



HSCRB

HARVARD DEPARTMENT OF STEM
CELL & REGENERATIVE BIOLOGY

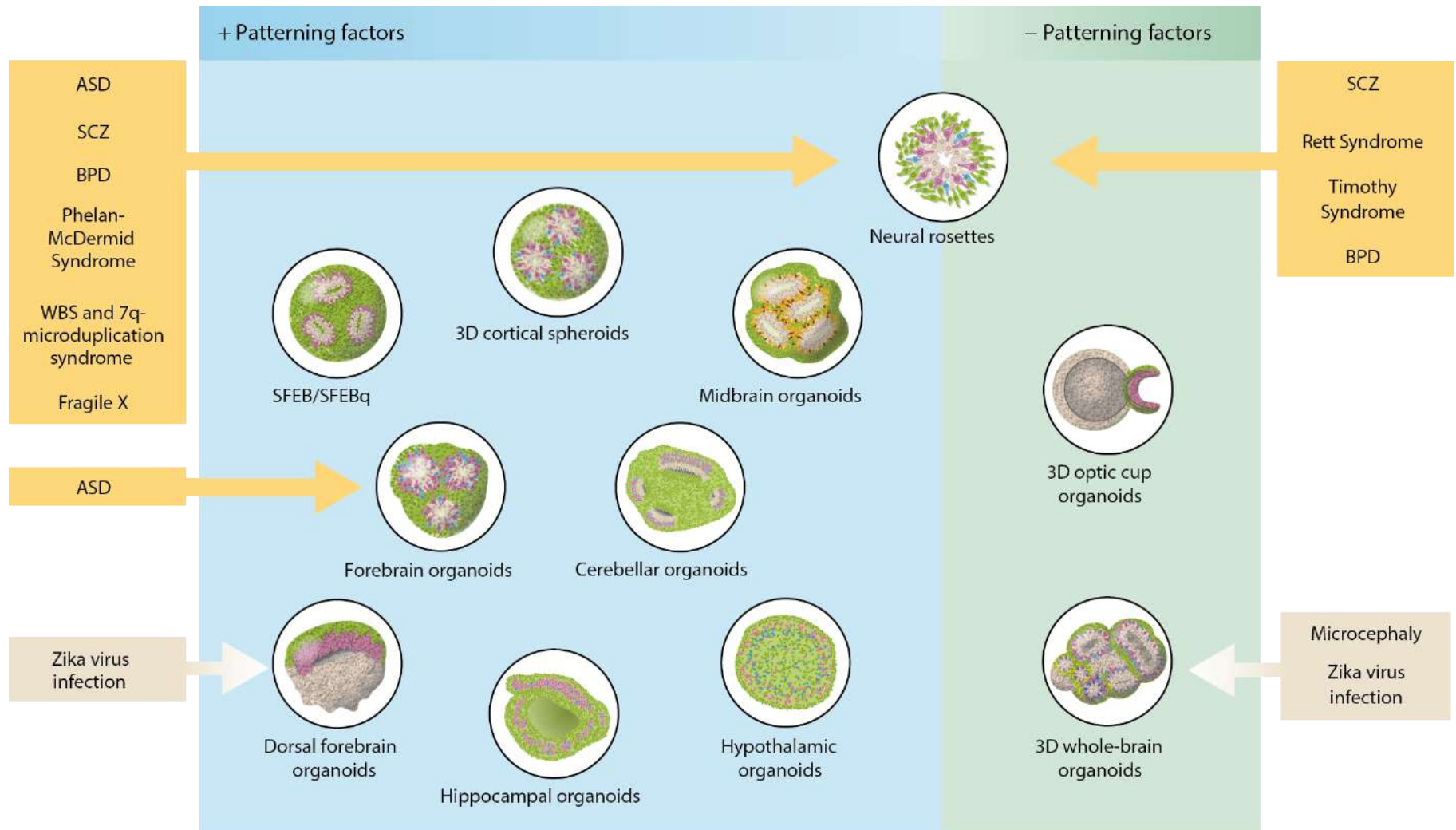


STANLEY CENTER
FOR PSYCHIATRIC RESEARCH

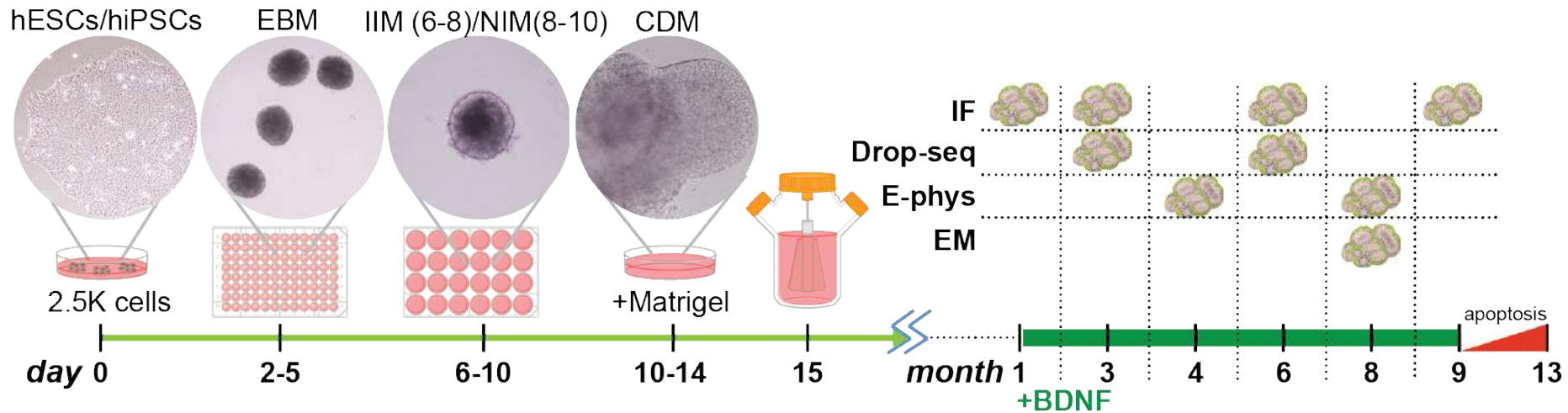
Modeling Human Brain Development and Disease at Single Cell Resolution with Brain Organoids

Giorgia Quadrato, PhD
Arlotta Lab

hPSC-derived brain organoids and spheroids



Long-term cultures of 3D human brain organoids

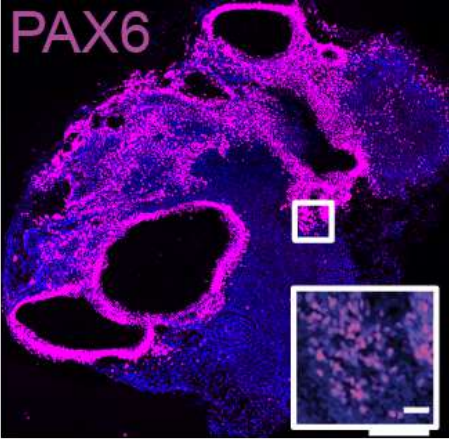


Quadrato *et al.*, *Nature* (2017)

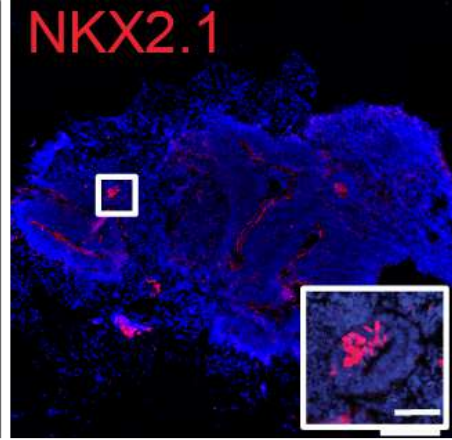
Quadrato*, Sherwood* *et al.*, *Nat.Prot.Ex.* (2017)

Early self-regionalization of brain organoids (1 mo)

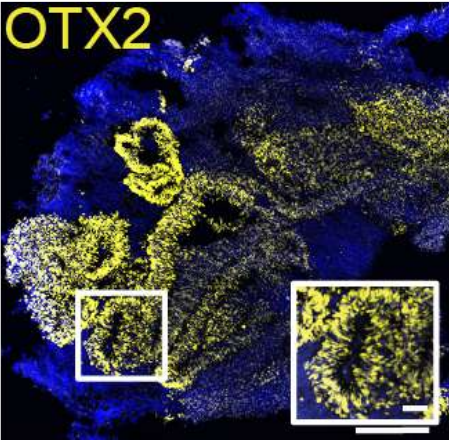
Dorsal forebrain



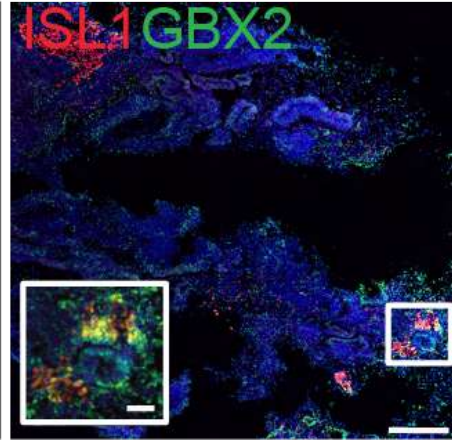
Ventral forebrain



Midbrain/retina



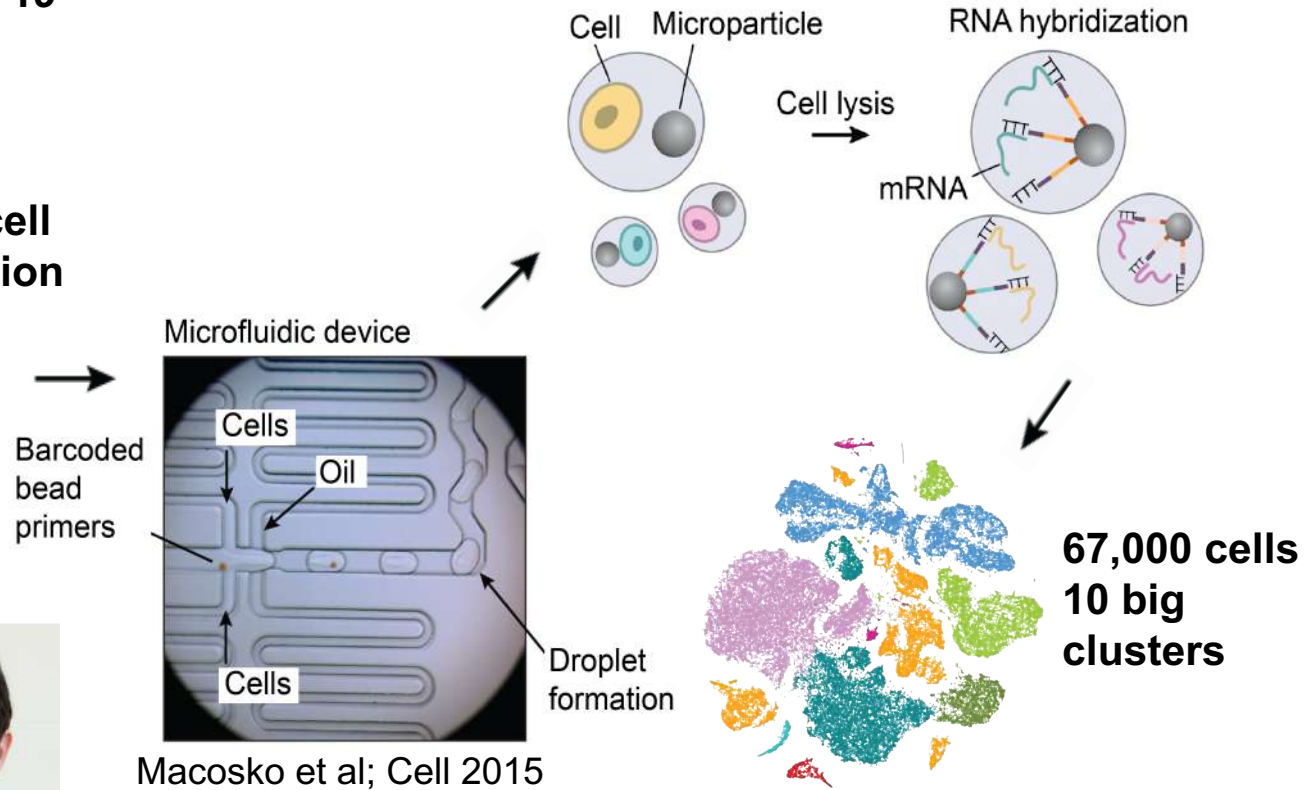
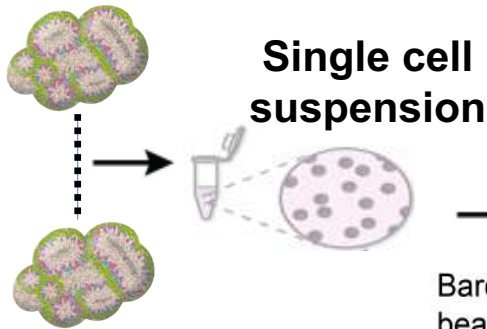
Hindbrain



PAX6
NKX2-1
OTX2
GBX2

What cells can be made in human brain organoids? --Drop-seq single cell analysis--

Organoids 6mo (n = 19
from 4 distinct
bioreactors)



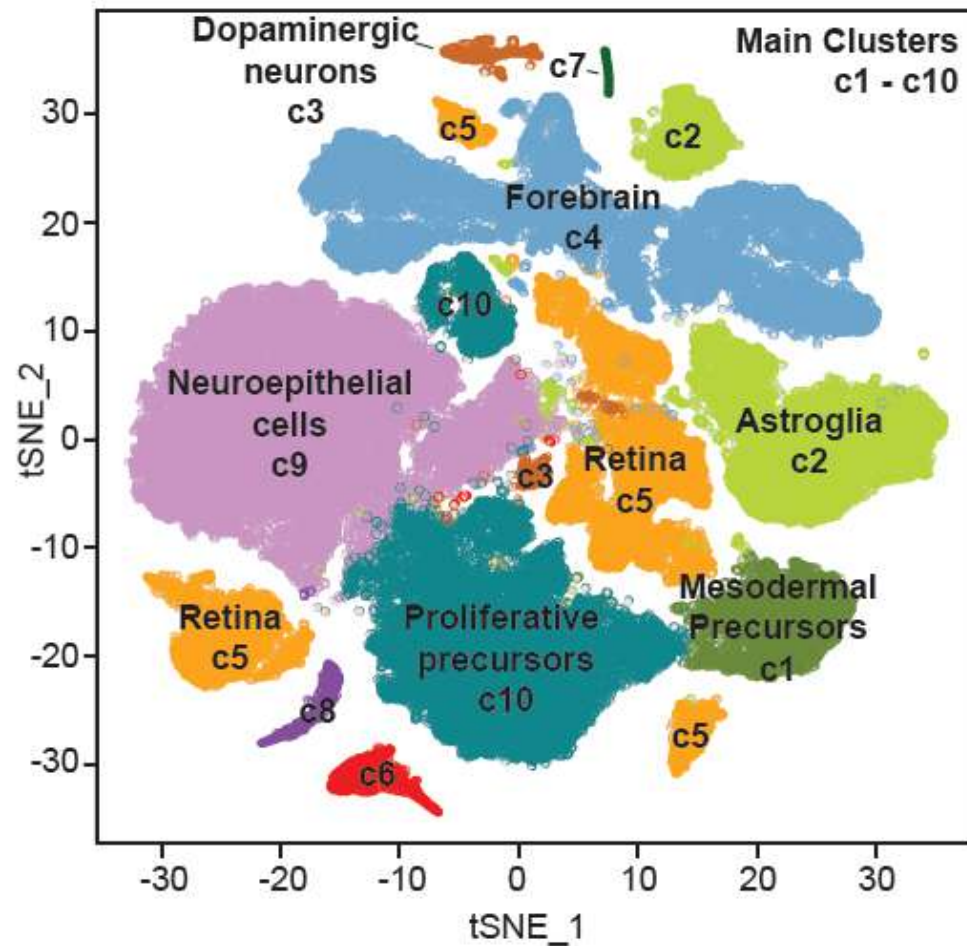
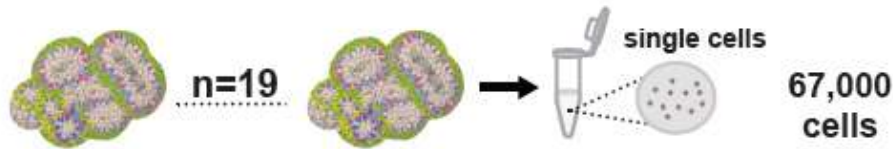
Steve McCarroll



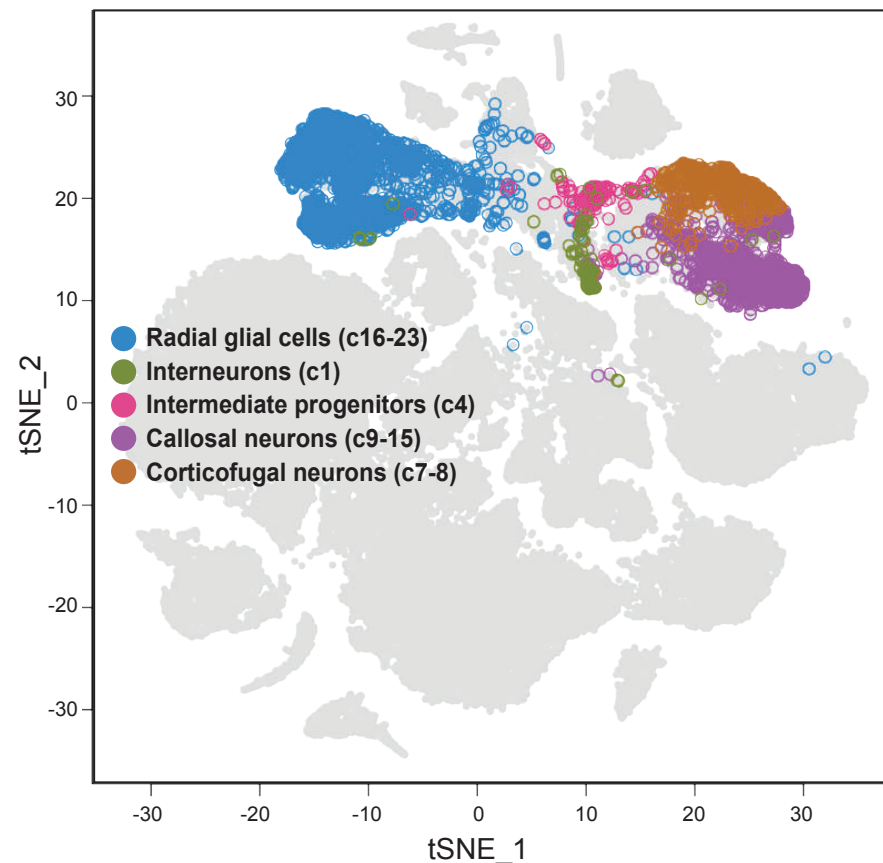
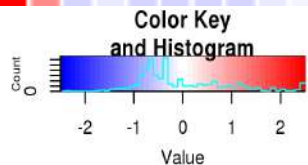
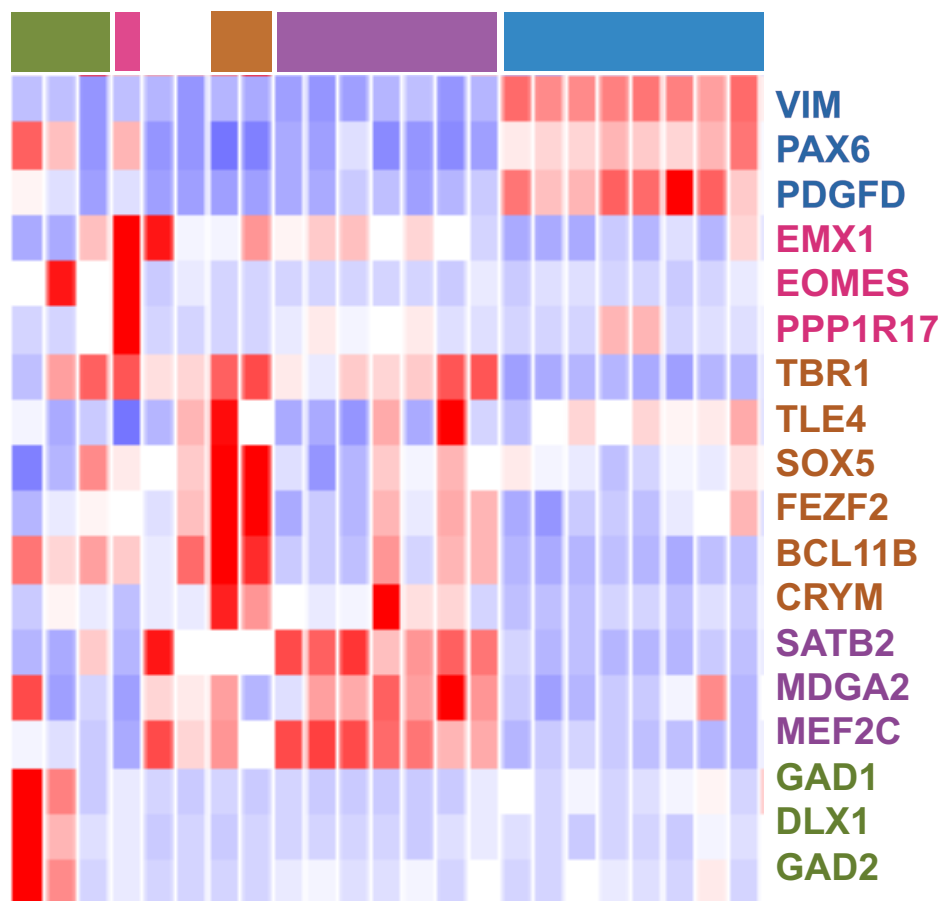
Evan Macosko

Macosko et al; Cell 2015

Decoding the identity of Drop-seq clusters

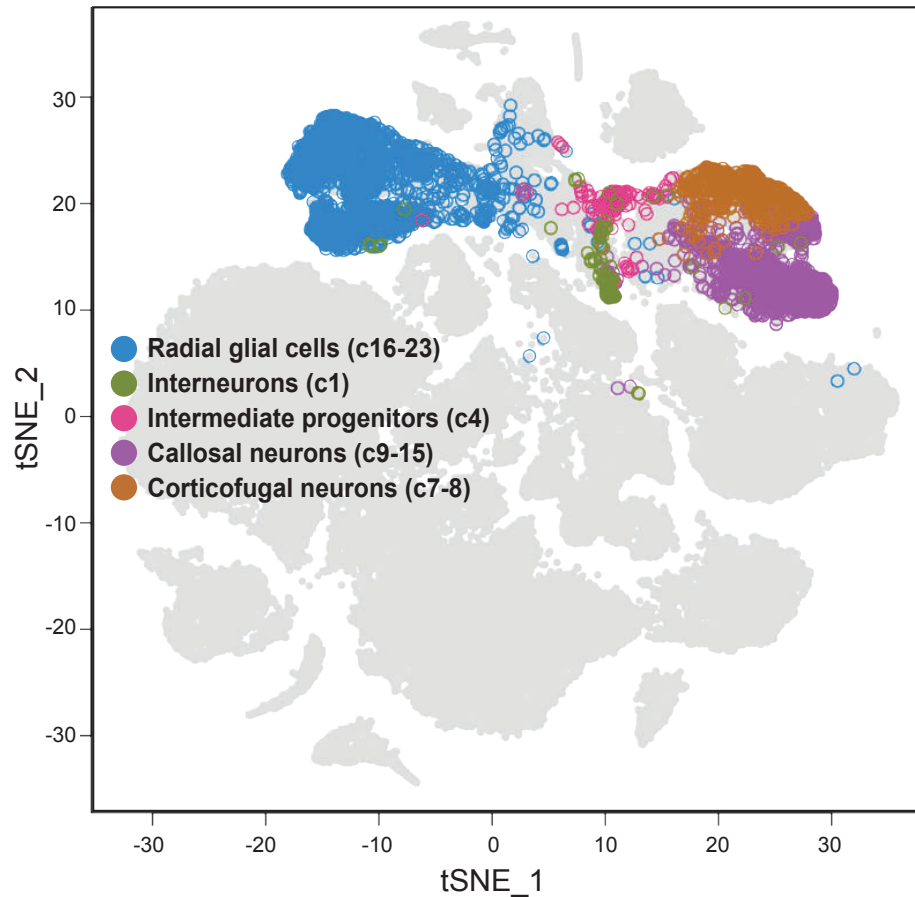


Many cell types of the endogenous human forebrain are identified within brain organoids

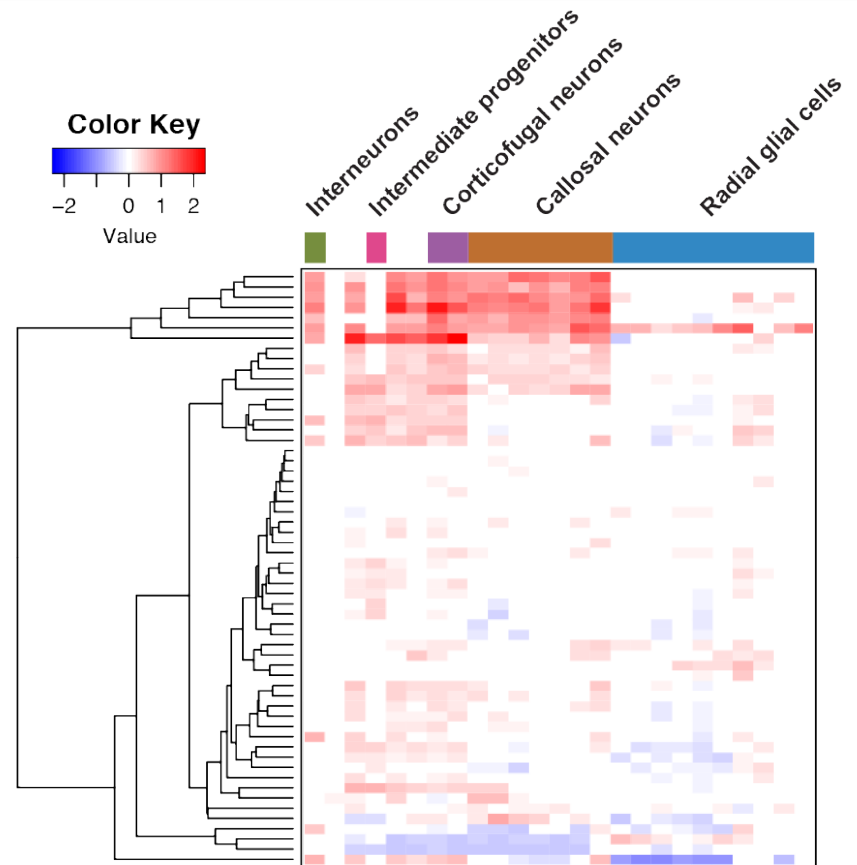


C

Expression of autism-risk genes in the forebrain cluster



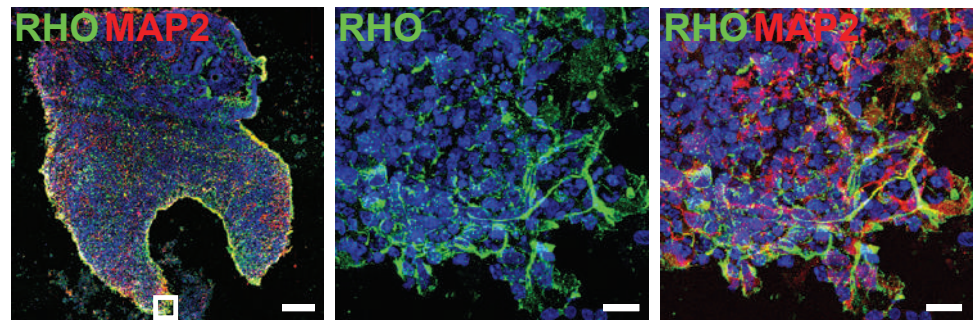
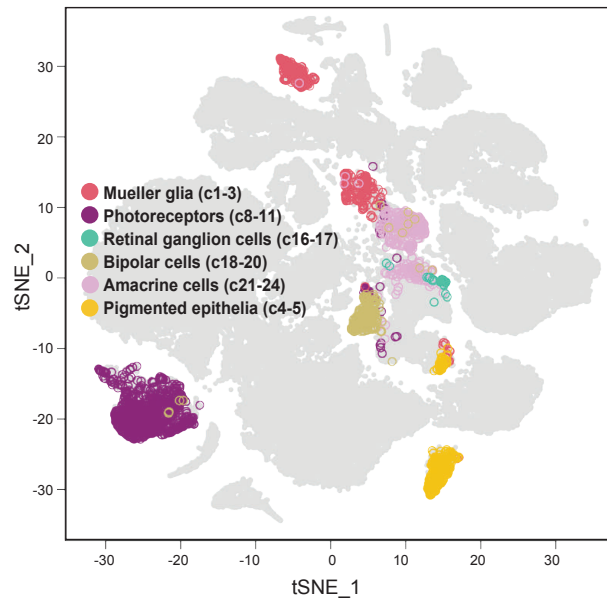
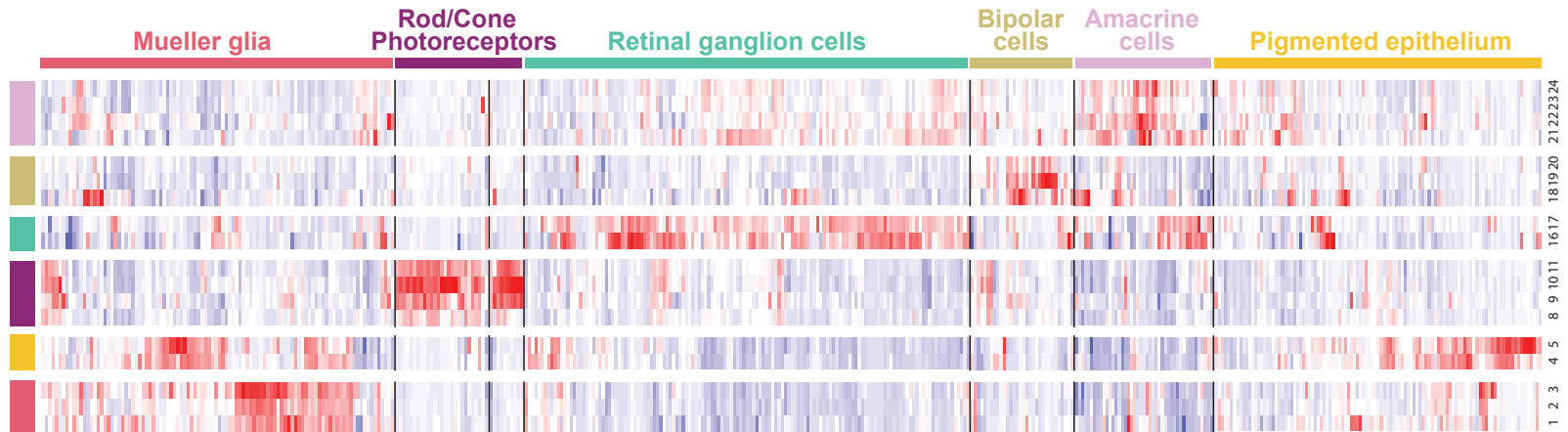
ASD-linked Genes Enriched in Forebrain Cluster



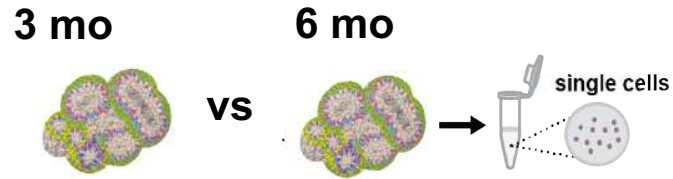
All genes from Simon Simplex Collection with FDR ≤ 0.01

(Sanders *et al.*, Neuron 2015)

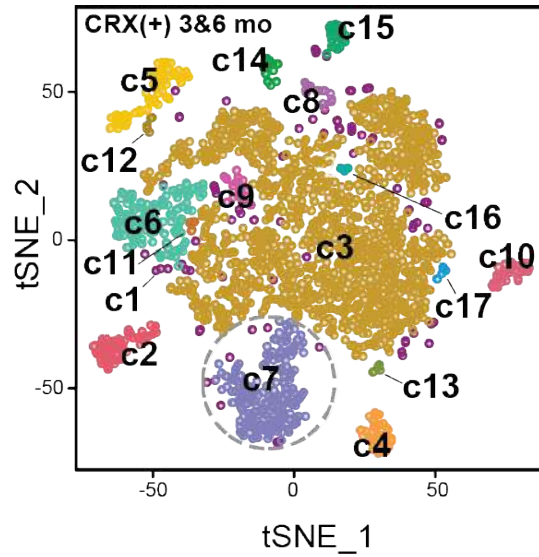
Decoding the identity of the retina cluster (6 mo)



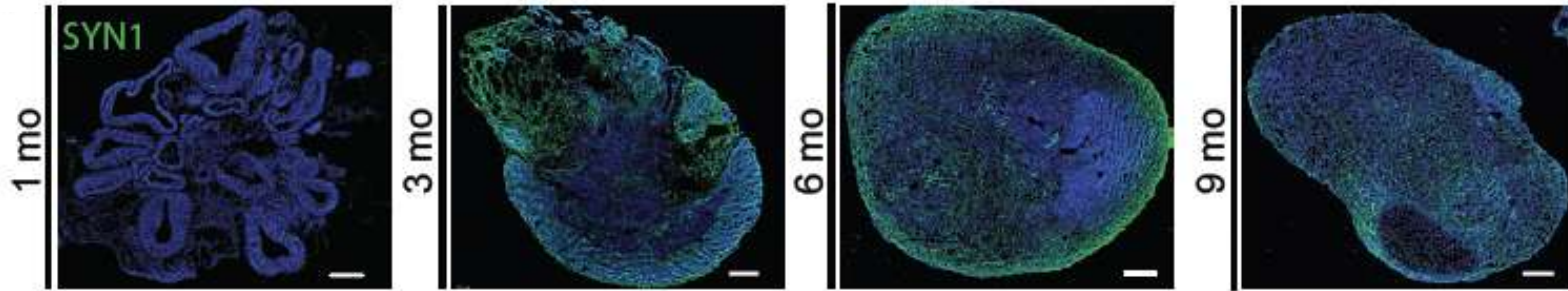
Protracted culture of human brain organoids leads to increased cellular diversity



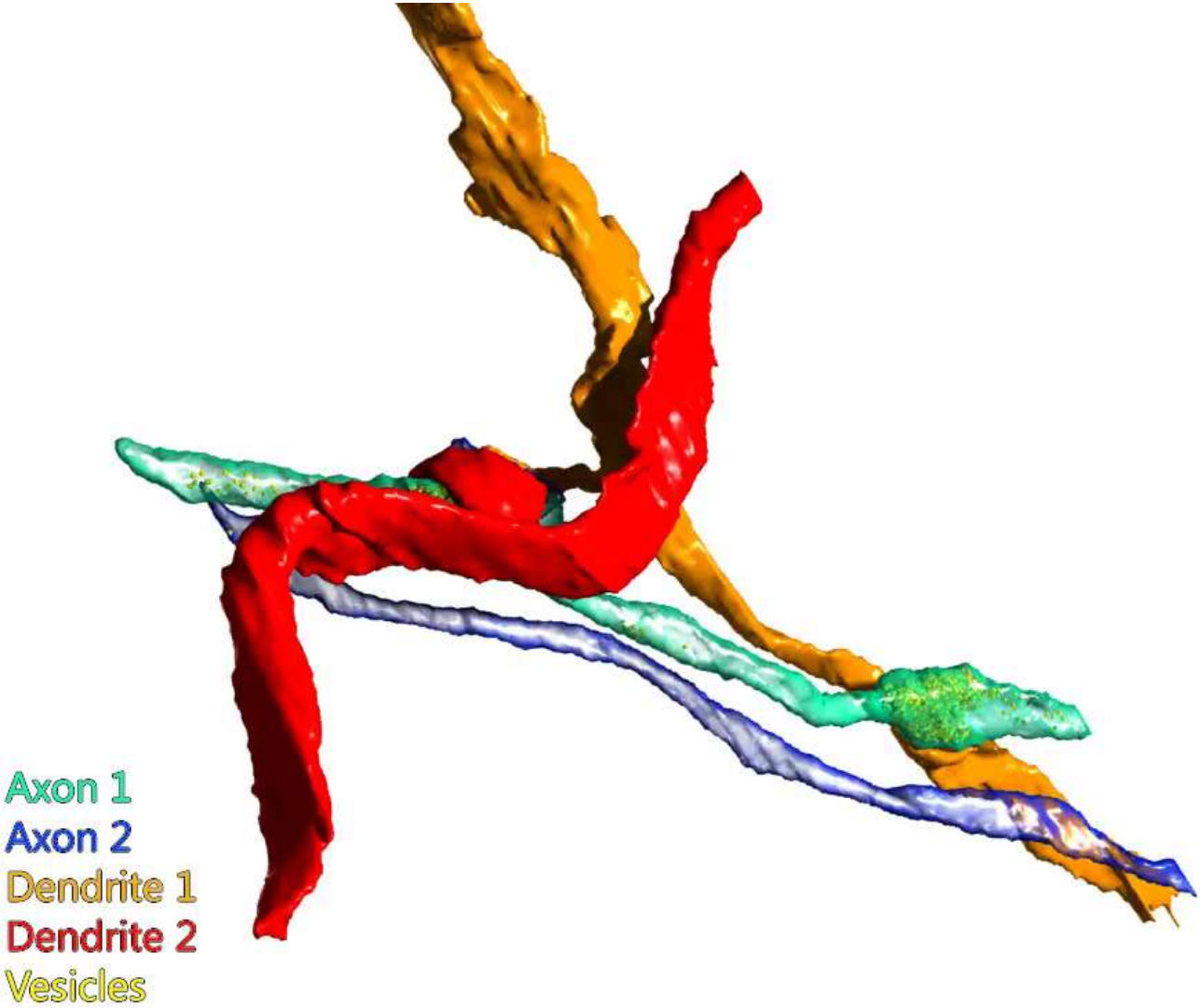
Extended organoid culture allows maturation of photoreceptors



Protracted culture of human brain organoids leads to advanced neuronal maturation

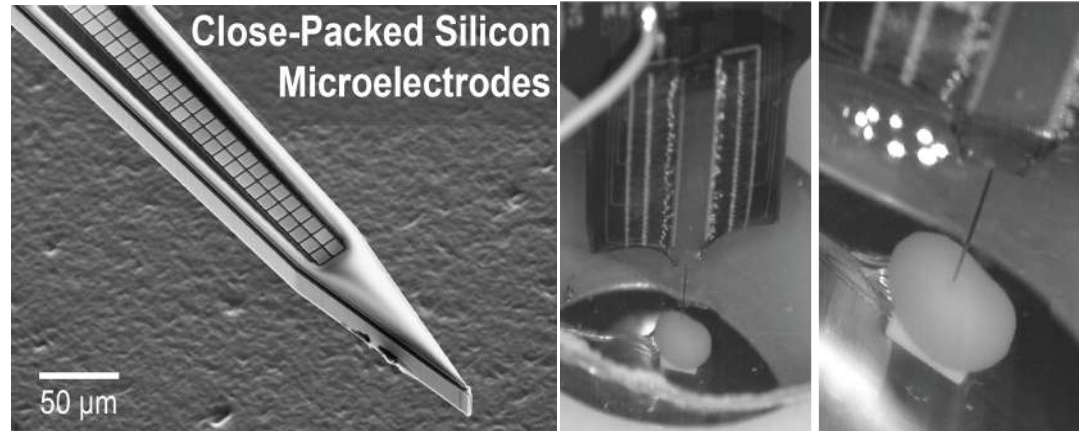
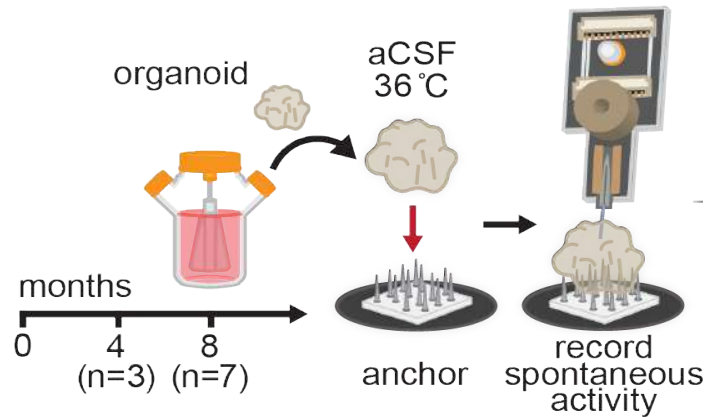


Human brain organoids mature dendritic spines



Brain organoids form spontaneously-active neuronal networks

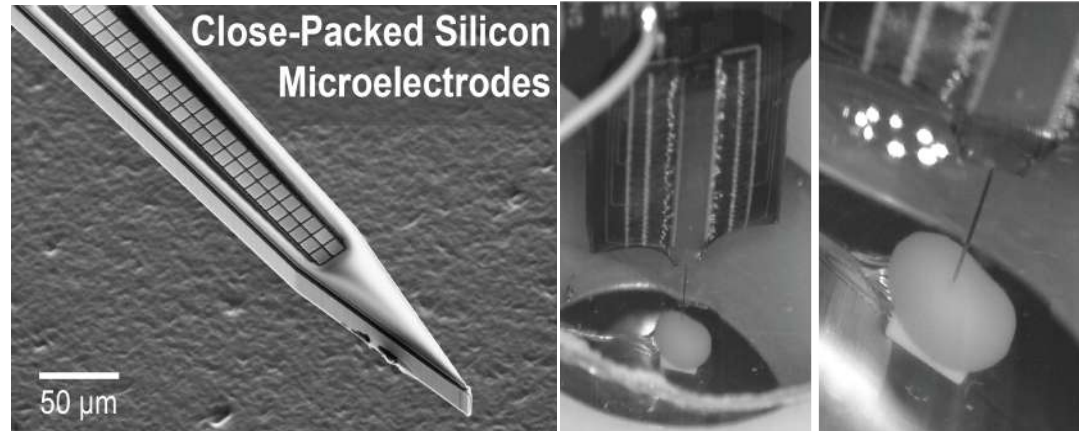
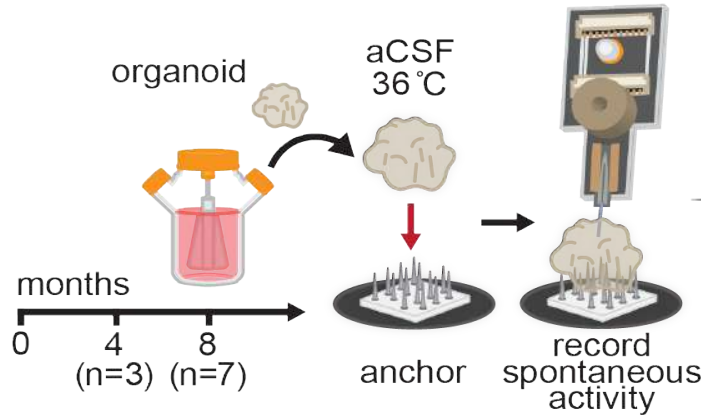
John Sherwood, Ed Boyden



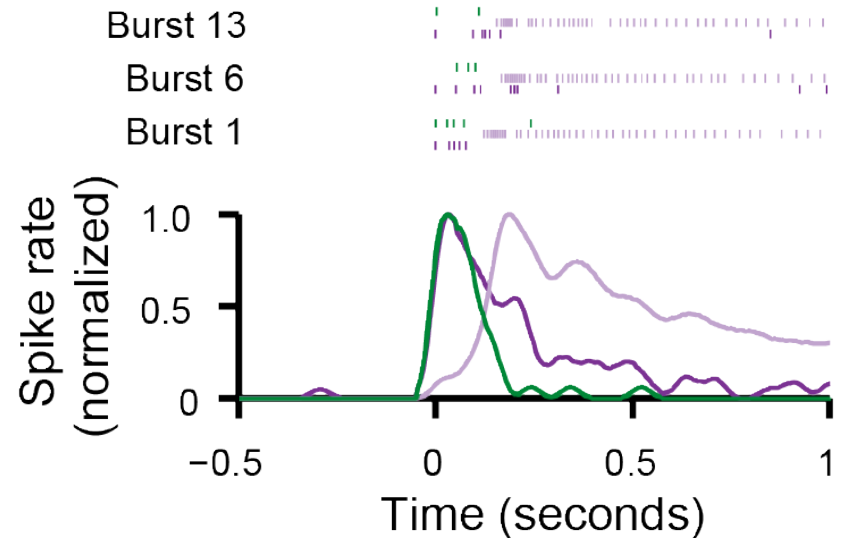
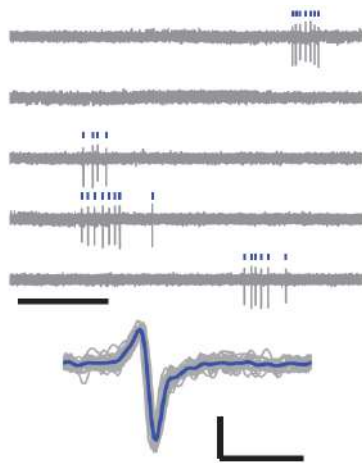
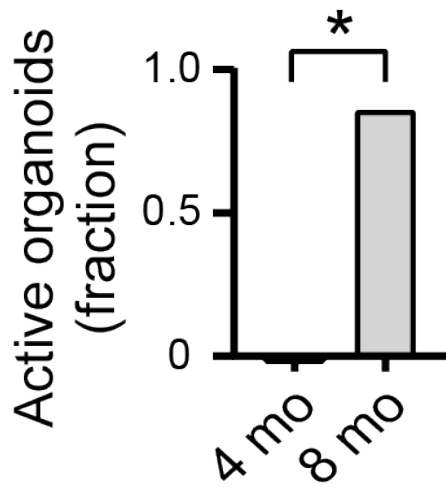
(Scholvin et al., 2016)

Brain organoids form spontaneously-active neuronal networks

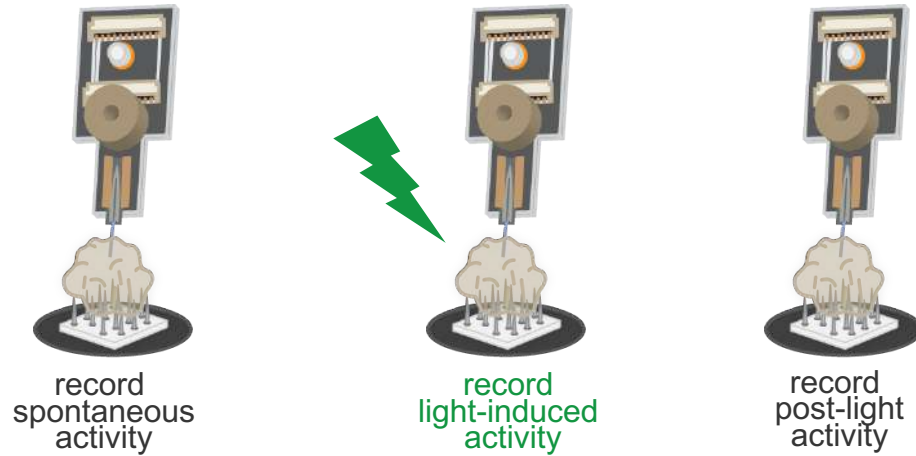
John Sherwood, Ed Boyden



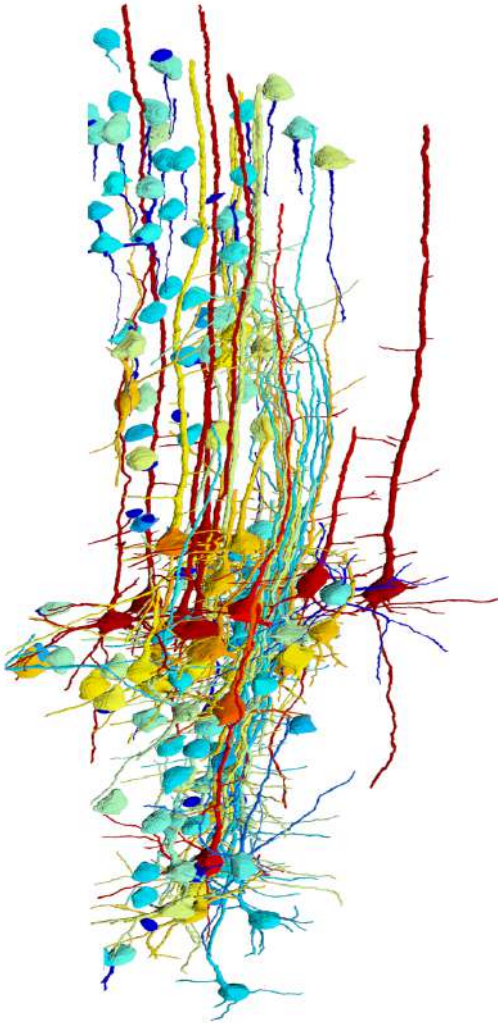
(Scholvin et al., 2016)



“Sensory stimulation” of brain organoids



Summary



- 3D human cerebral organoids can be “developed” over a long timeline (over 1 yr).
- Cerebral organoids can generate regional and cellular diversity and mature spontaneously active networks.
- Neuronal activity in organoids can be modulated by sensory stimulation of light-sensing cells

Arlotta Lab

Paola Arlotta

Jojo Nguyen

John Sherwood

Natalie Maria

Yang Ming Sun

Juliana Brown

Helen Zhang

Emauela Zuccaro



Collaborators

Steve McCarroll (HMS)

Evan Macosko (HMS)

Ziv Williams (HMS)

Ed Boyden (MIT)

Jeff Lichtman (Harvard U.)

Daniel Berger (Harvard U.)

Joshua Levin (Broad)

Aviv Regev (MIT)

Lee Rubin (HSCR B)

Francesca Rapino (HSCR B)

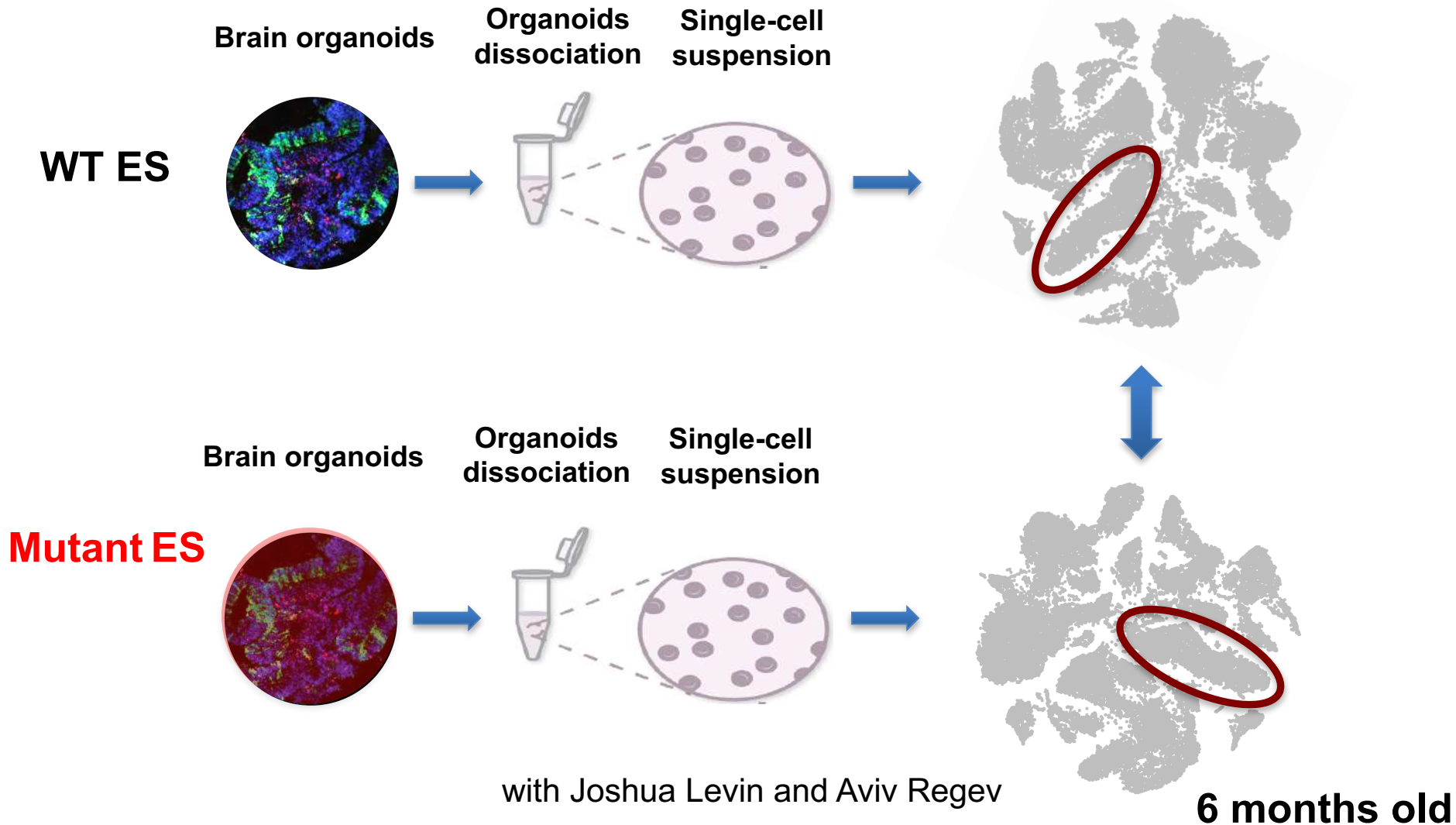


HSCR B

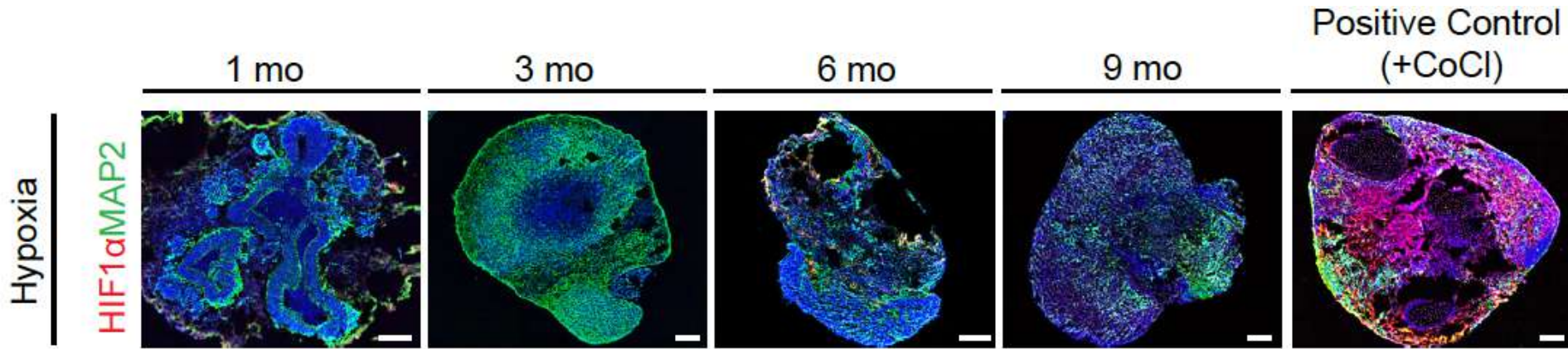
HARVARD DEPARTMENT OF STEM
CELL & REGENERATIVE BIOLOGY



Single Cell RNA-seq analysis of Brain Organoids derived from mutant ES lines

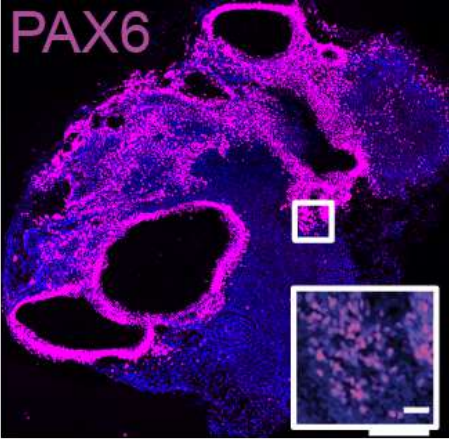


Long-term development of 3D brain organoids

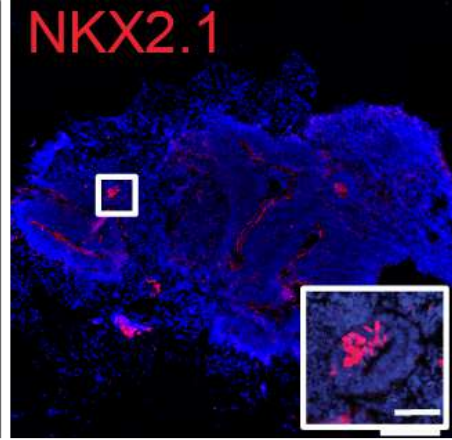


Early self-regionalization of brain organoids (1 mo)

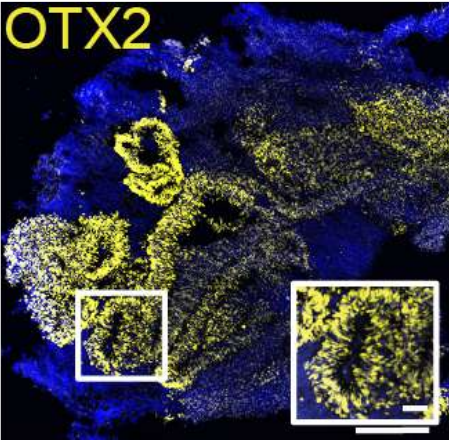
Dorsal forebrain



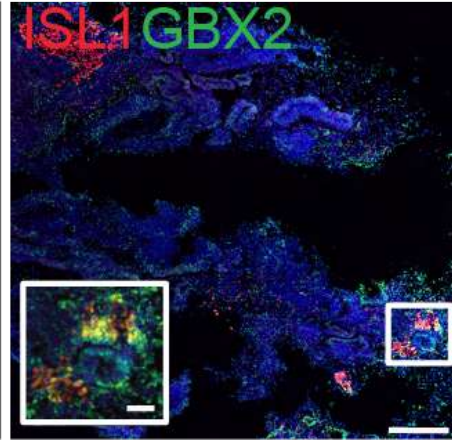
Ventral forebrain



Midbrain/retina



Hindbrain



PAX6
NKX2-1
OTX2
GBX2

Long-term development of 3D brain organoids

