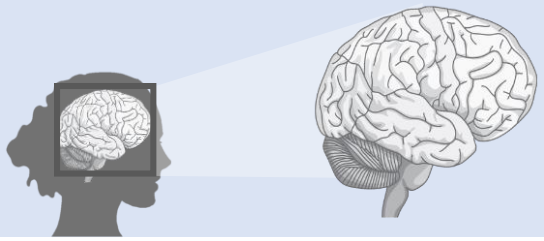
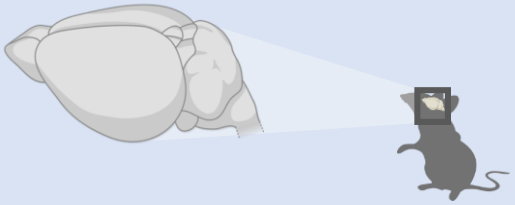
Modeling Psychiatric Disease in Human Brain Organoids: From Genetics to Mechanisms

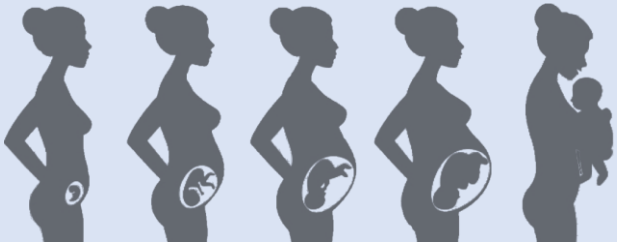
Paola Arlotta, Ph.D.
Harvard University

The Need for Models of the Human Cortex



HUMAN BRAIN *vs.* OTHER SPECIES

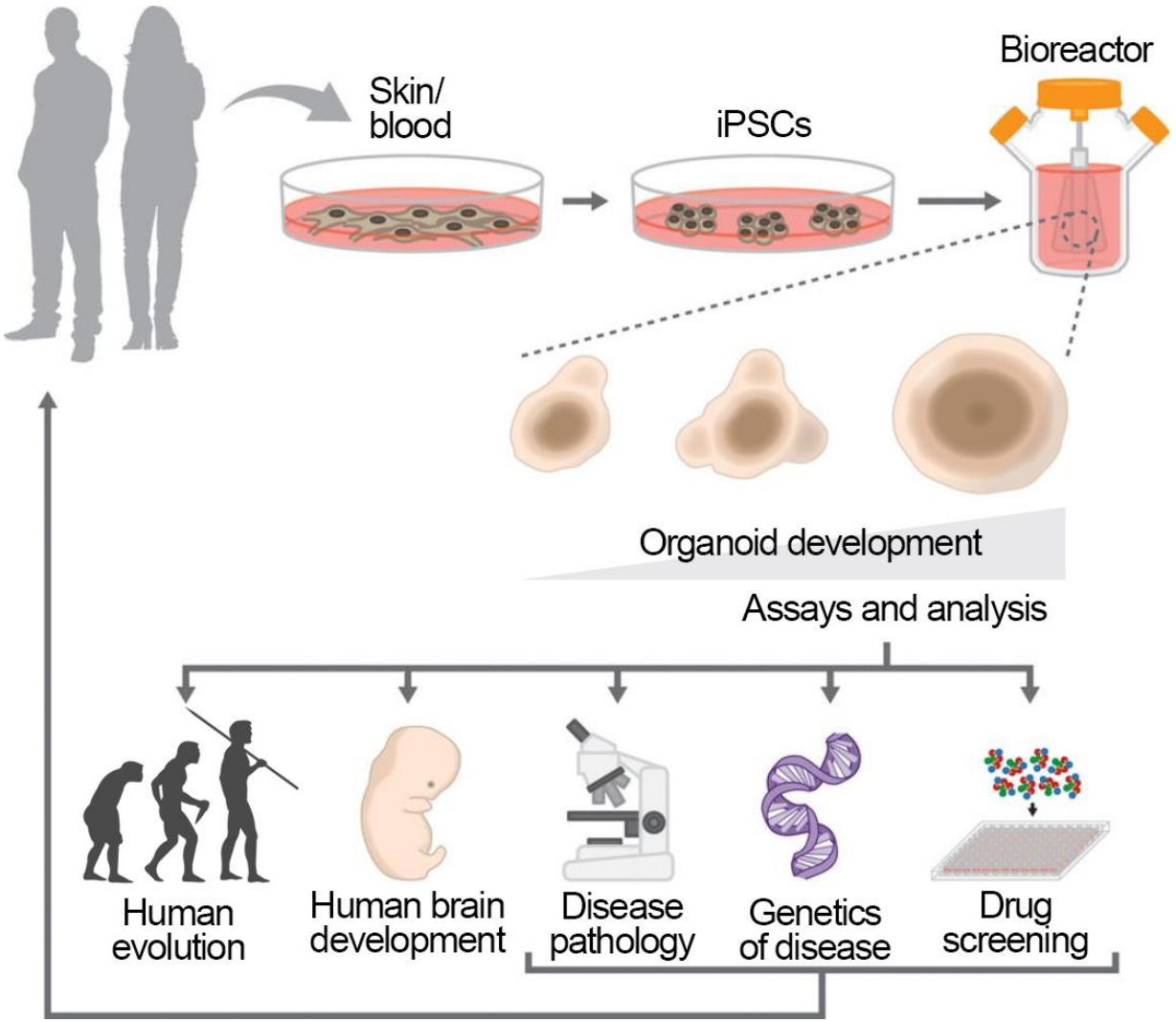




LIMITED ACCESS TO HUMAN BRAIN DEVELOPEMENT

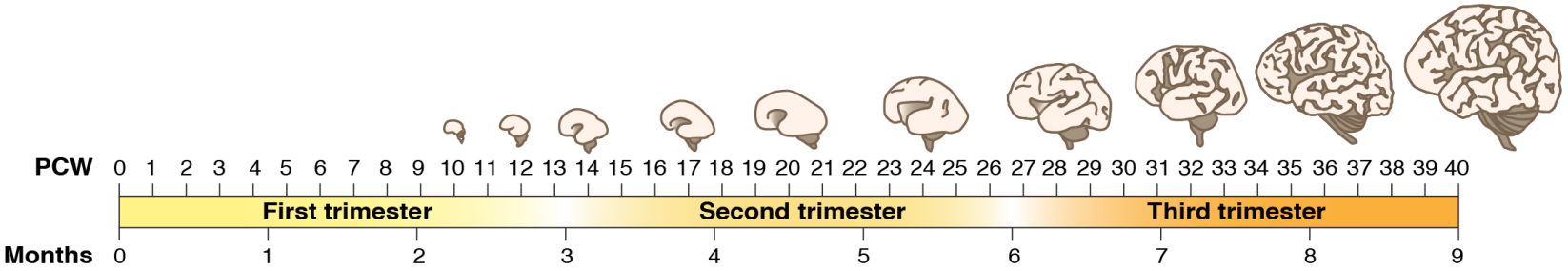
COMPLEX GENETICS OF NEURODEVELOPMENTAL DISEASE

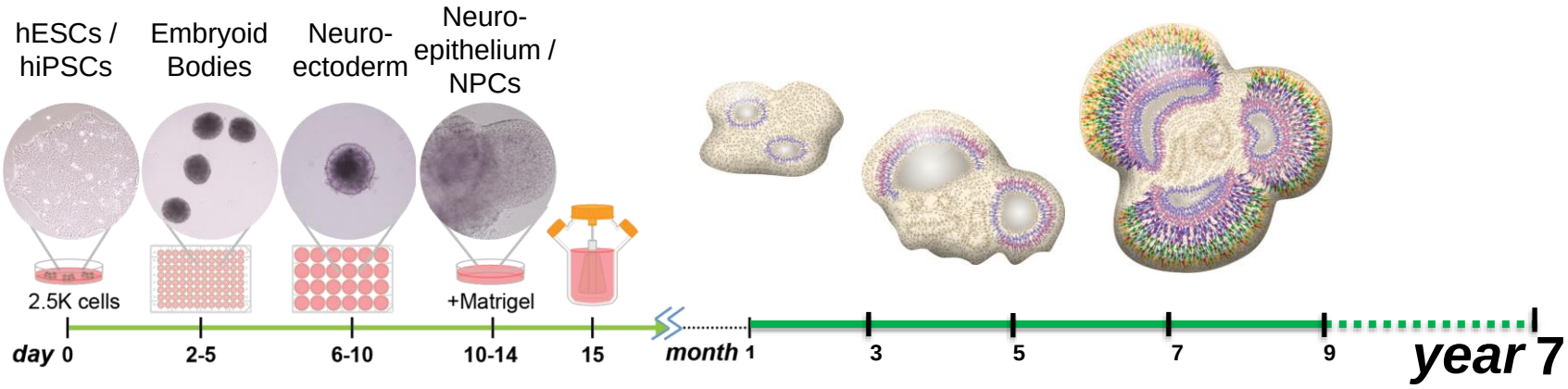
Brain Organoids: What Could They Teach Us?



Human Brain Development is Long: How far Can Brain Organoids Go?

Giorgia Quadrato



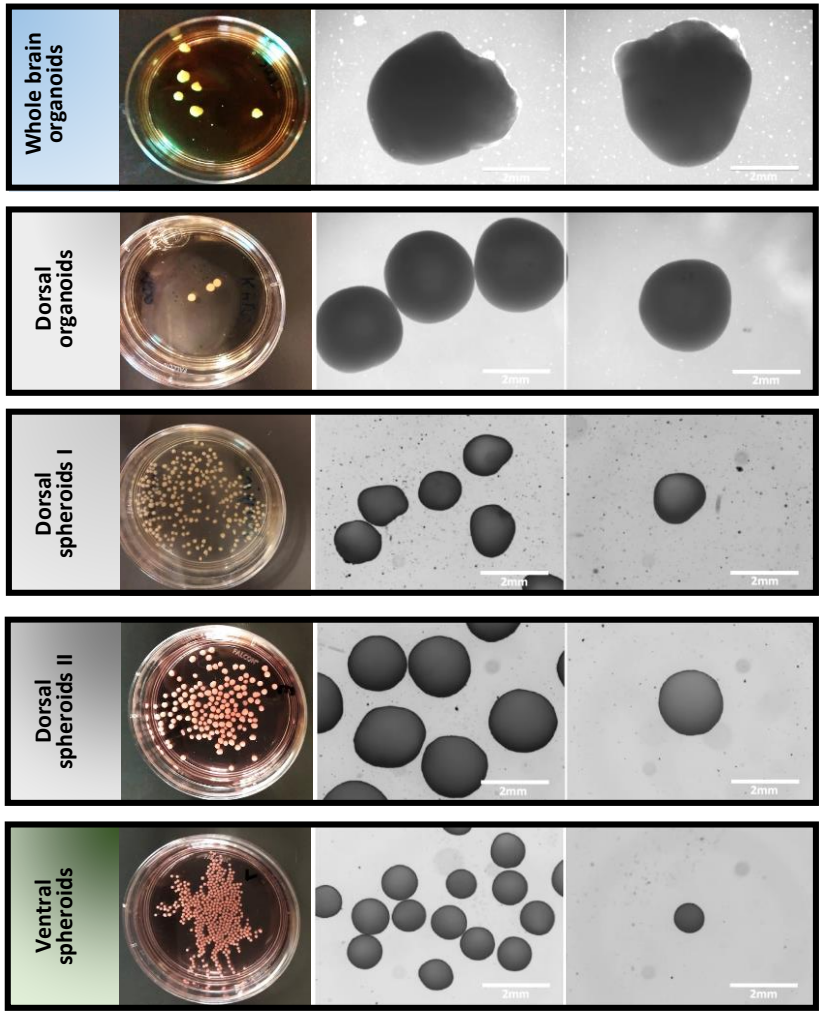


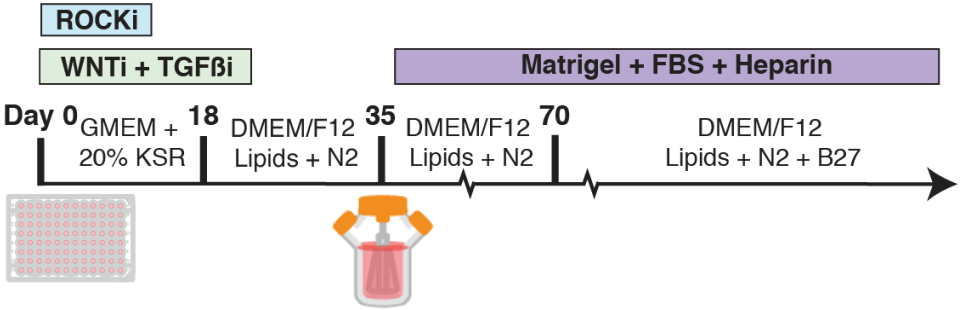
Quadrato et al., *Nature Med* (2016)

Quadrato et al., *Nature* (2017)

Quadrato *et al. Nature (*2017)

Towards Reproducible Models of the Human Cerebral Cortex





Adapted from Kadoshima et al., *PNAS* (2013)

- Long-term development
- Generation of cell diversity
- Multiple stem cell lines
- **Reproducible**

Silvia Velasco

Velasco *et al. Nature (*2019)

VELASCO ORGANOIDS DAY34

A. ALBANESE

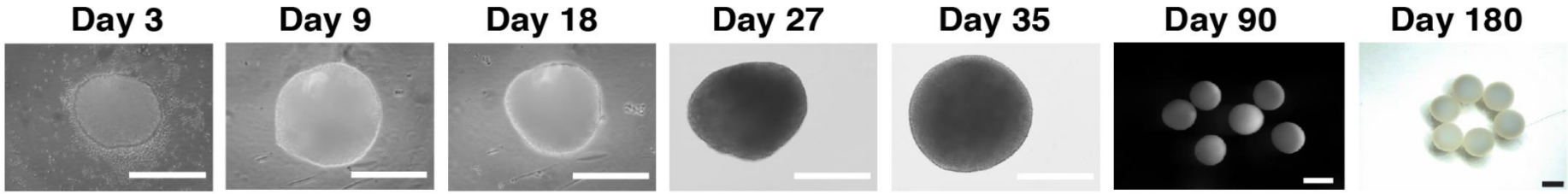
KWANGHUN CHUNG GROUP (MIT)

TECHNOLOGIES:

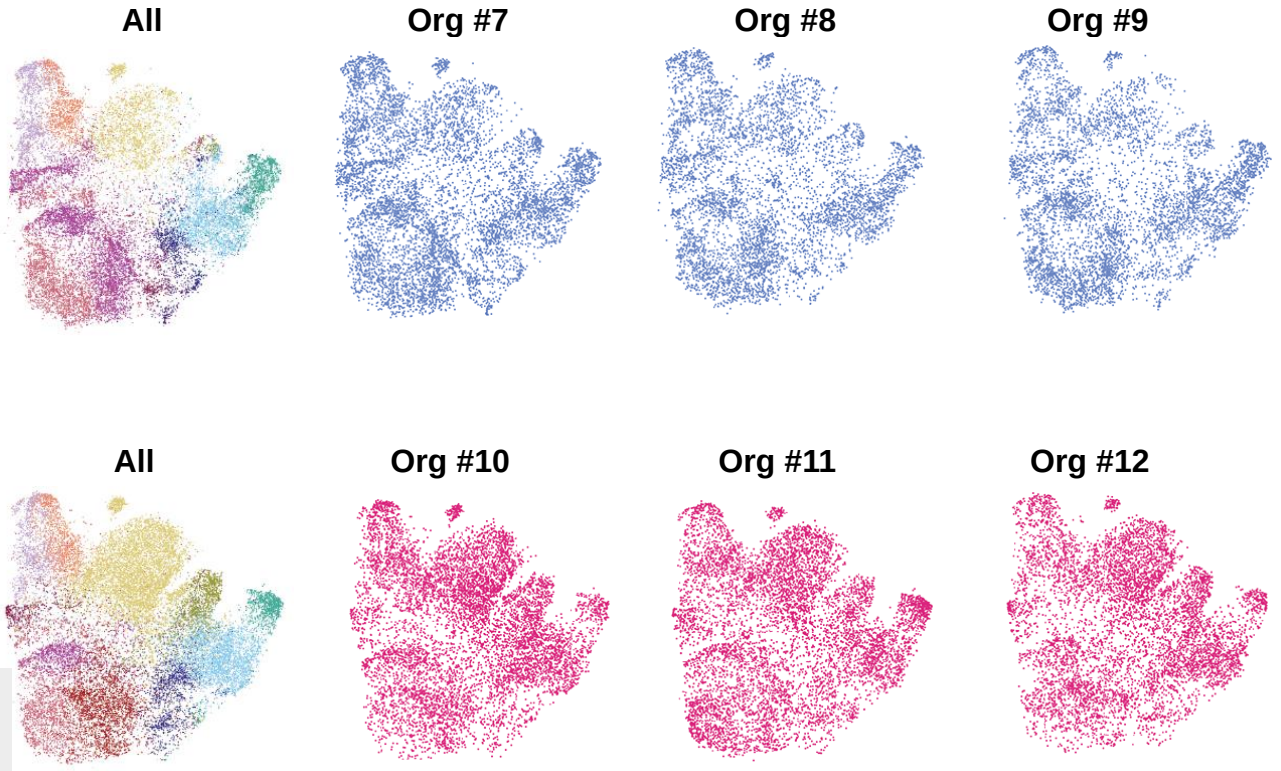
* SHIELD (tissue preservation)

* eFLASH (staining)

Reproducible Cell Diversity in brain organoids (6 months)



- Immature PNs
- Immature CPNs
- CPNs
- Immature CFuPNs
- CFuPNs
- IPCs
- Immature INs
- Cycling IN precursors
- Astroglia
- RG
- oRG
- Cycling progenitors
- oRG & Astroglia



Total: 488,965 single cells
69 individual organoids
20 batches, 5 cell lines

Velasco *et al. Nature* (2019)

With Joshua Levin and Aviv Regev

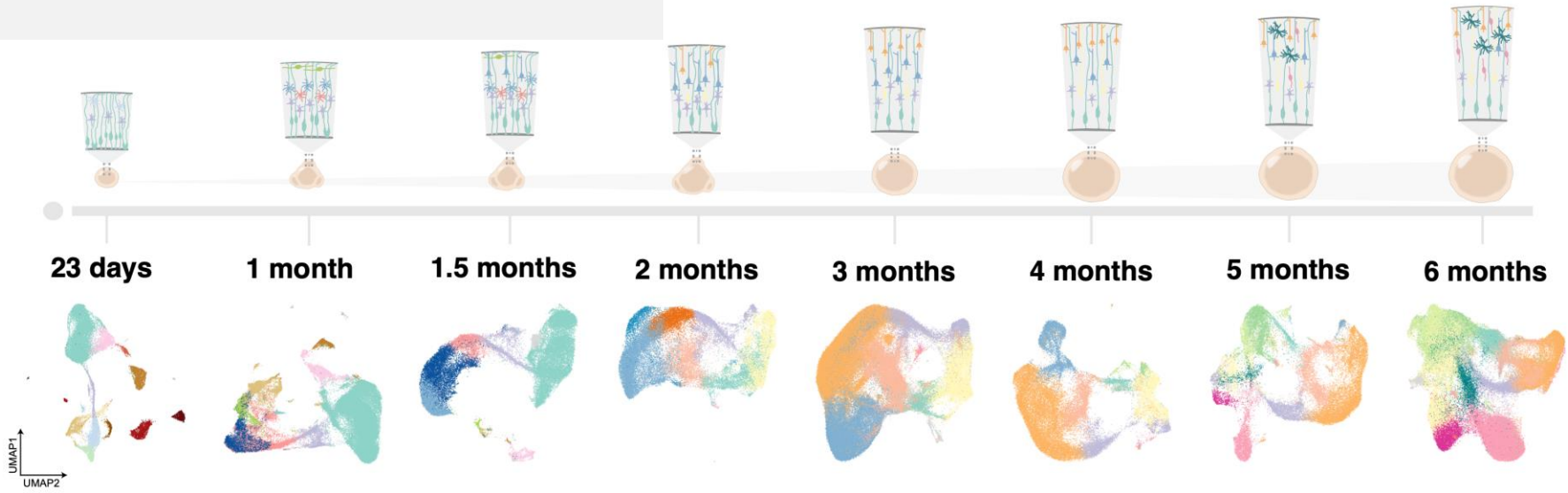
Reliable Corticogenesis in Human Cortical Organoids

7 TIMEPOINTS

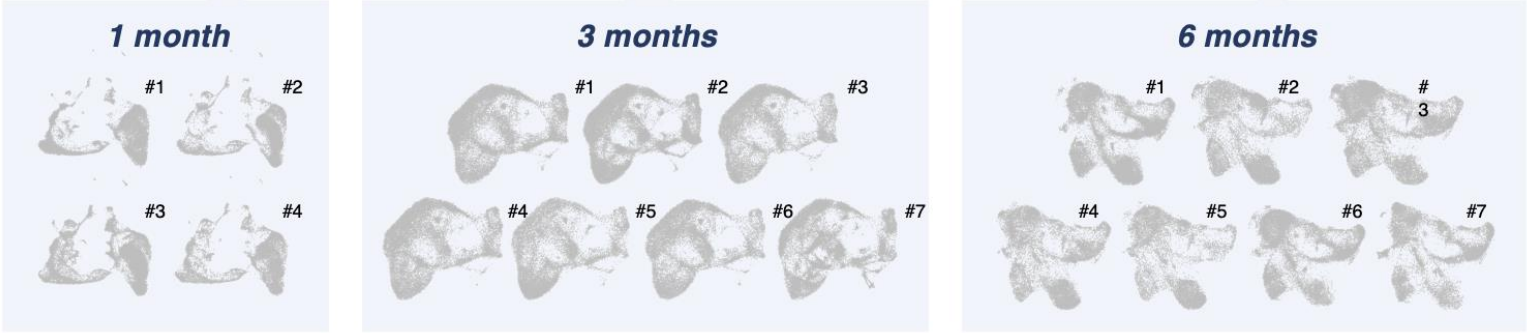
83 ORGANOIDS

18 BATCHES

533,545 SINGLE CELLS



REPRODUCIBLE

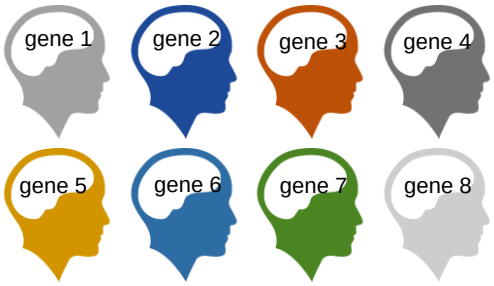


With Joshua Levin and Aviv Regev

Keidagle* / Uzquiano* et al., *unpublished*

Understanding complex human brain diseases

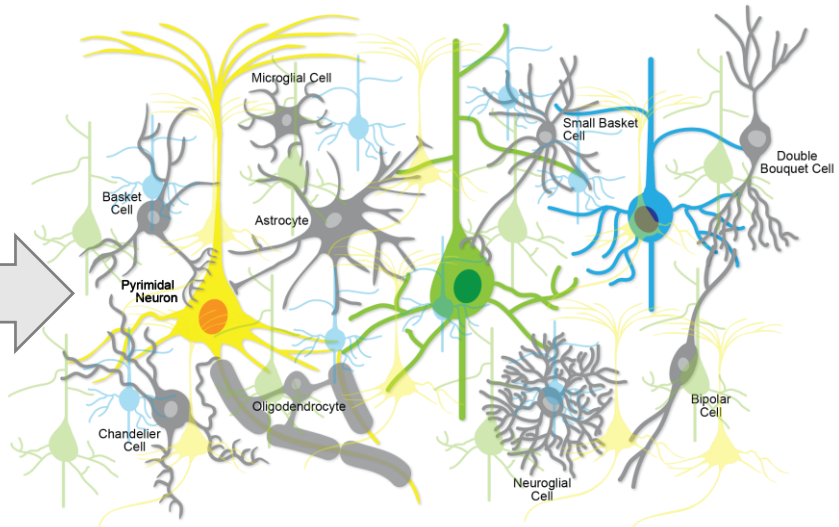
NEURODEVELOPMENTAL DISORDERS



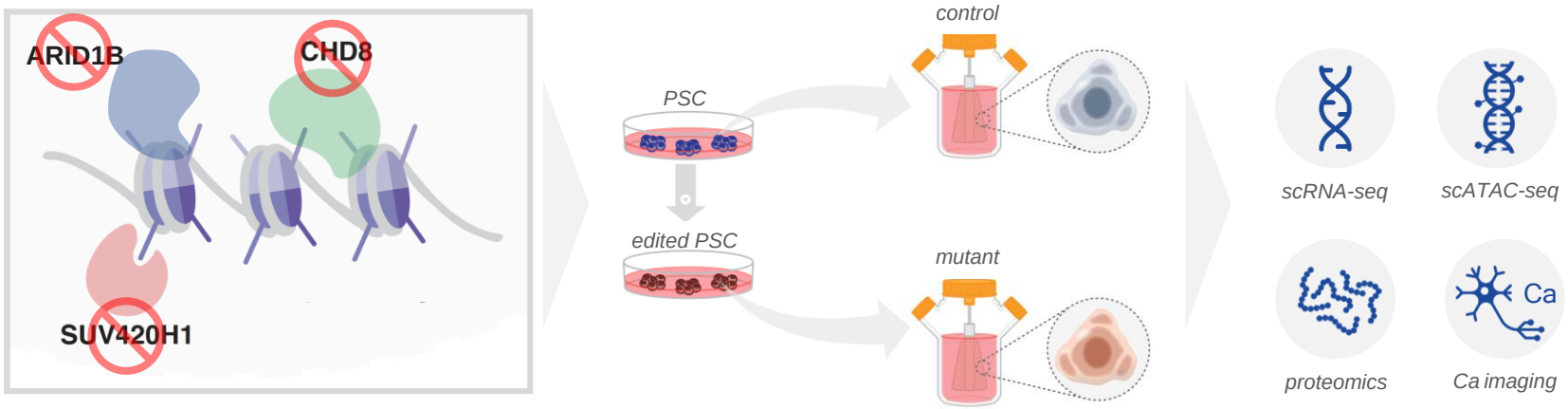
GENETICS

?

NEUROBIOLOGY



Modeling ASD risk gene mutations in brain organoids



QUESTIONS

What **cell types** are affected?

What **biological processes** are affected?

When are they affected?

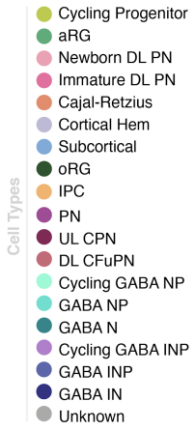
Do these alterations **converge** across mutations?

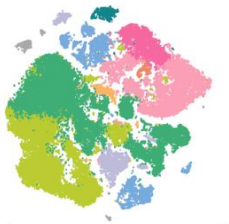
Does **human genomic background** affect penetrance?

Paulsen*, Velasco*, Keidagle*, Pigoni* et al., Biorxiv 2020

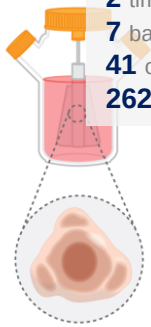
With Joshua Levin and Aviv Regev

SUV420H1, *ARID1B*, and *CHD8* Haploinsufficiencies Converge on Accelerated Development of **GABAergic Neurons**





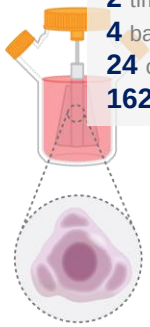
57,941 cells



3 cell lines
2 timepoints
7 batches
41 organoids
262,660 cells

SUV420H1$^{+/-}$

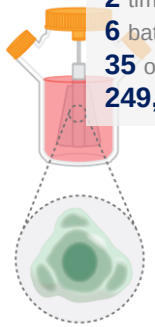
35,000 cells



2 cell lines
2 timepoints
4 batches
24 organoids
162,399 cells

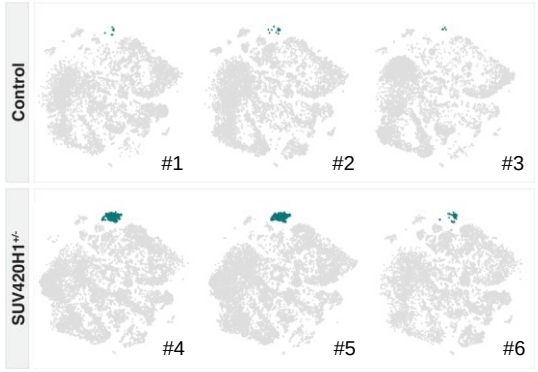
ARID1B$^{+/-}$

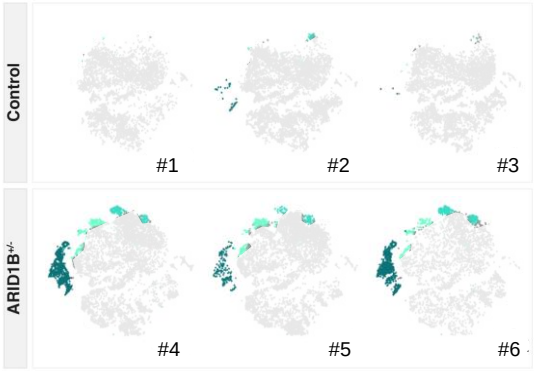
39,285 cells

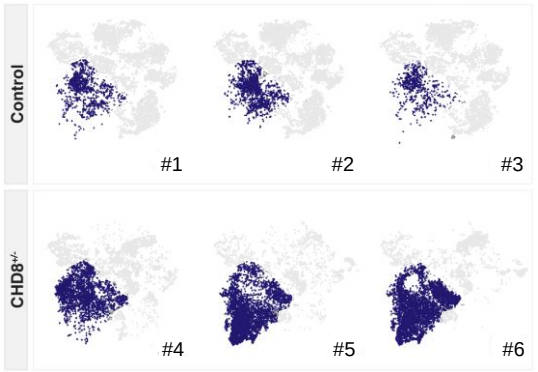


3 cell lines
2 timepoints
6 batches
35 organoids
249,588 cells

CHD8$^{+/-}$

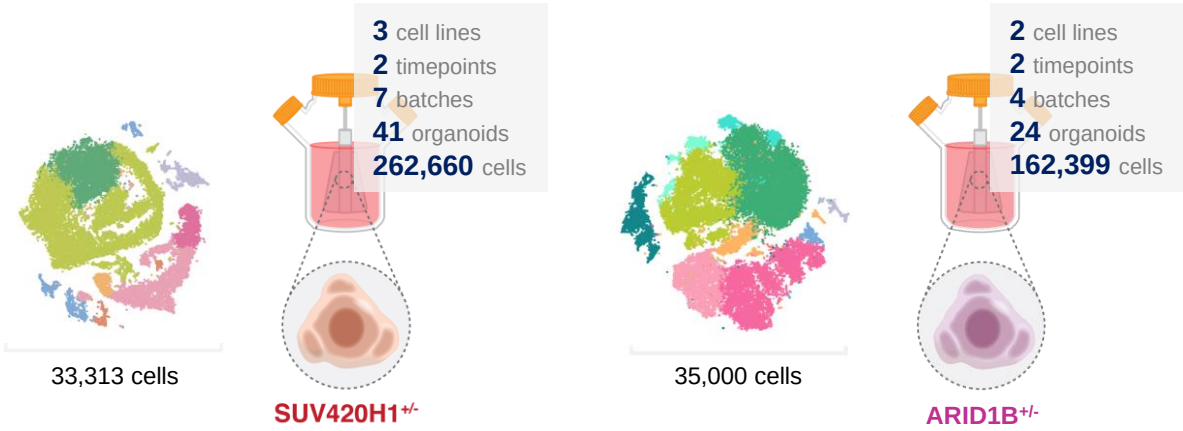


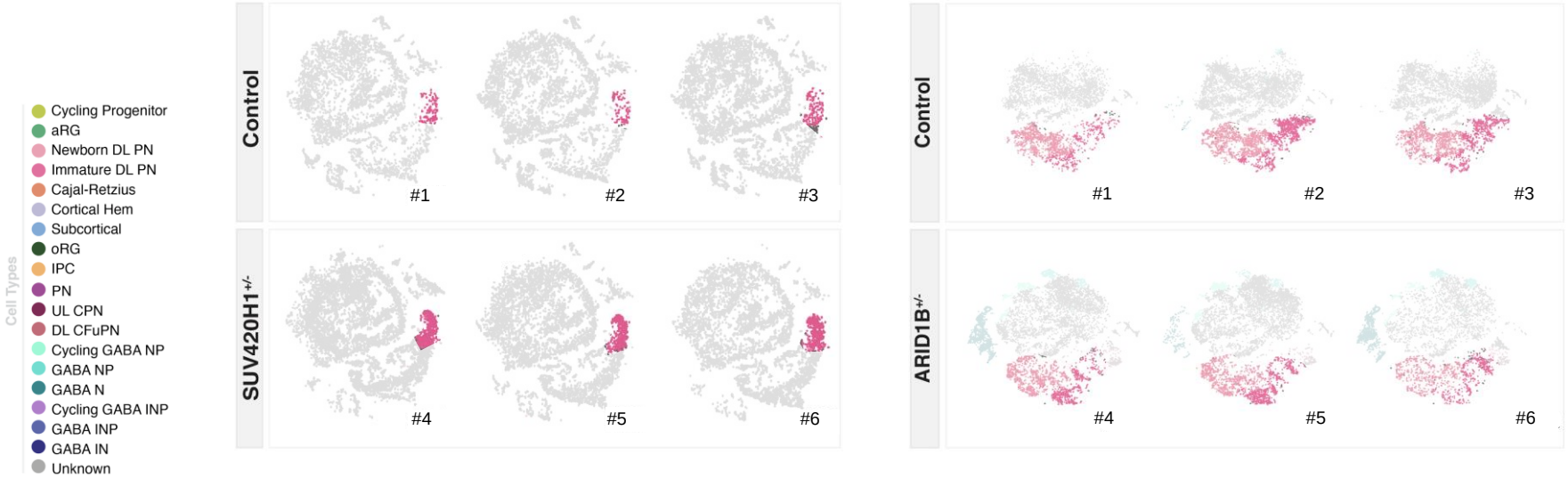




Paulsen, Velasco*, Kedaigle*,Pigoni* et al., Biorxiv, 2020*

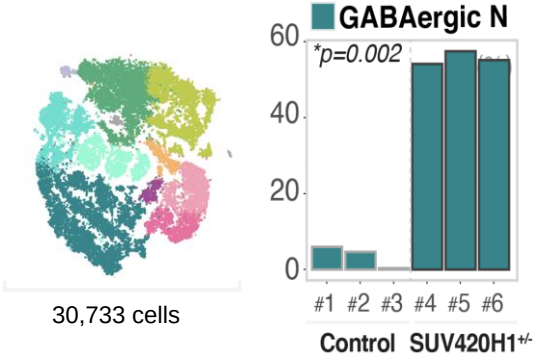
Asynchronous Development of **Deep-Layer Projection Neurons** in both *SUV420H1* and *ARID1B* Mutant Organoids

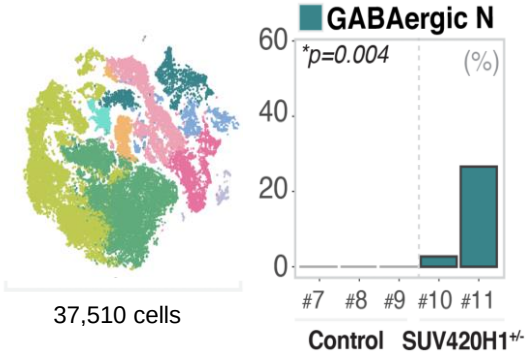


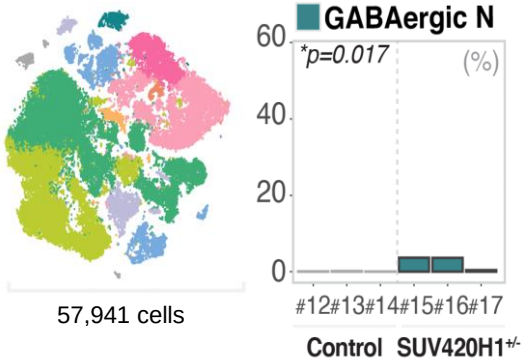


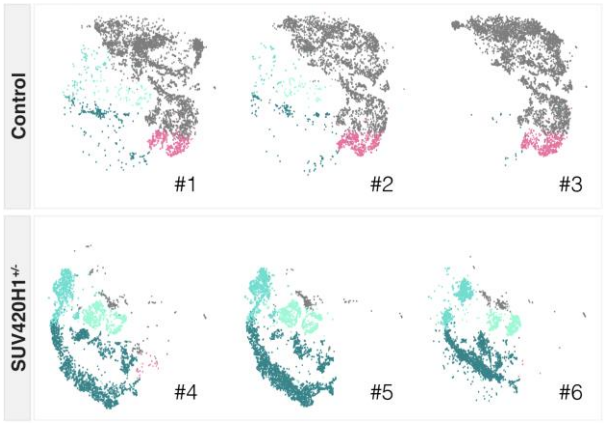
Paulsen, Velasco*, Kedaigle*,Pigoni* et al., Biorxiv, 2020*

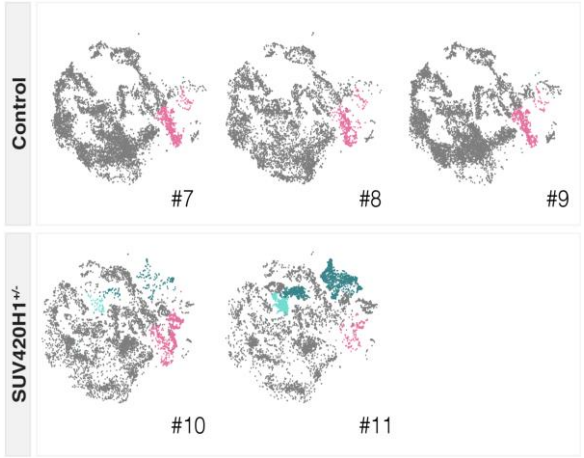
Penetrance of **GABAergic Neuron** Phenotype in *SUV420H1* Mutant Organoids Depends on Genomic Context

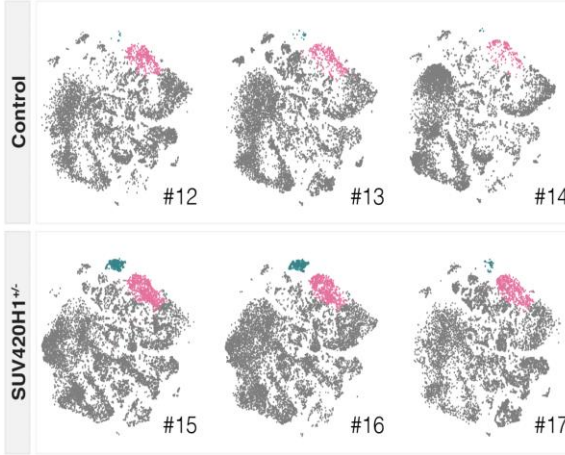




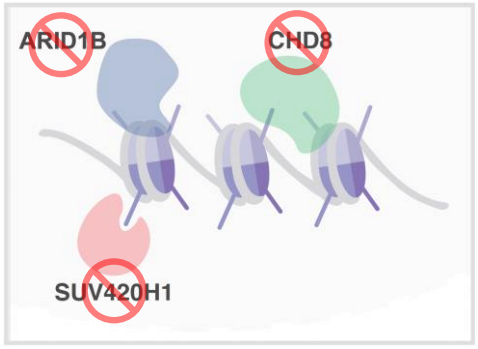








Paulsen, Velasco*, Kedaigle*,Pigoni* et al., Biorxiv, 2020*



CONVERGENCE ON CELL TYPES:

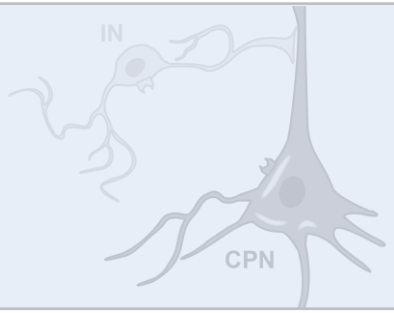
GABAergic neurons and deep layer projection neurons

+

CONVERGENCE ON PROCESS:

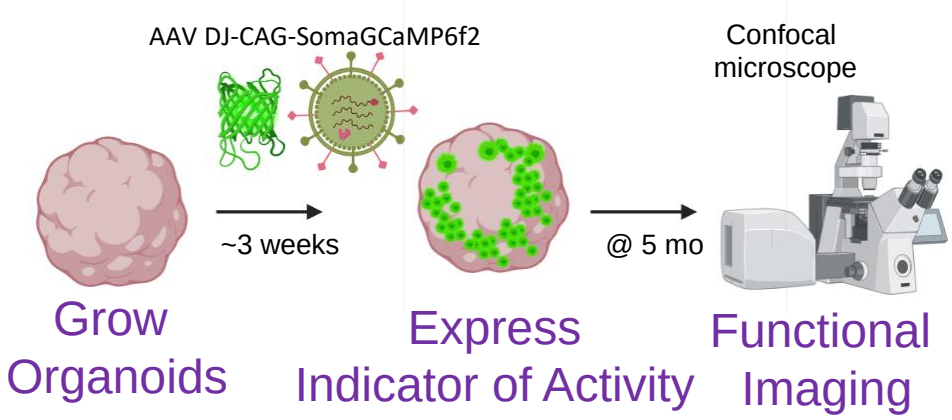
asynchronous development

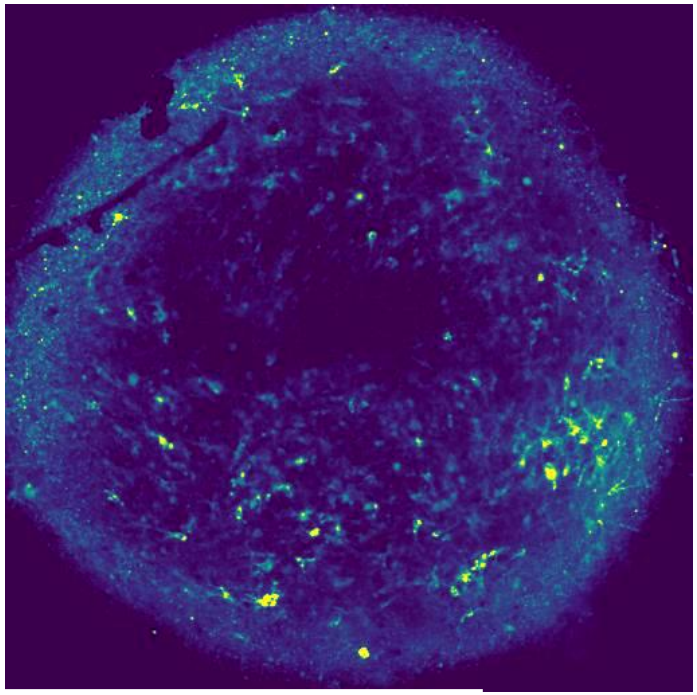
through largely distinct molecular pathways

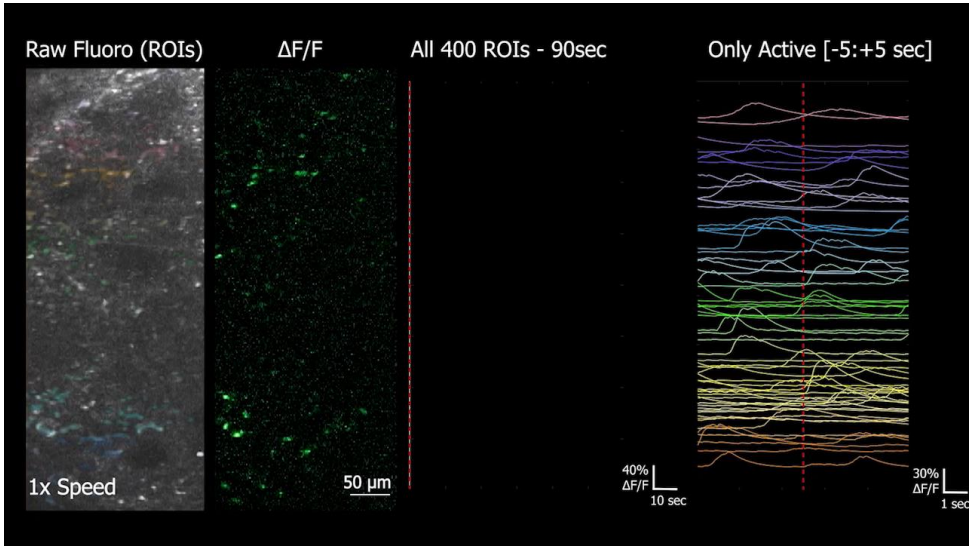


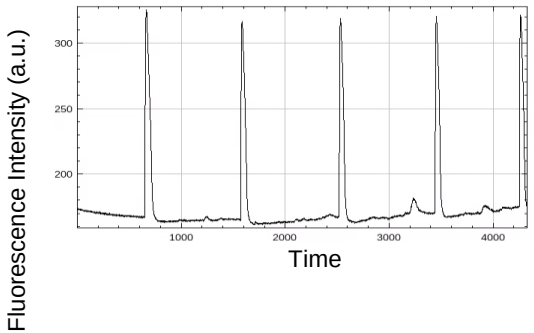
HYPOTHESIS:

abnormal activity of local circuits?



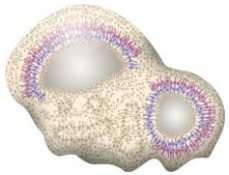






Yang Sung Min

With Ed Boyden (MIT)



Summary

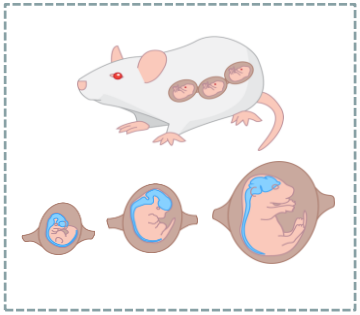
- Organoids can serve as **reductionist experimental models** of human brain development

- Cell diversity of cerebral cortex is generated **reproducibly** “organoid-to-organoid” and across stem cell lines

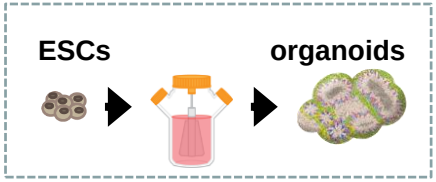
- Organoids identify **early convergent phenotypes** across multiple ASD genes: asynchronous development of GABAergic neurons and deep layer corticofugal neurons

Thank You

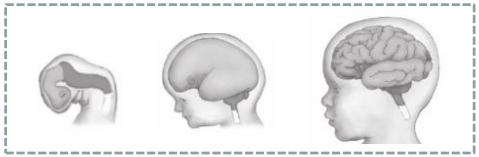
Embryo
Ashwin Shetty
Juliana Brown
Vahbiz Jokhi
Yang Sung Min
Daniela Di Bella
Jeff Stogsdill
Michal Lipinski
Rahel Kastli
Michael Borrett
Juliana Brown
Zeke Benshirim



Organoids
Bruna Paulsen
Noelia Anton Bolanos
Rafaela Sartore
Martina Pigoni
Ana Uzquiano Lopez
Irene Faravelli



Bioinformatics
Amanda Kedaigle
Sean Simmons
Kwanho Kim
Tyler Faits



Collaborators

Aviv Regev (Broad Inst./ MIT/Genentech), Joshua Levin and Xian Adiconis (Broad Inst.), Jeff Lichtman (Harvard), Feng Zhang (Broad Inst./MIT), Ed Boyden (MIT)

STANLEY CENTER FOR PSYCHIATRIC RESEARCH

NIH

CHAN ZUCKERBERG INITIATIVE

BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES
BRAIN INITIATIVE