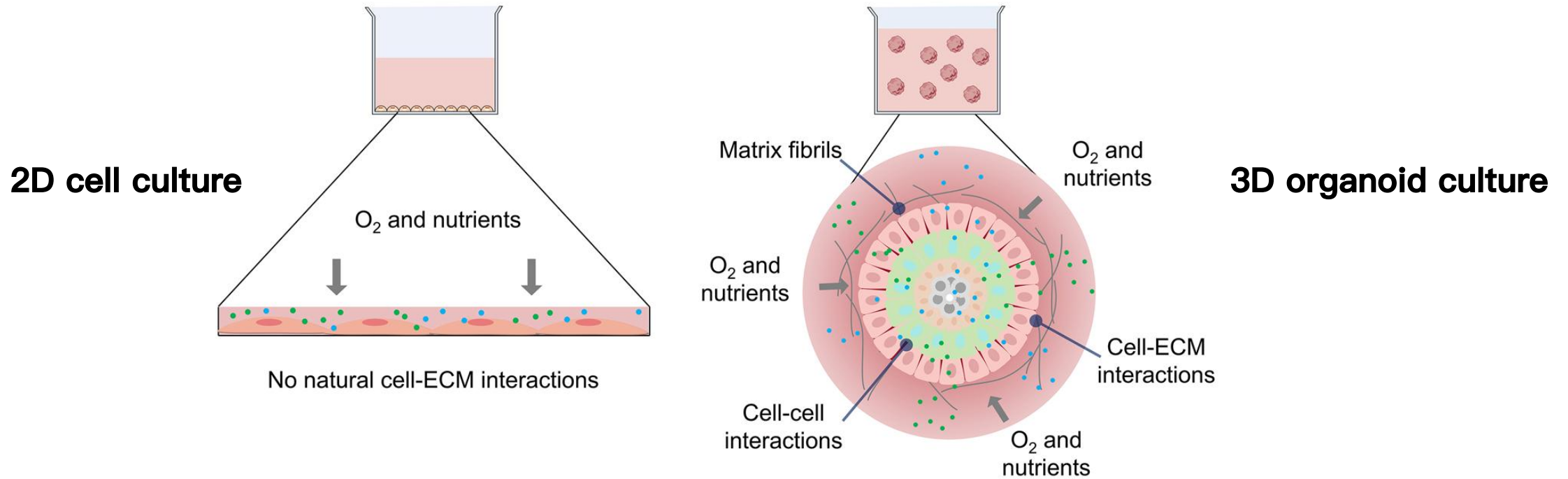


B. Organoid cultured *in vitro*



- Organoids are 3D self-organizing systems that partially recapitulate the cell types, tissue architecture, and developmental programs of real organs
- More than 3D cell aggregates, organoids can self-organize into tissue-like structures

What organoids matter?

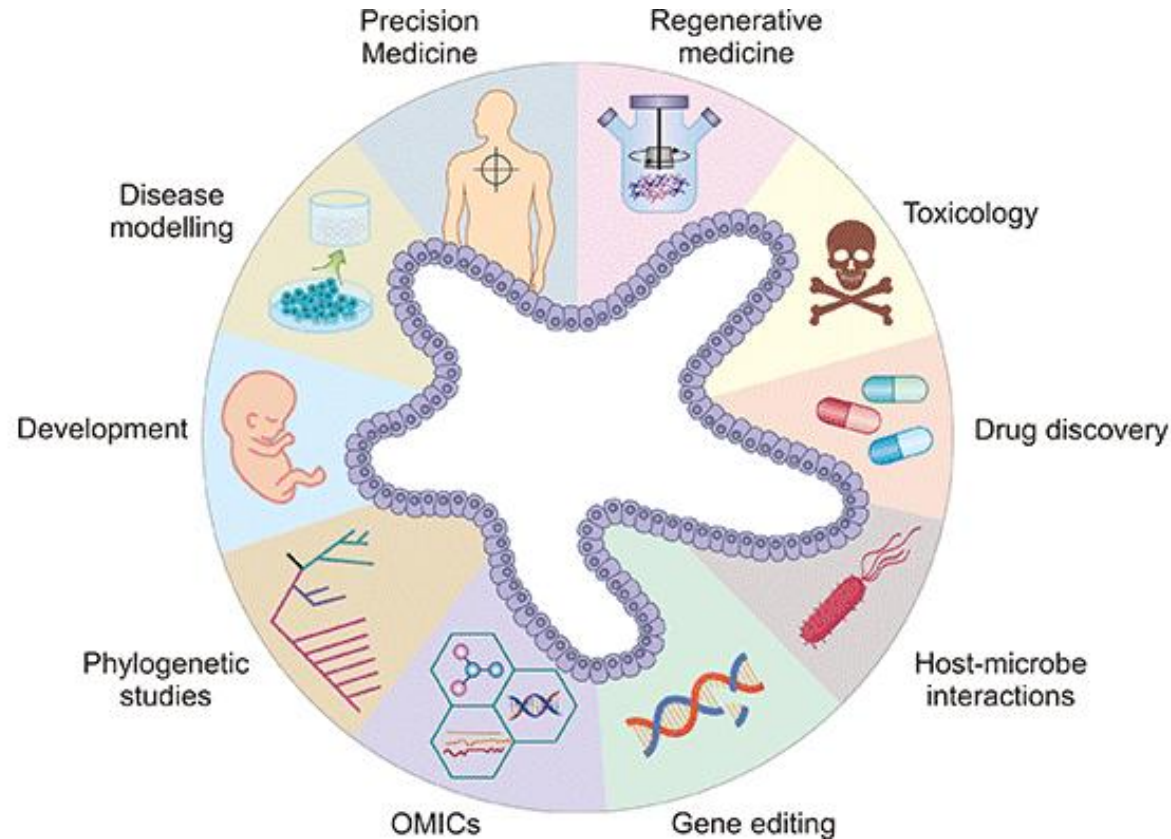


Organoids provide experimental access to biology development in a system that is more realistic than 2D culture and more tractable than in vitro studies

why fidelity matters

Why organoids matter

- development
- disease modeling
- drug discovery
- ...



Why fidelity matters

- biological relevance
- interpretability
- translational value
- ...

Organoids are increasingly used to study development, disease, and therapy, their value depends on how faithfully they recapitulate real tissues

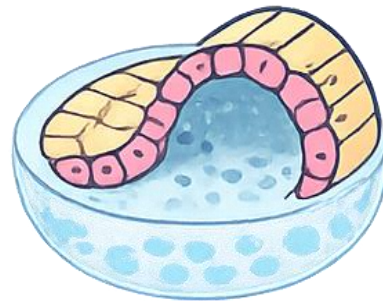
A framework for thinking about fidelity

What does it mean for an organoid to resemble a real organ?



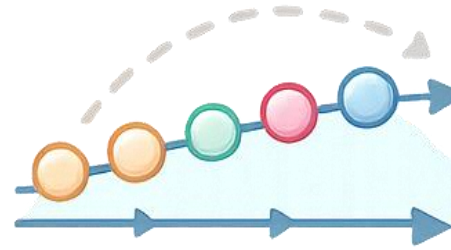
Cell identity

cell types and states



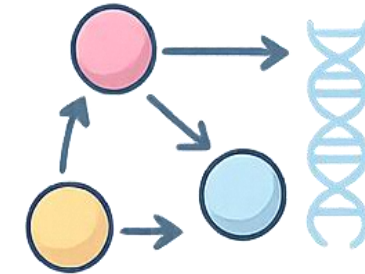
Tissue architecture

tissue organization and polarity



Developmental dynamics

morphogenesis over time

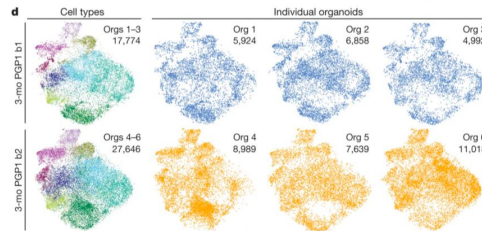
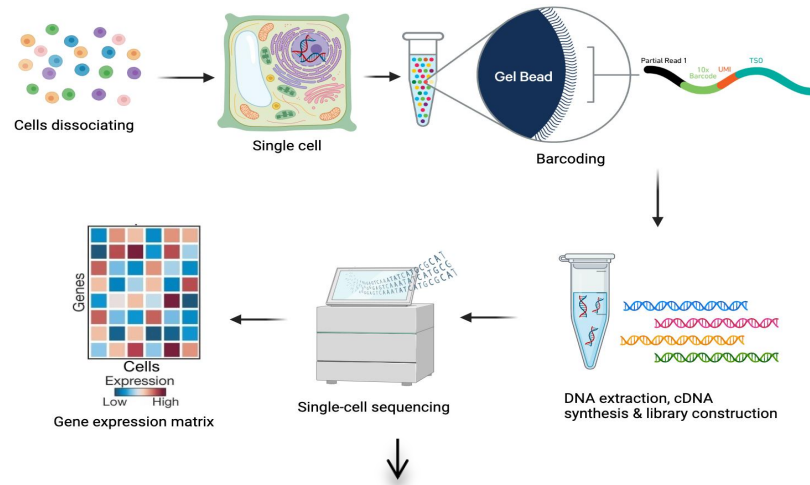


Regulatory programs

signaling and gene networks

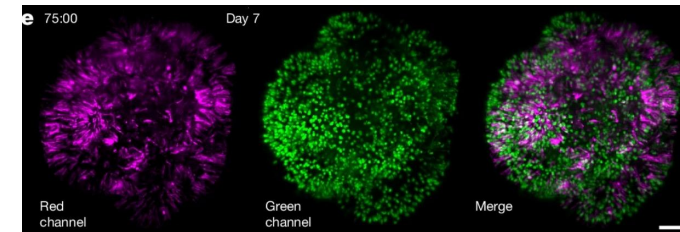
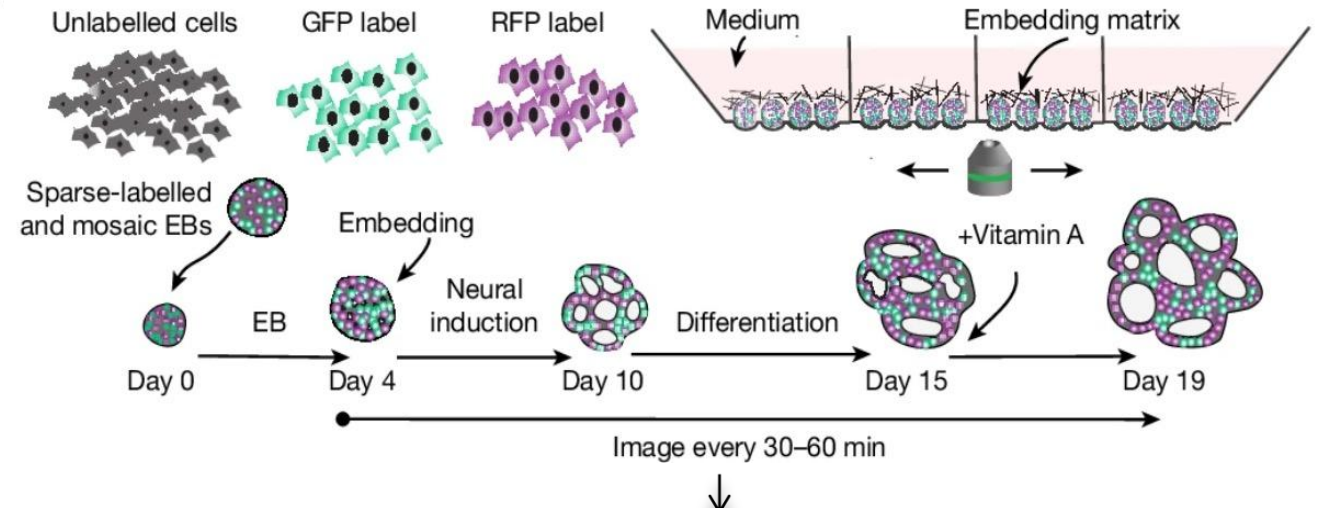
From endpoint profiling to developmental process

What most studies capture



final cell states

What this study captures



morphogenesis over time

Study overview

Article

Morphodynamics of human early brain organoid development

<https://doi.org/10.1038/s41586-025-09151-3>

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Akanksha Jain^{1,5}✉, Gilles Gut^{1,5}, Fátima Sanchis-Calleja¹, Reto Tschannen¹, Zhisong He¹, Nicolas Luginbühl¹, Fides Zenk¹, Antonius Chrisnandy², Simon Streib¹, Christoph Harmel^{3,4}, Ryoko Okamoto¹, Malgorzata Santel¹, Makiko Seimiya¹, René Holtackers¹, Juliane K. Rohland¹, Sophie Martina Johanna Jansen¹, Matthias P. Lutolf^{2,3}, J. Gray Camp^{3,4} & Barbara Treutlein¹✉

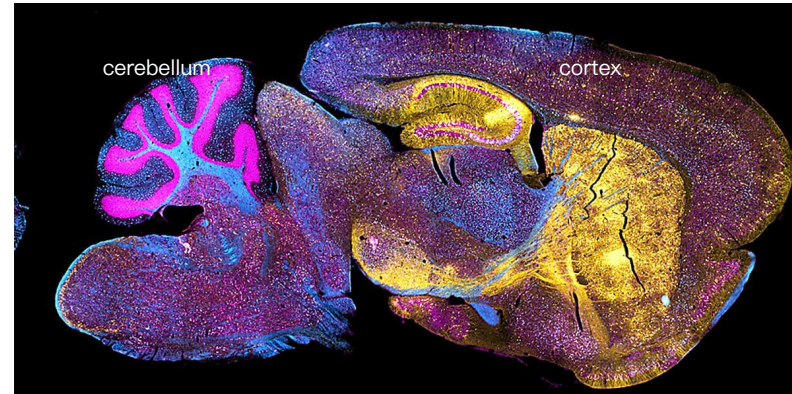
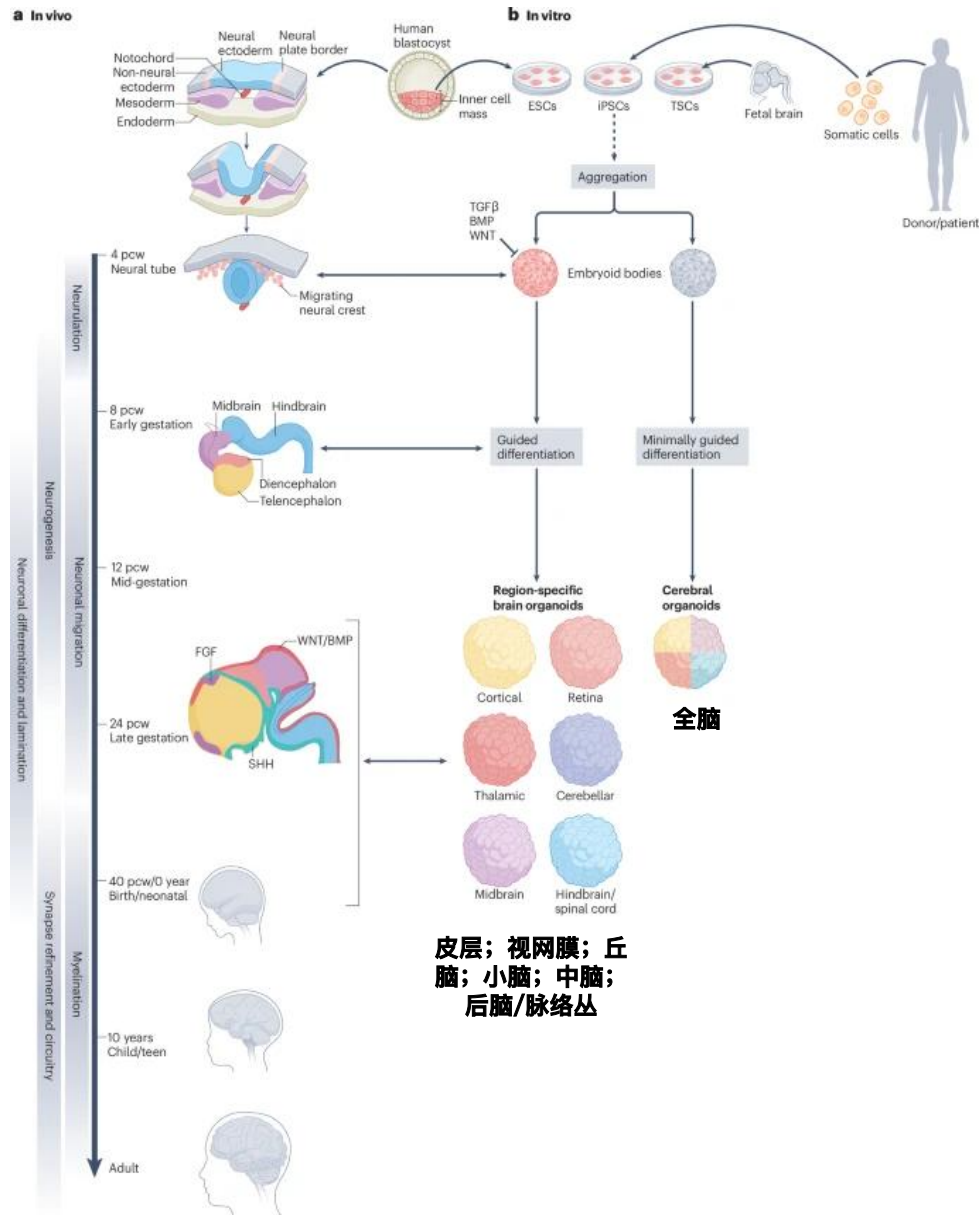
- ▶ Published in Nature in 2025
- ▶ Focus: early human brain organoid morphogenesis
- ▶ Approach: live imaging + molecular profiling + computation



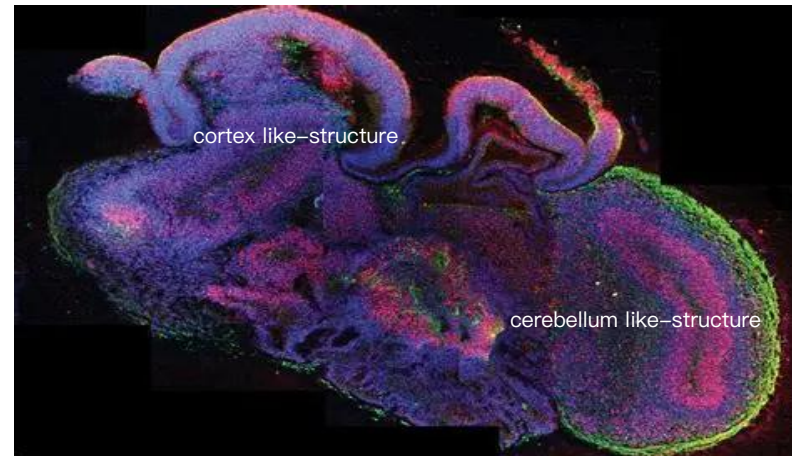
“What we aim to get when we make organoids, and what we actually get, are not usually the same. Without the atlas, it’s more challenging to interpret the data from a single organoid protocol.”

Barbara Treutlein, ETH-Professor of Quantitative Developmental Biology at D-BSSE.

The development of brain organoids



mouse brain map with IF staining



human organoid with IF staining

Lumen

脑类器官里出现的腔样结构，类似早期神经管/脑室样空腔

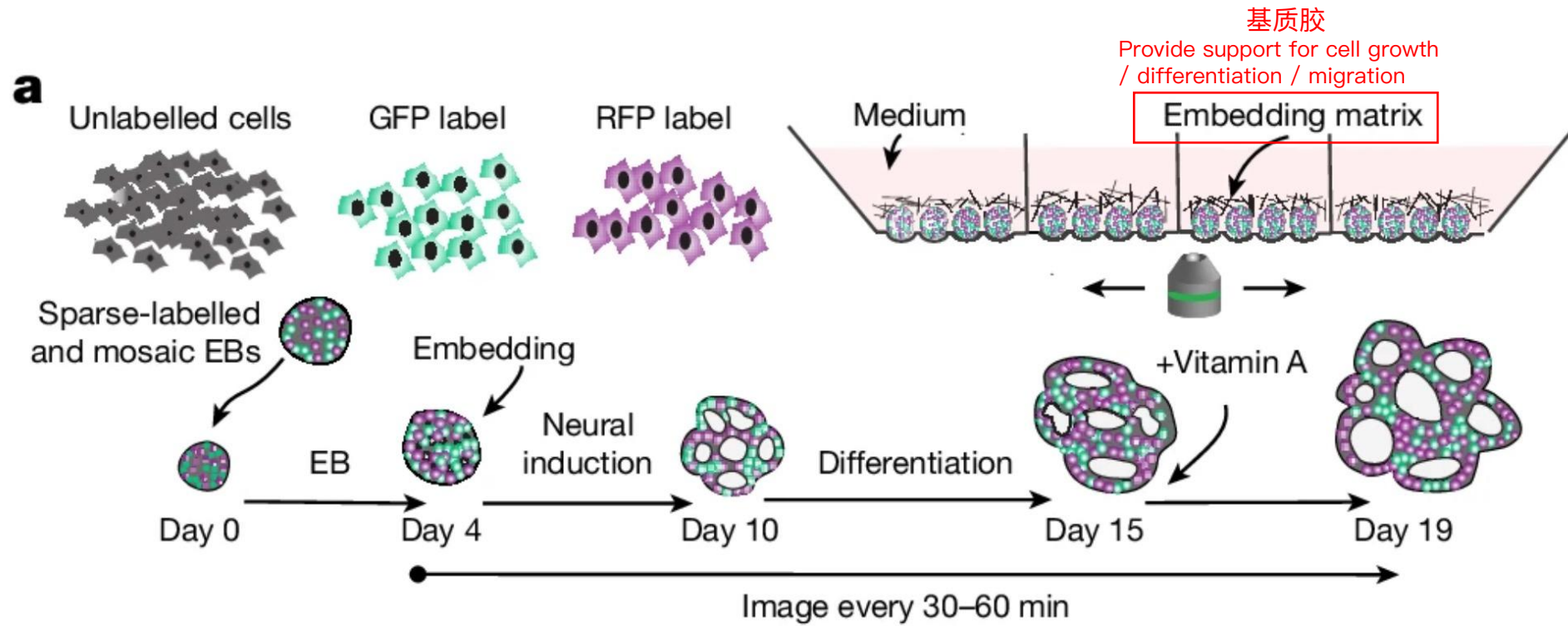
Neuroepithelium

围绕 lumen 排列的神经上皮样组织

Polarity

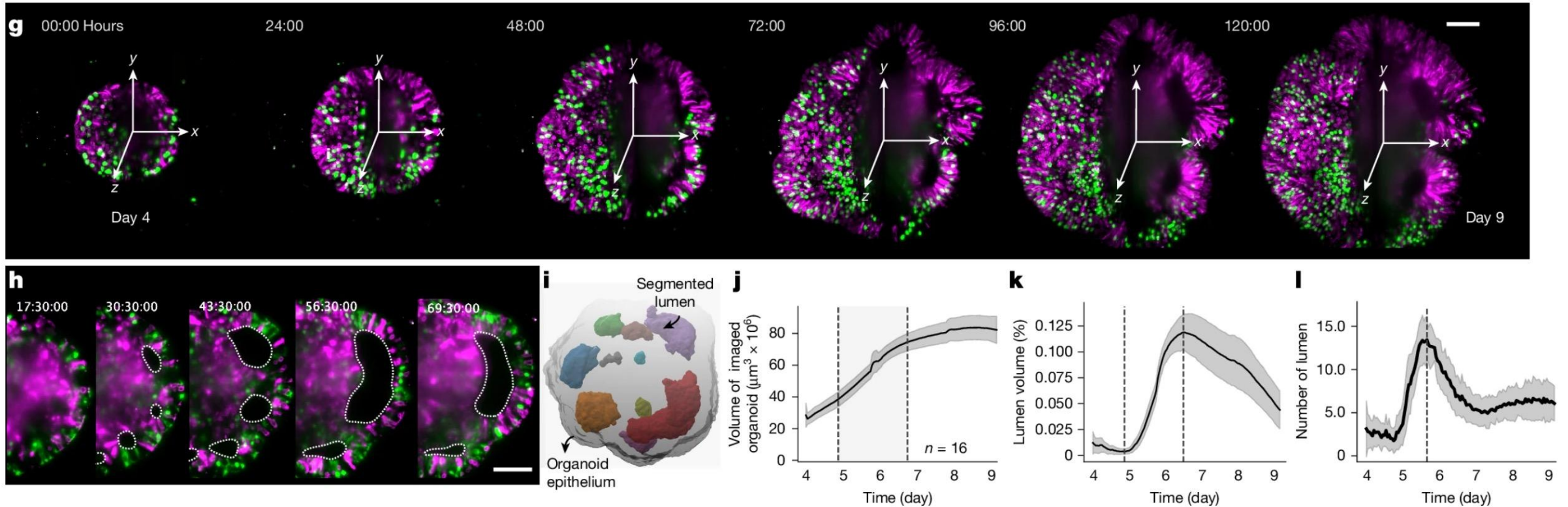
细胞形成的明确的内外方向/极性

Organoids show reproducible morphogenesis



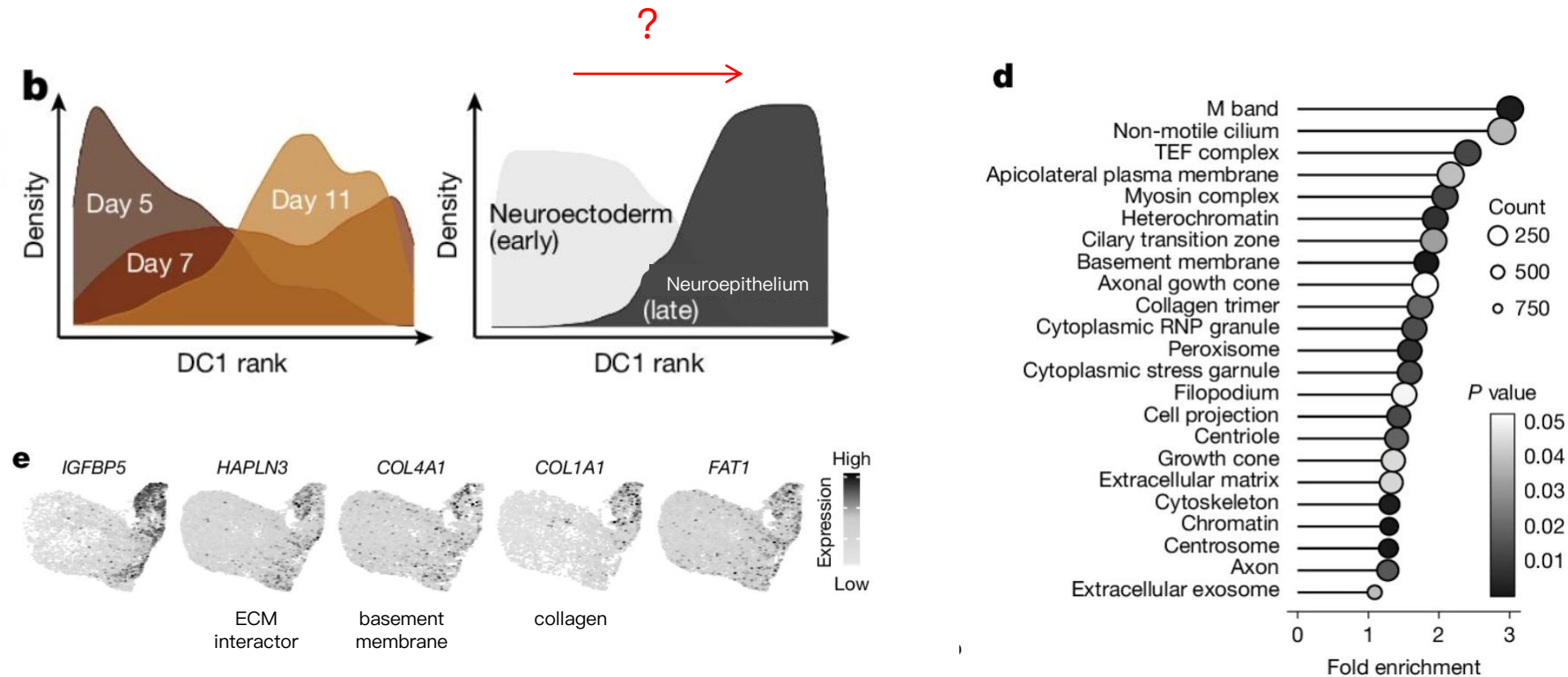
- ▶ Unguided human iPSC-derived brain organoids
- ▶ Sparse mosaic fluorescent labeling
- ▶ Long-term live light-sheet imaging

Organoids show reproducible morphogenesis



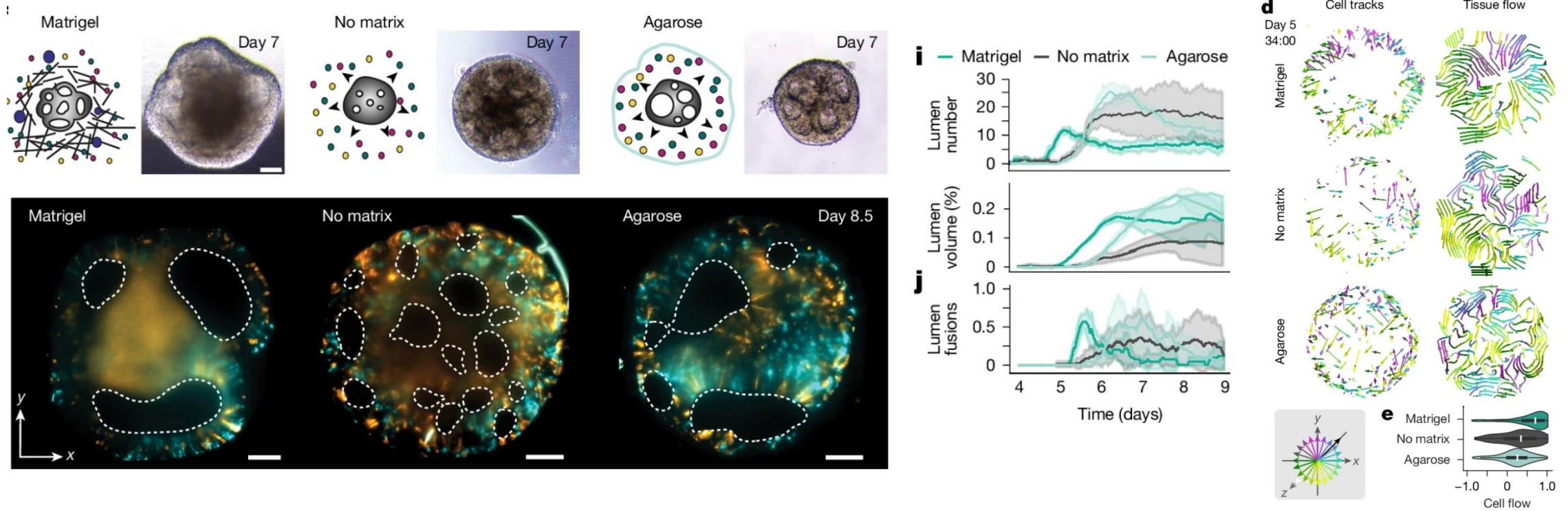
- Brain organoids undergo organized and trackable morphogenesis, including continuous lumen formation, fusion, and tissue remodeling over time

scRNA-seq reveals ECM-related programs



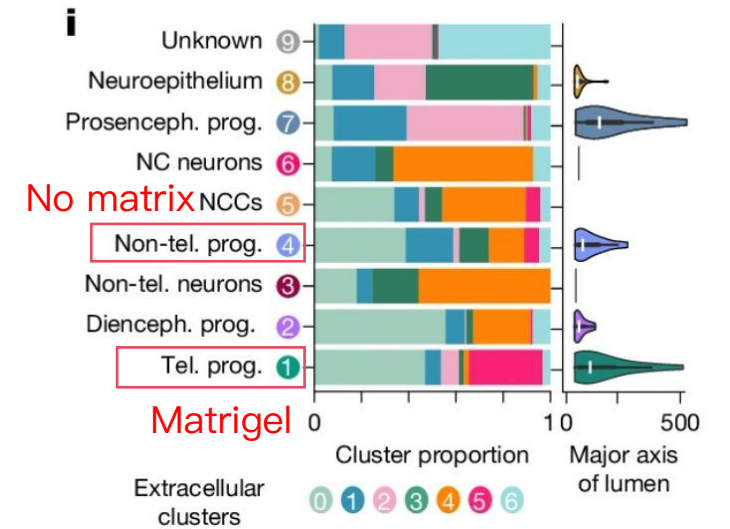
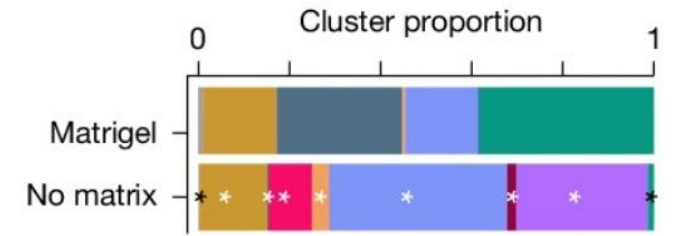
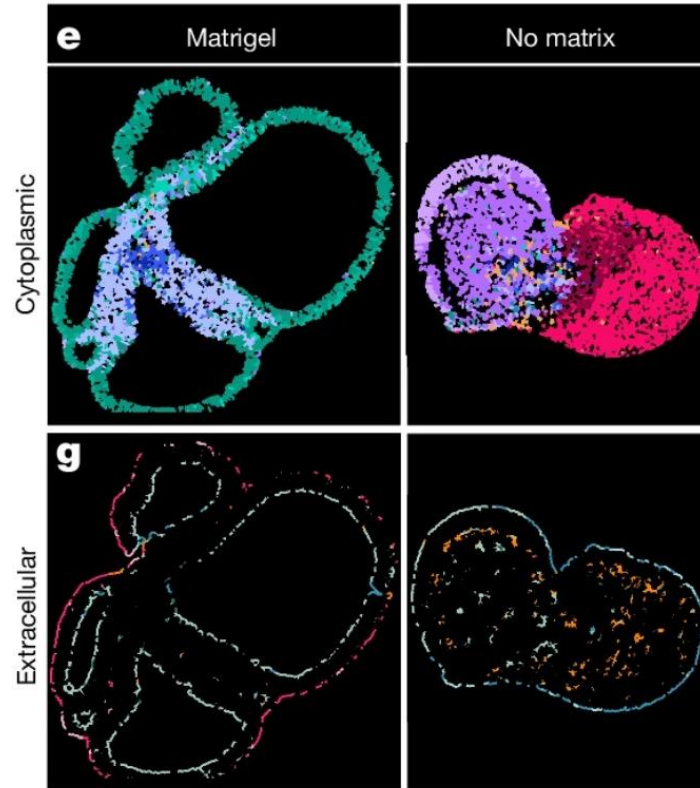
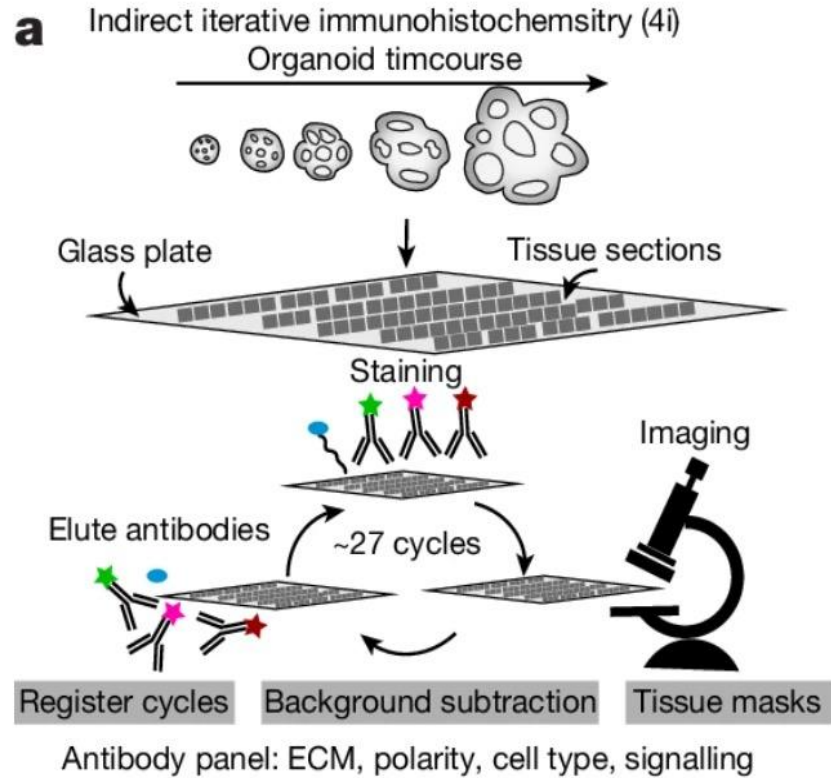
- ▶ Pseudotime analysis reveals a transition from early neuroectoderm-like to neuroepithelial states
- ▶ Along this trajectory, ECM-related programs, including basement membrane and collagen-associated genes, become upregulated

ECM shapes cell morphology and tissue organization



► Extrinsic ECM actively shapes brain organoid morphogenesis, and show more coordinated tissue flow, earlier cell elongation, and stronger alignment perpendicular to the organoid surface

ECM also reshapes regional patterning and cell identity



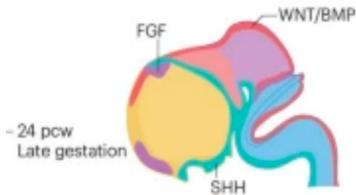
► Extrinsic ECM biases organoid development toward more rostral, telencephalic identities (前脑/端脑)

Organoid development is shaped by signaling pathways

morphogenesis

ECM

regional patterning

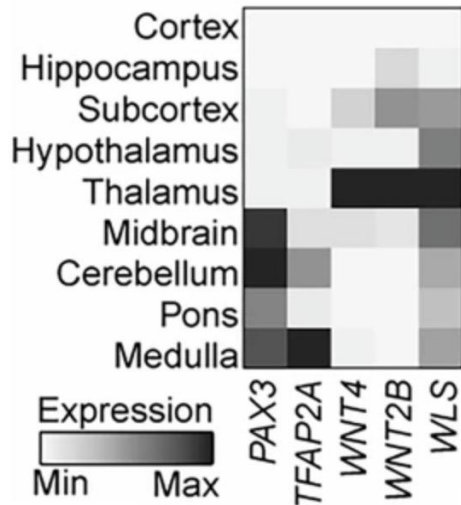


YAP1

- Hippo pathway effector
- Mechanosensitive regulator
- Links ECM to gene expression

GO/KEGG terms

- WNT signaling pathway
- Actin cytoskeleton
- Transcription regulation
- Hippo signaling pathway
- Notch signaling pathway



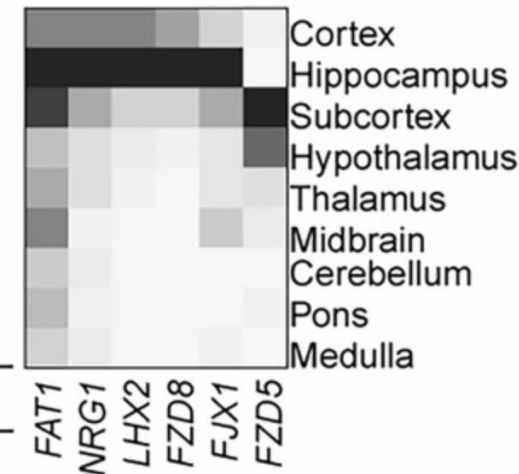
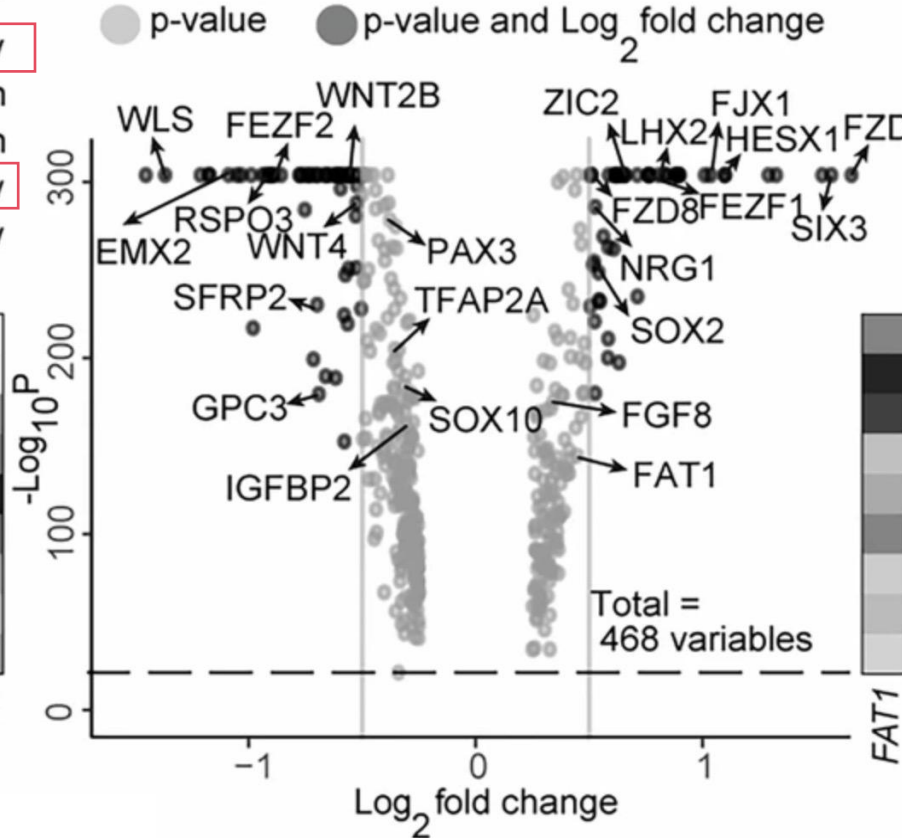
Molecular mechanism

Upregulated in no matrix

Upregulated in matrigel

GO/KEGG terms

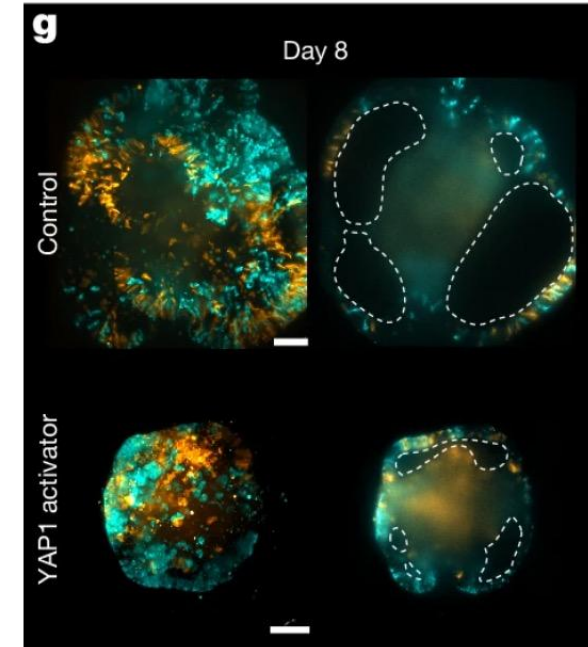
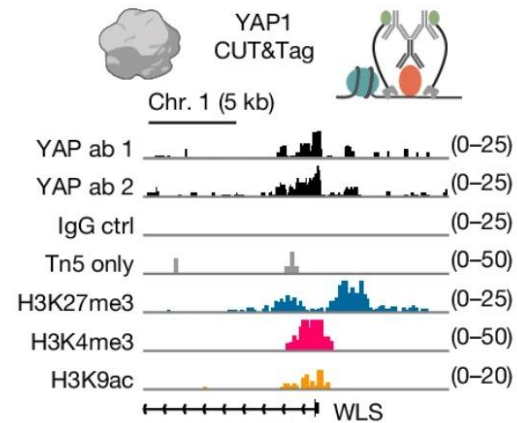
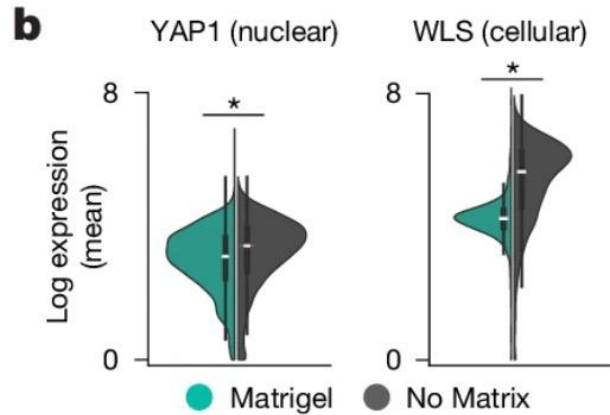
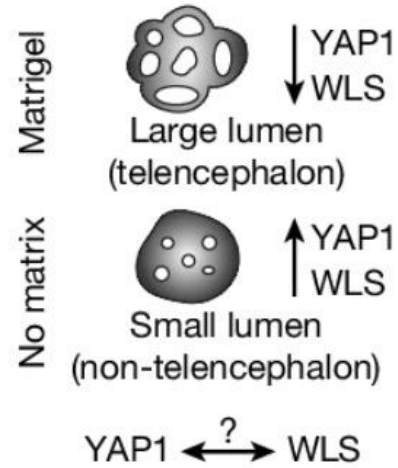
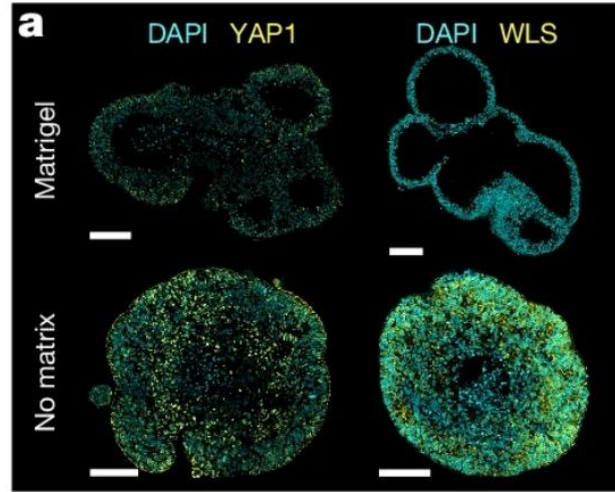
- WNT signaling pathway
- Stem cell proliferation
- Transcription regulation
- Reg. of actin cytoskeleton
- FGF signaling pathway



WLS

- Wnt ligand mediator
- Required for WNT secretion
- Supports developmental patterning

YAP1-mediated WLS activation

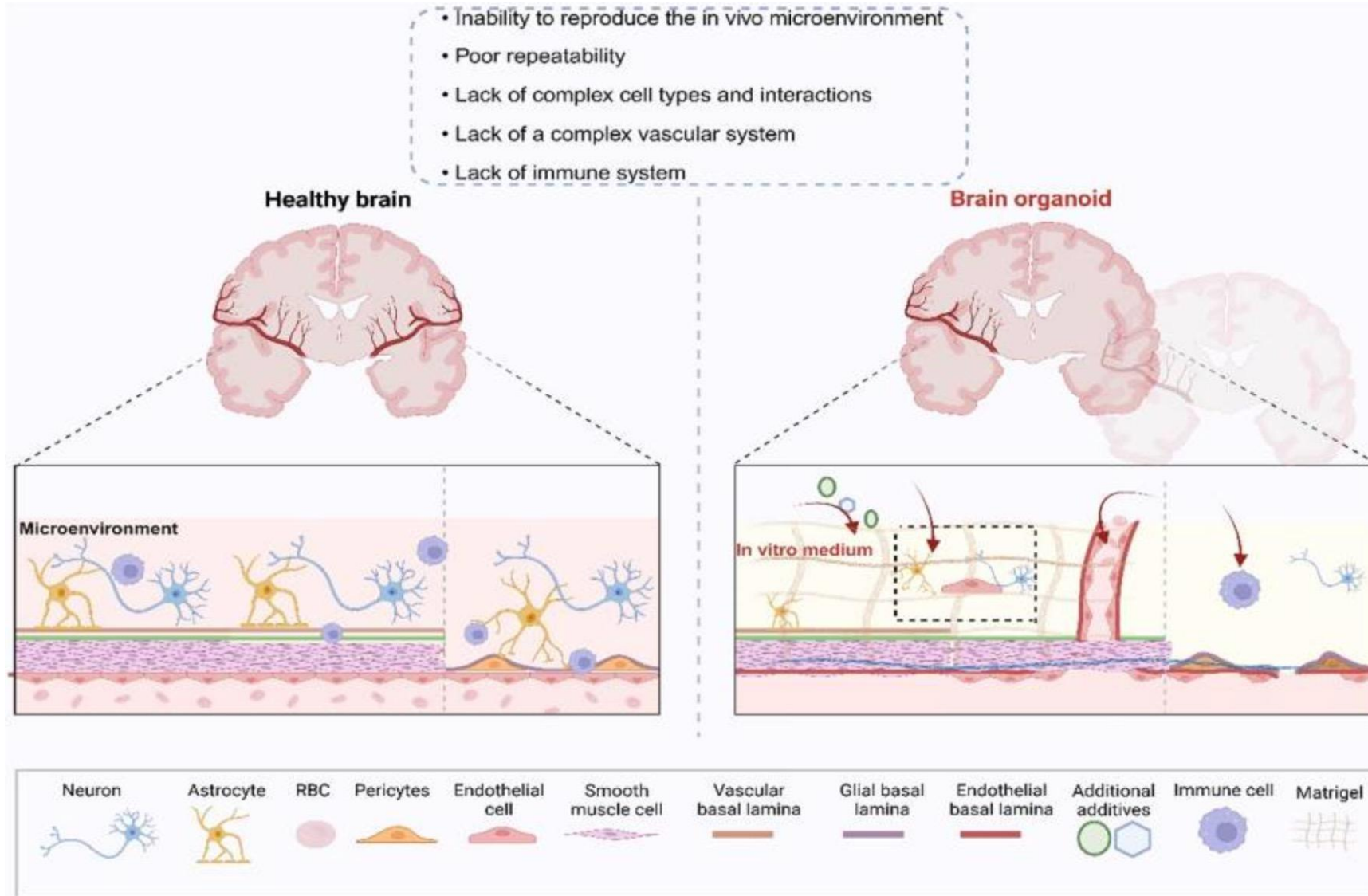


► Matrix-dependent morphogenesis and regional patterning are linked to a YAP1-WLS axis

What organoids still do not fully capture

Level	What organoids recapitulate	Current limitations
Cell identity	Major neural cell states and regional progenitors can be generated	Cell diversity is still incomplete
Tissue architecture	lumen formation, and polarity can emerge	Architecture is simplified and condition-dependent
Developmental dynamics	Early morphogenesis can be tracked and reconstructed	Later developmental stages remain limited
Regulatory programs	Some matrix-responsive pathways can be modeled	Full in vivo regulatory complexity is not captured
Overall conclusion	Organoids faithfully model key layers of early organogenesis	They do not yet fully reproduce mature organs in vivo

What organoids still do not fully capture

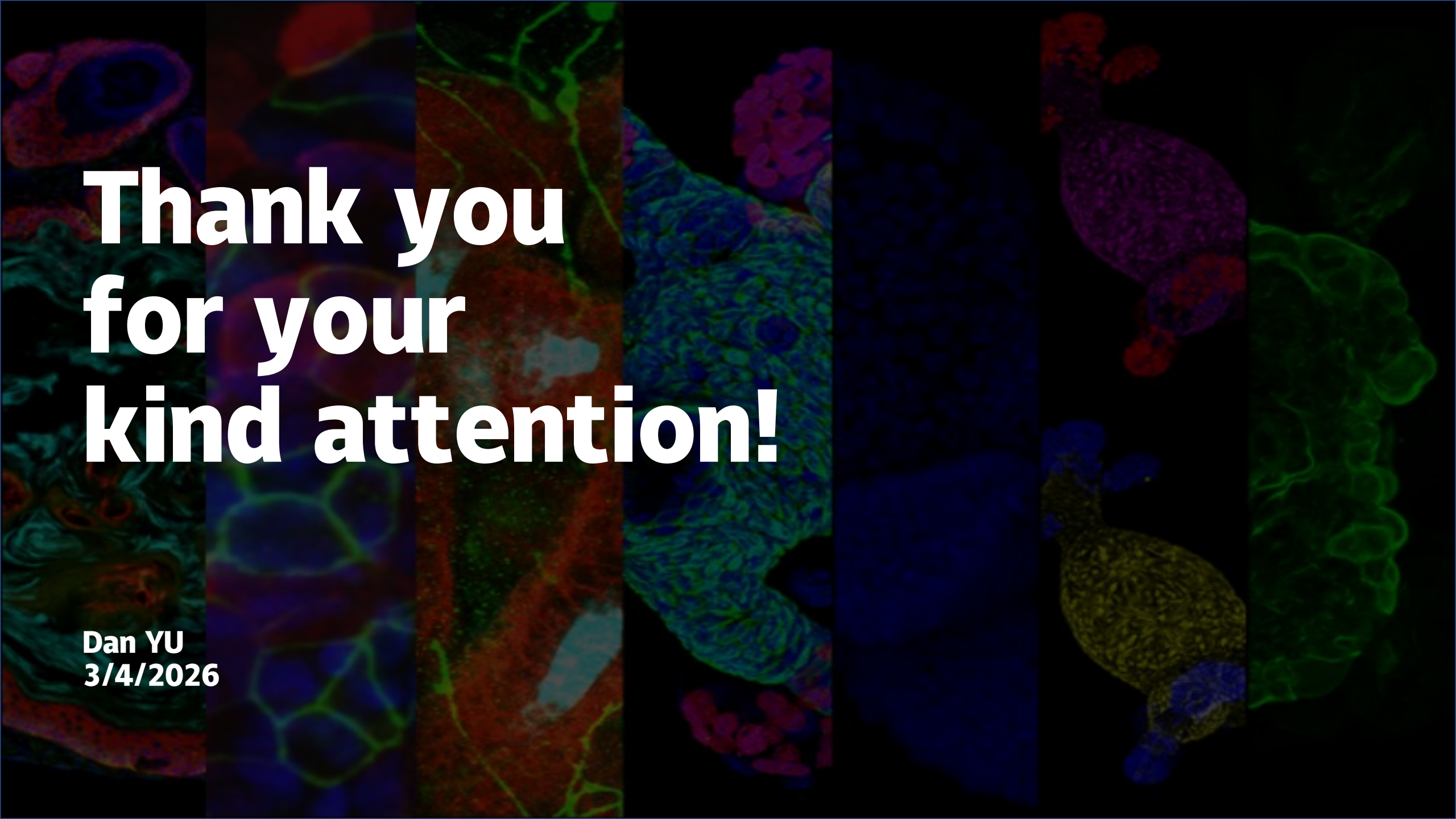


Organoids as an intermediate model system

a

	Monolayer cultures	Brain organoids	In vivo models
Recapitulation of human brain cell type diversity	X	✓	✓✓
Spatial segregation of progenitors and postmitotic progeny	X	✓	✓✓
Functional screening of disease associated genes	✓✓	✓✓	✓
High-throughput screening of therapeutic agents	✓✓	✓	X

Organoids do not fully reproduce real organs, but they faithfully model selected layers of early organogenesis



**Thank you
for your
kind attention!**

**Dan YU
3/4/2026**