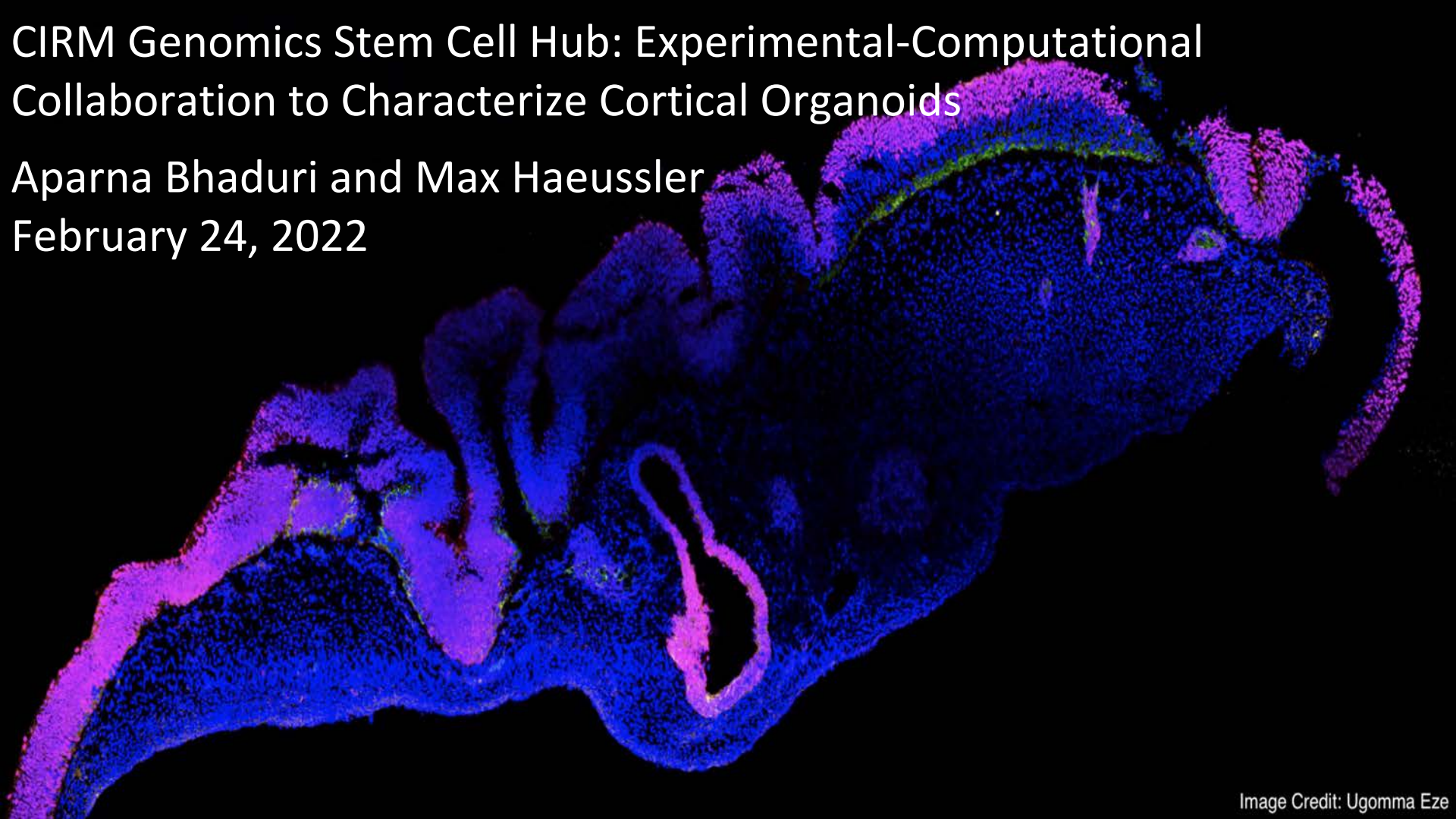
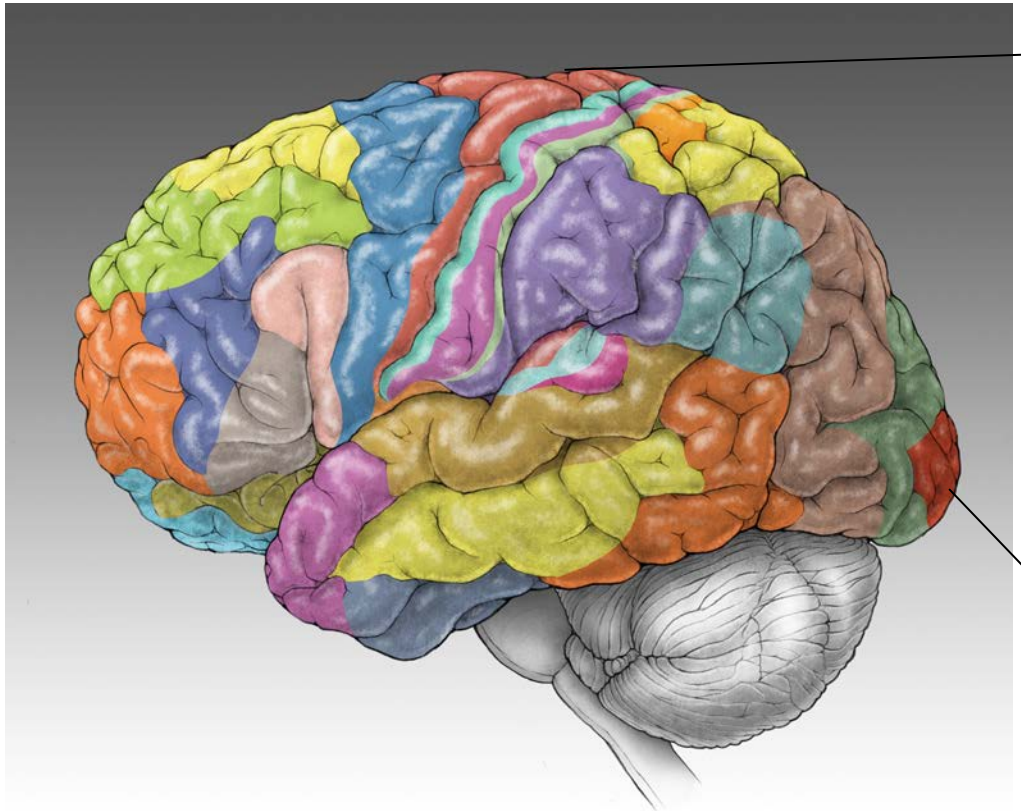
CIRM Genomics Stem Cell Hub: Experimental-Computational Collaboration to Characterize Cortical Organoids

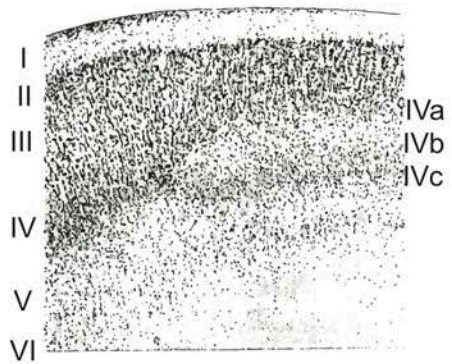
Aparna Bhaduri and Max Haeussler

February 24, 2022



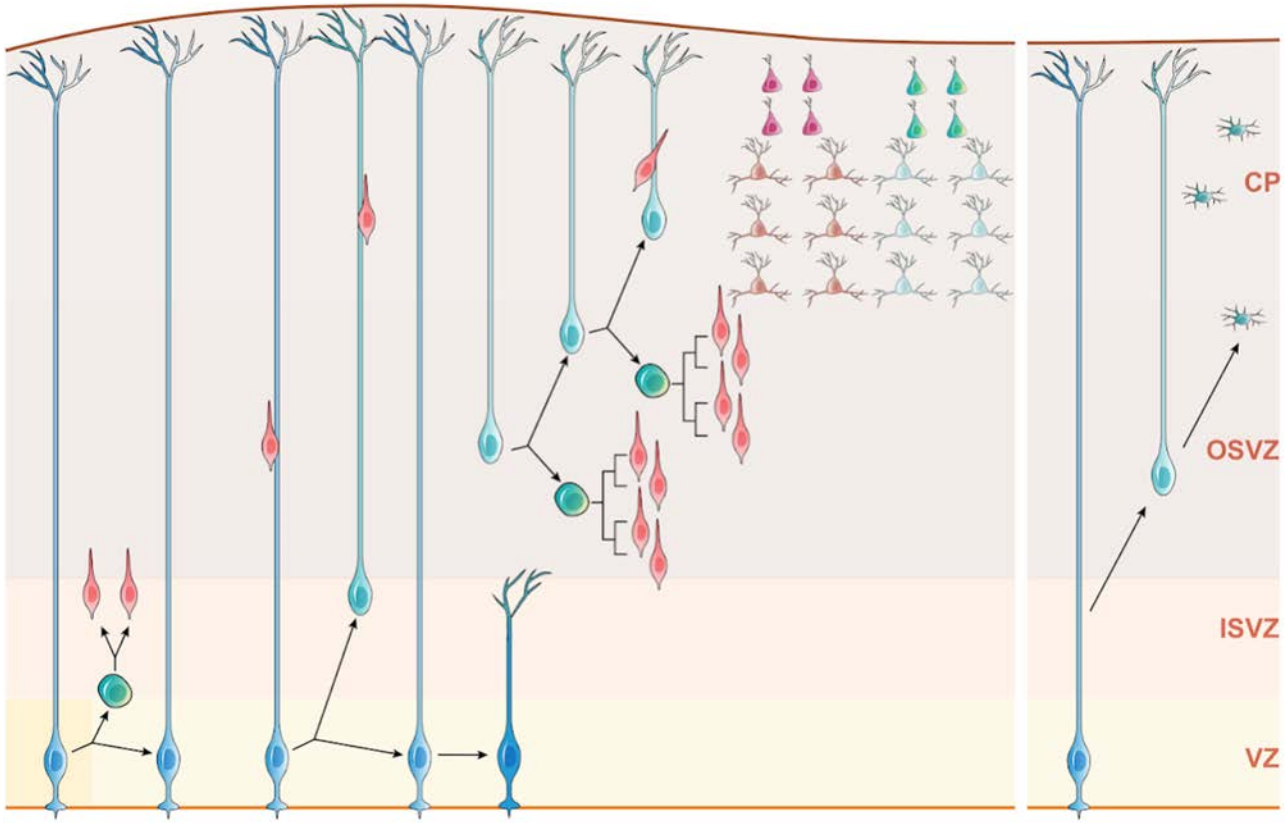
The Human Brain





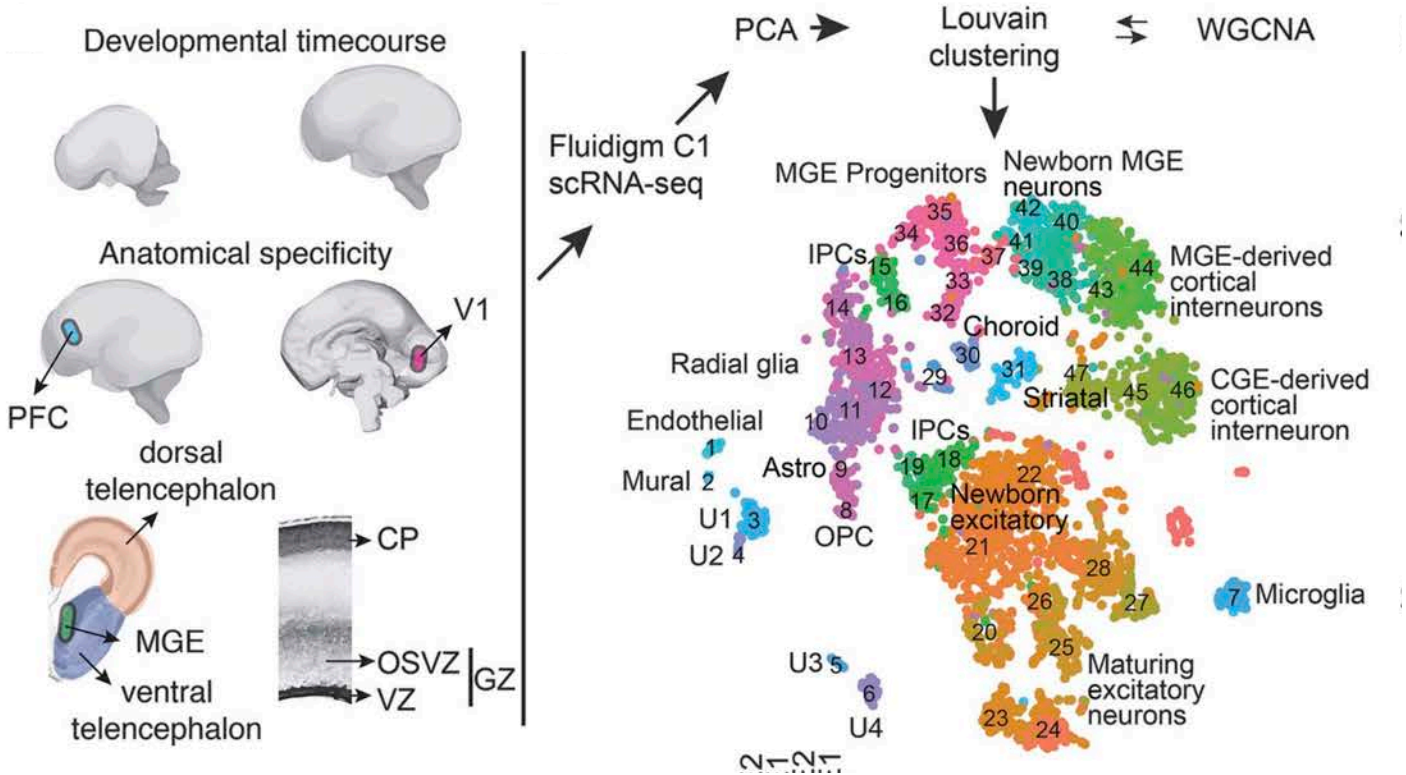
Cadwell*, Bhaduri*, et al . *Neuron,* 2019

Overview of Cortical Development



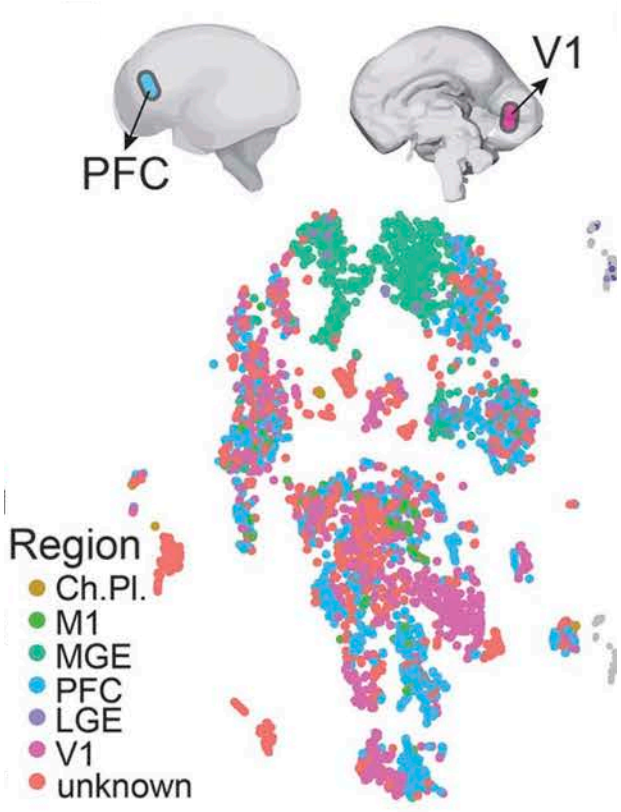
Miller*, Bhaduri*, et al . *Curr Opin Neurobiology,* 2019

Landscape of Cell Diversity



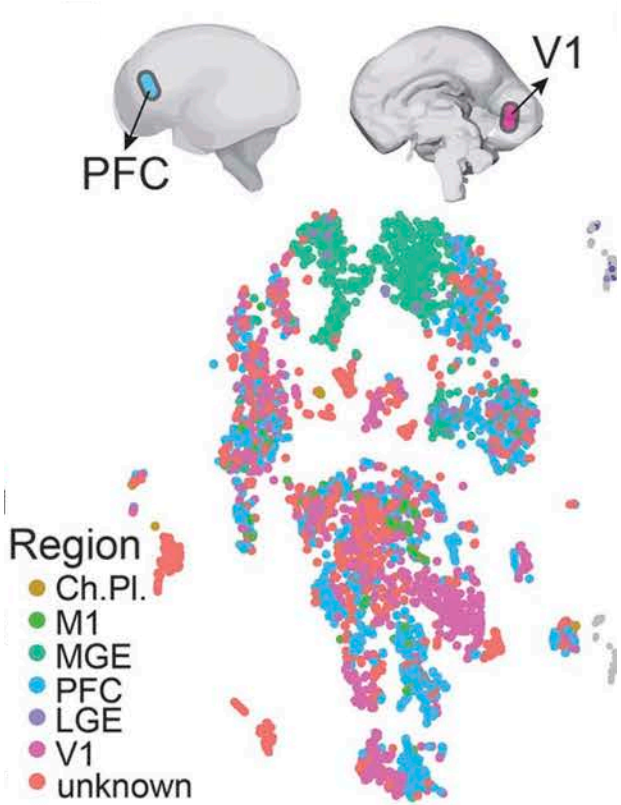
Nowakowski*, Bhaduri* et al. *Science.* 2017

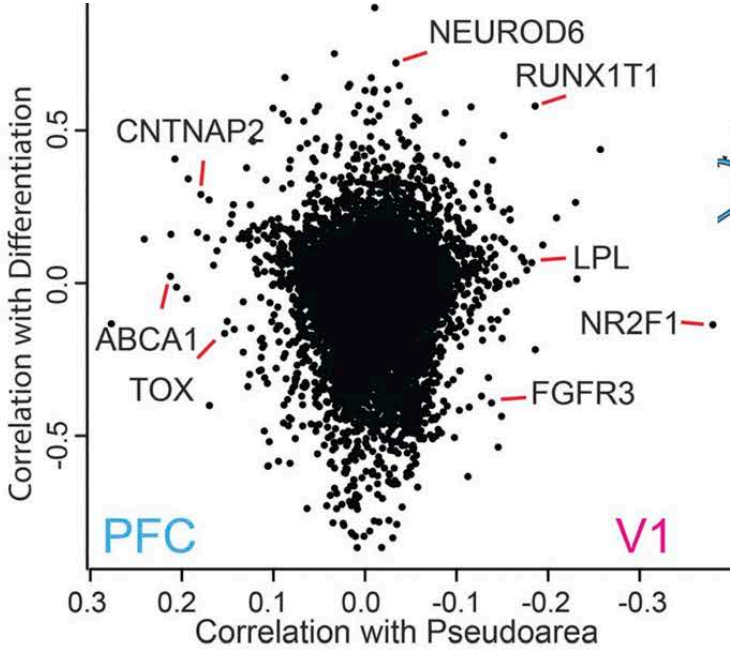
Area – Specific Cell Types

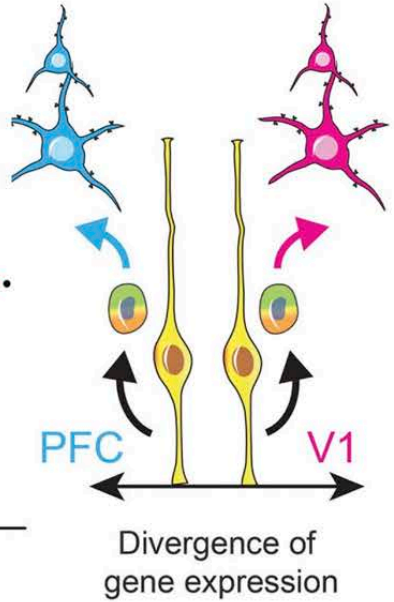


Nowakowski*, Bhaduri* et al. *Science.* 2017

Area – Specific Cell Types



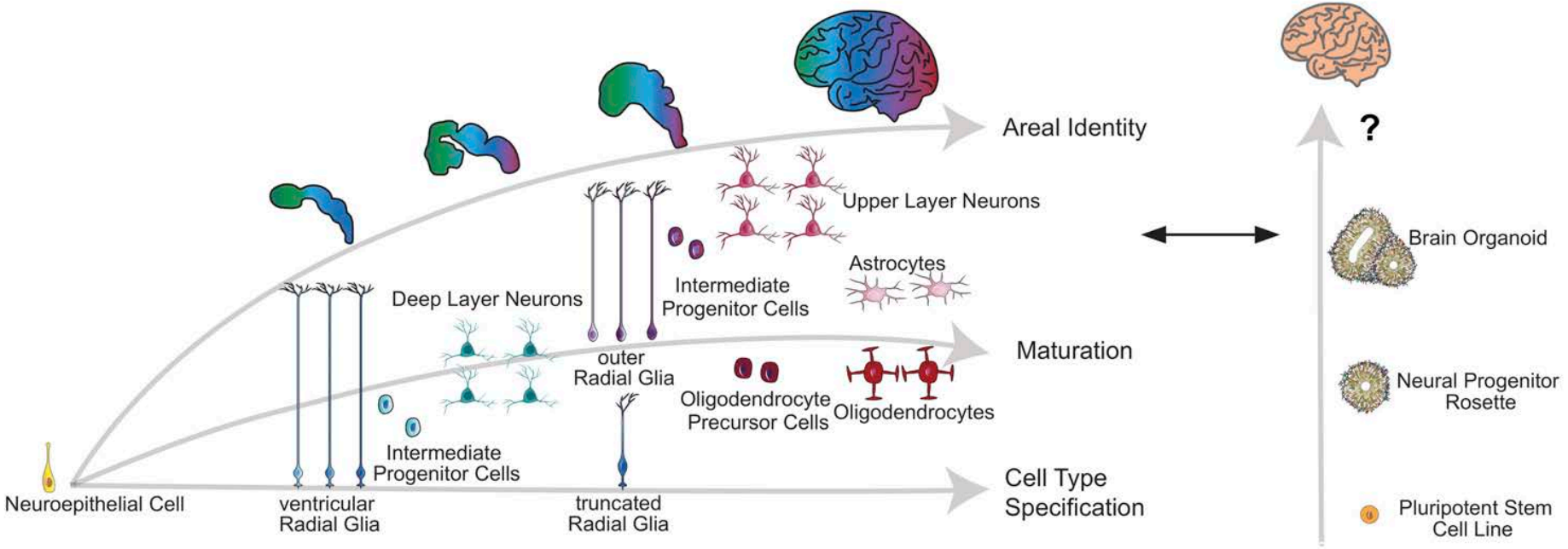




Nowakowski*, Bhaduri* et al. *Science.* 2017

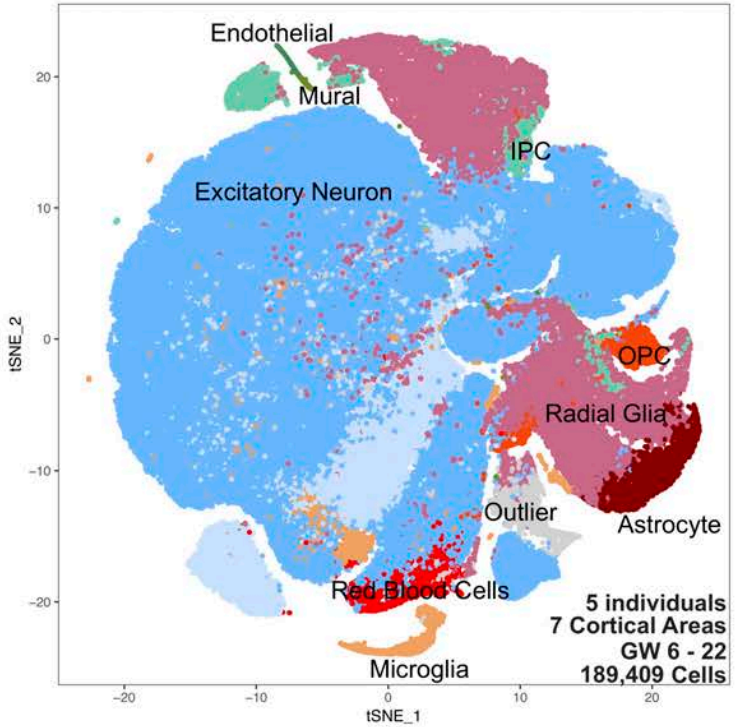
Modeling Cortical Development with Organoids

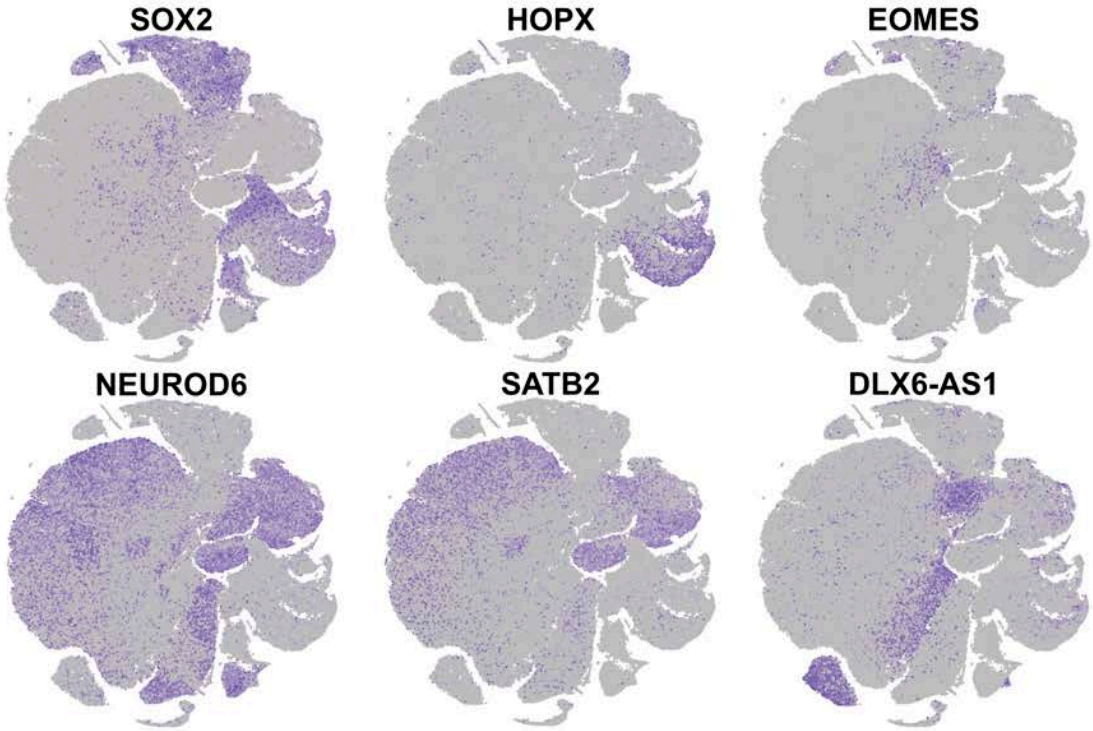
Studying Primary Human Development and Cortical Organoids



Bhaduri*, Andrews*, et al, *Nature* 2020

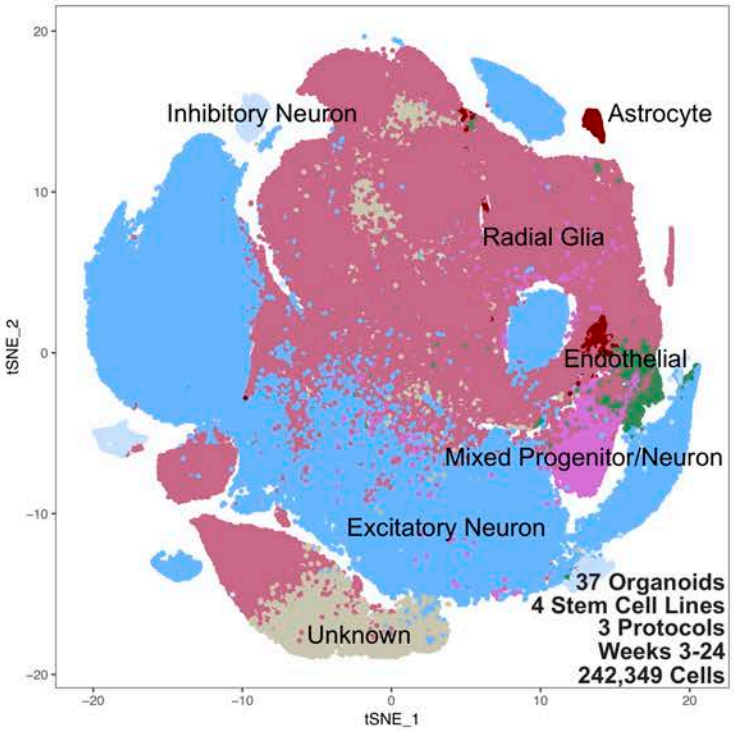
Cortical Development During Peak Neurogenesis

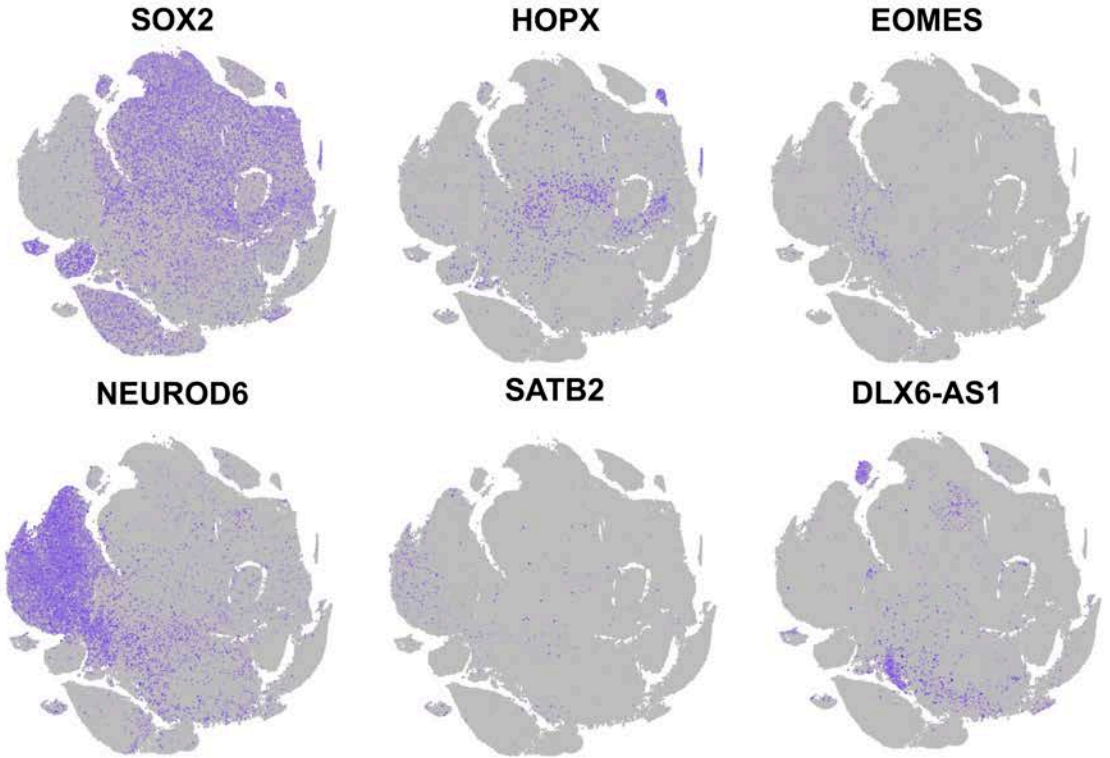




Bhaduri*, Andrews*, et al, *Nature* 2020

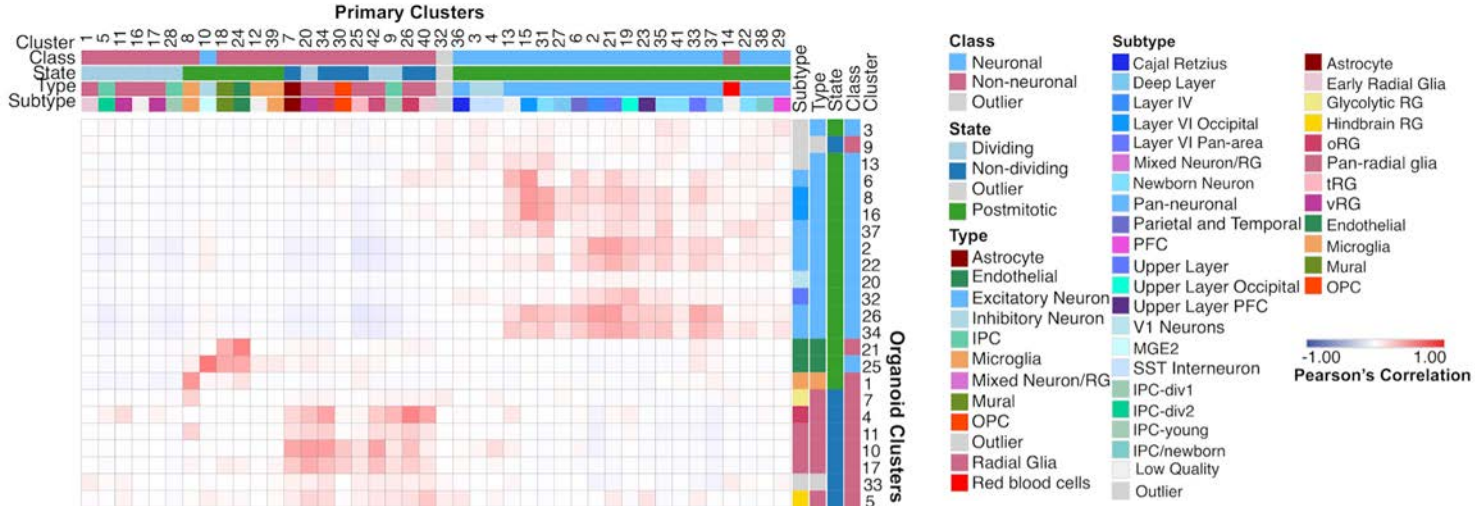
Cortical Development in the Organoid





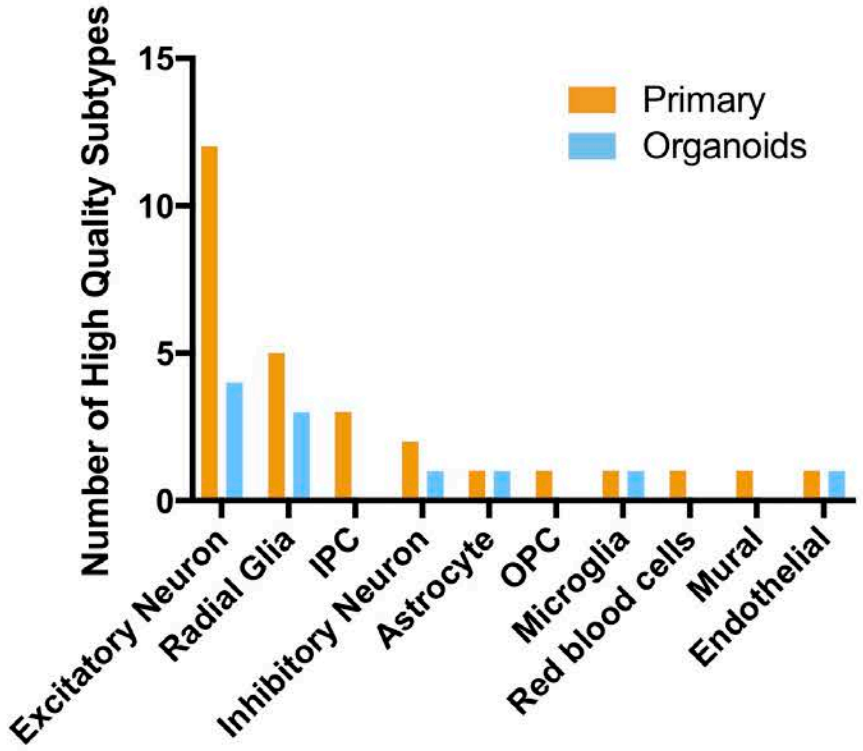
Bhaduri*, Andrews*, et al, *Nature* 2020

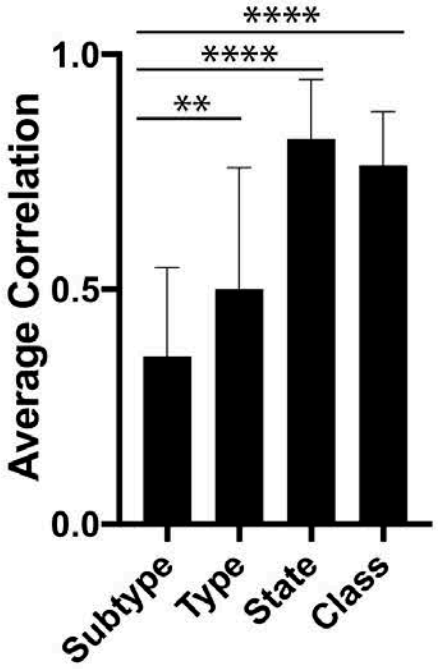
Comparison of Organoid and Primary Clusters



Bhaduri*, Andrews*, et al, *Nature* 2020

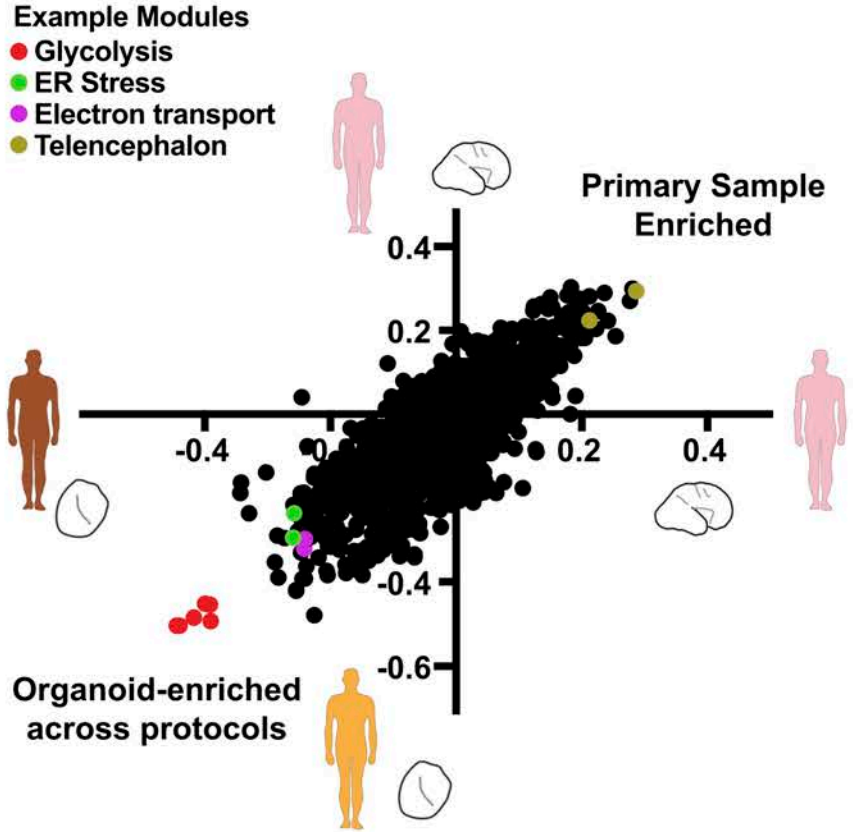
Quantification of Correspondence





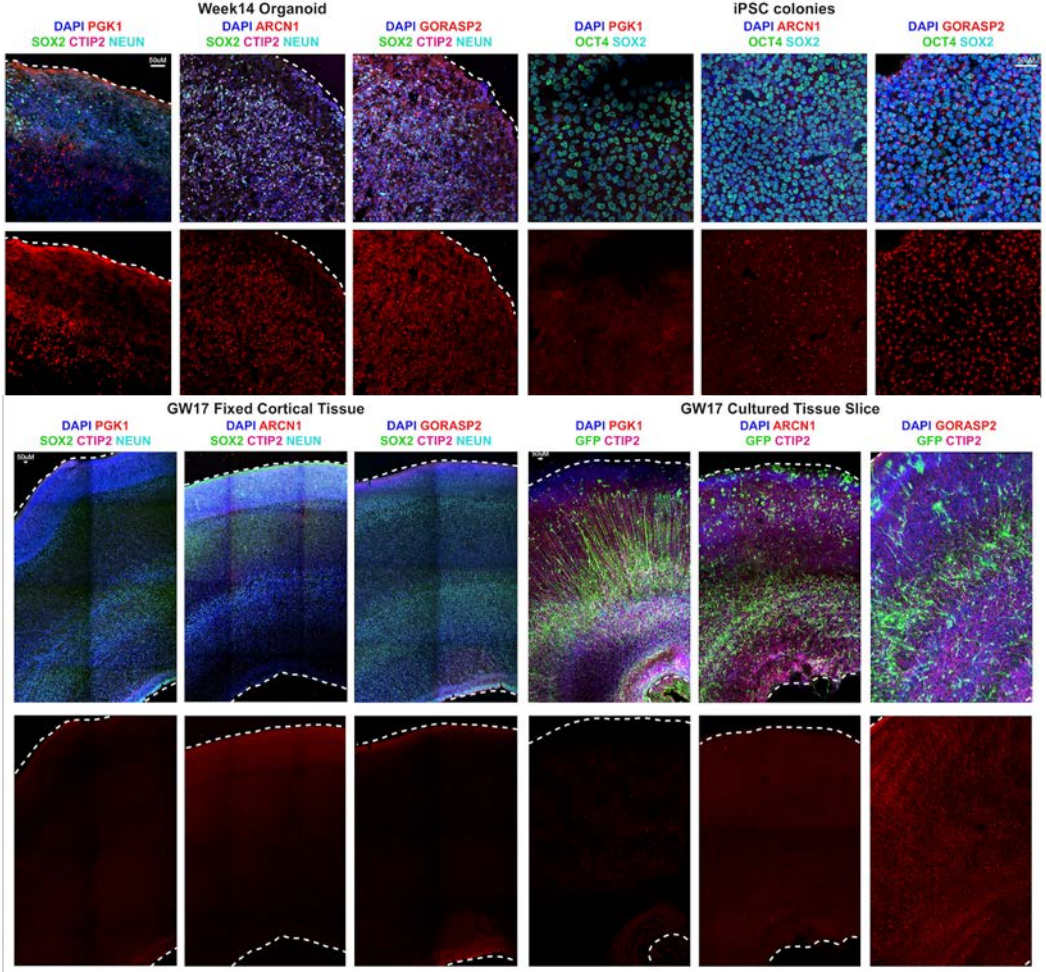
Bhaduri*, Andrews*, et al, *Nature* 2020

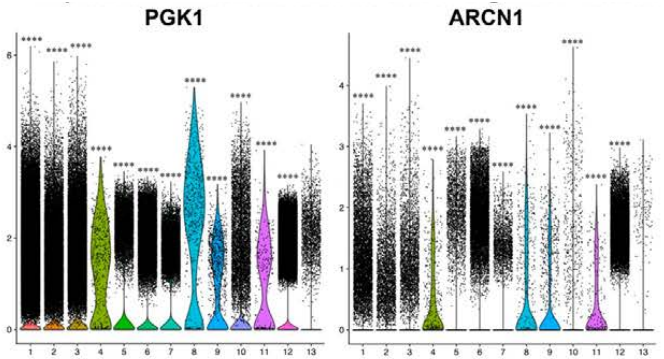
Stress Pathway Expression in Organoids

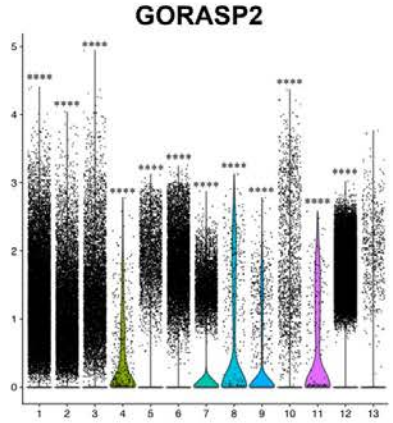


Pollen*, Bhaduri* et al. *Cell*. 2019

Expression of Stress Genes





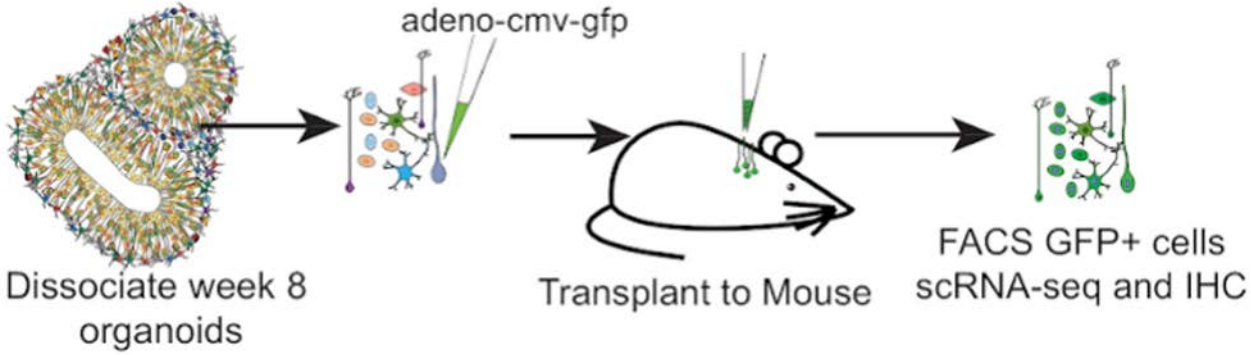


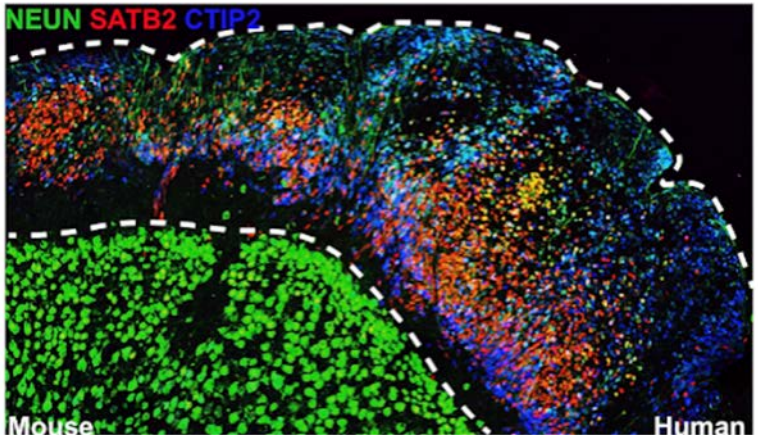
Protocol

1 - Less Directed
2 - Directed
3 - More Directed
4 - Camp et al
5 - Quadrato et al 3 months
6 - Quadrato et al 6 months
7- Giandomenico et al
8 - Sloan et al
9 - Pollen et al
10 - Amiri et al
11 - Marton et al
12 - Velasco et al
13 - Primary GW14

Bhaduri*, Andrews*, et al, *Nature* 2020

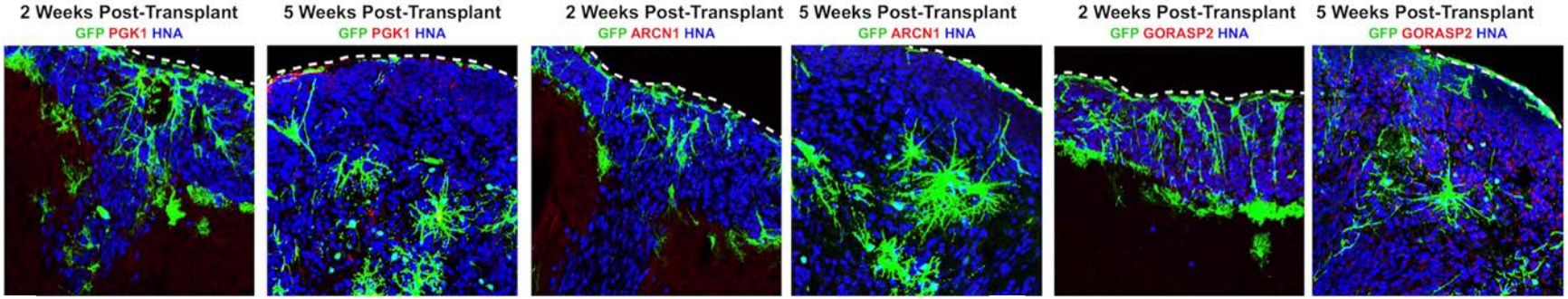
Transplantation of Organoids into Mouse Cortex





Bhaduri*, Andrews*, et al, *Nature* 2020

Transplanted Cells Decrease Stress and Improve Subtypes



Bhaduri*, Andrews*, et al, *Nature* 2020

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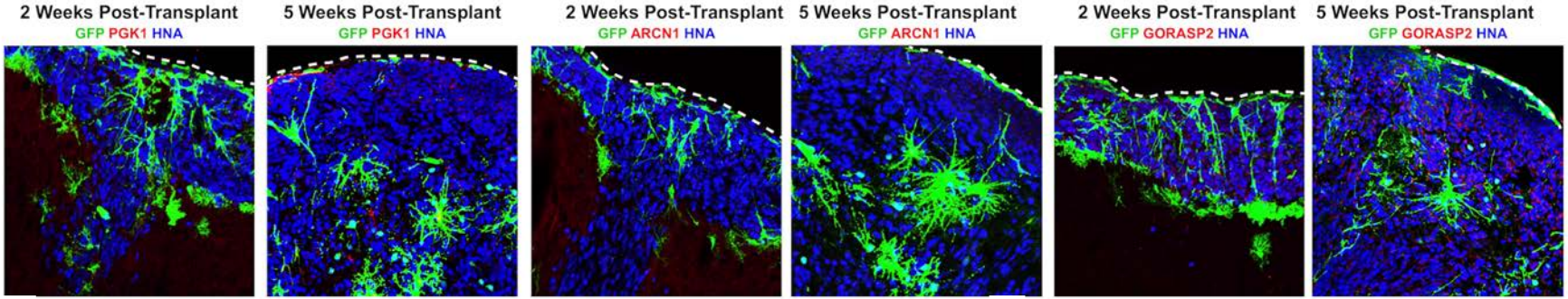

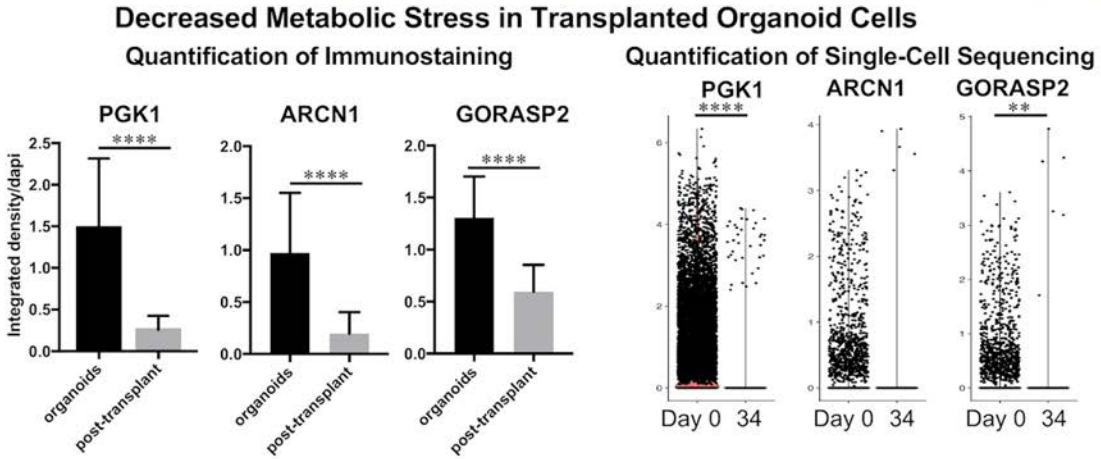

Bhaduri*, Andrews*, et al, *Nature* 2020

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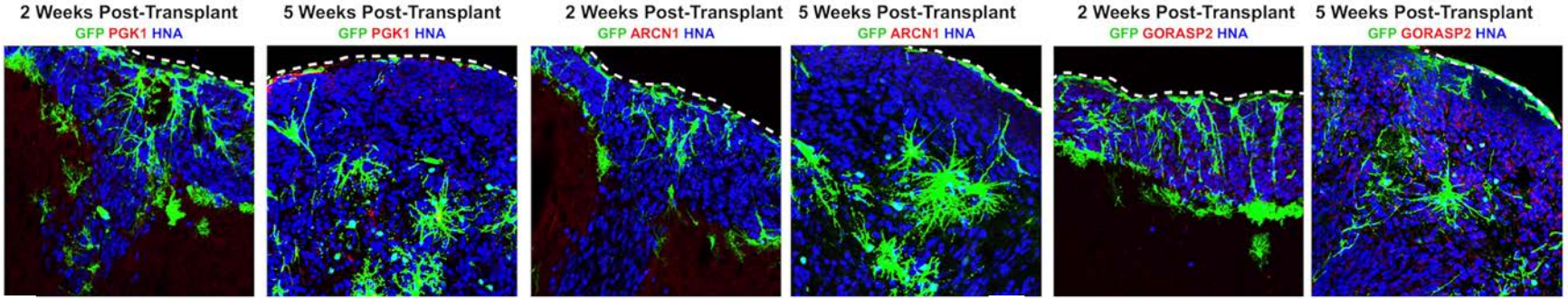
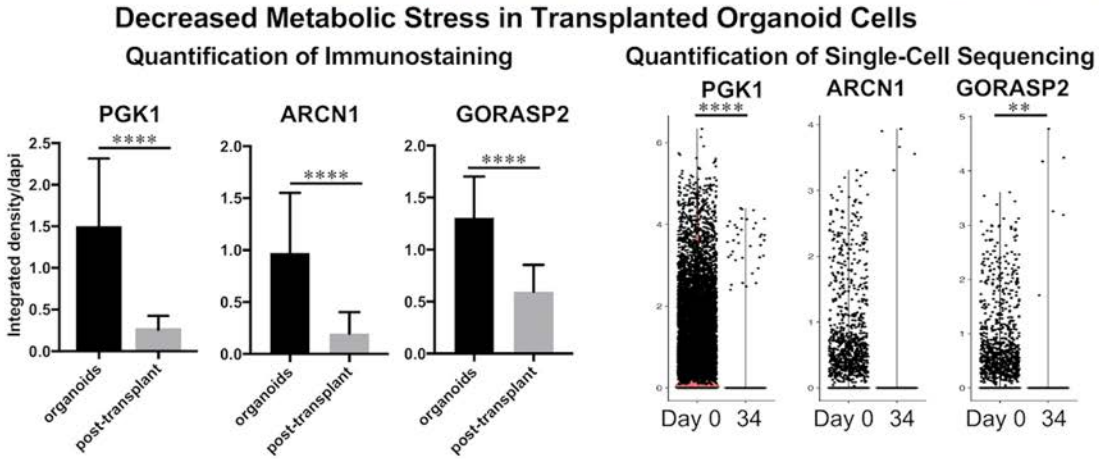
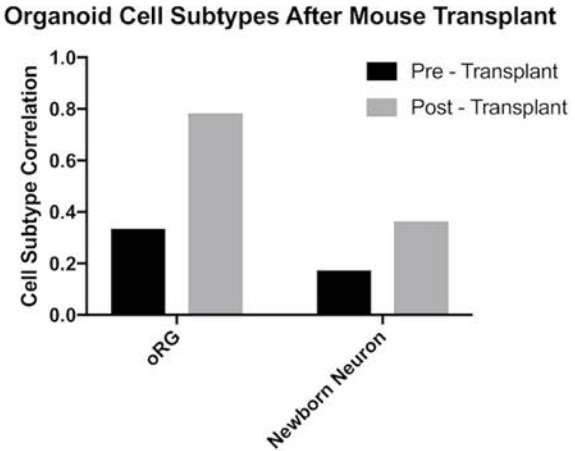
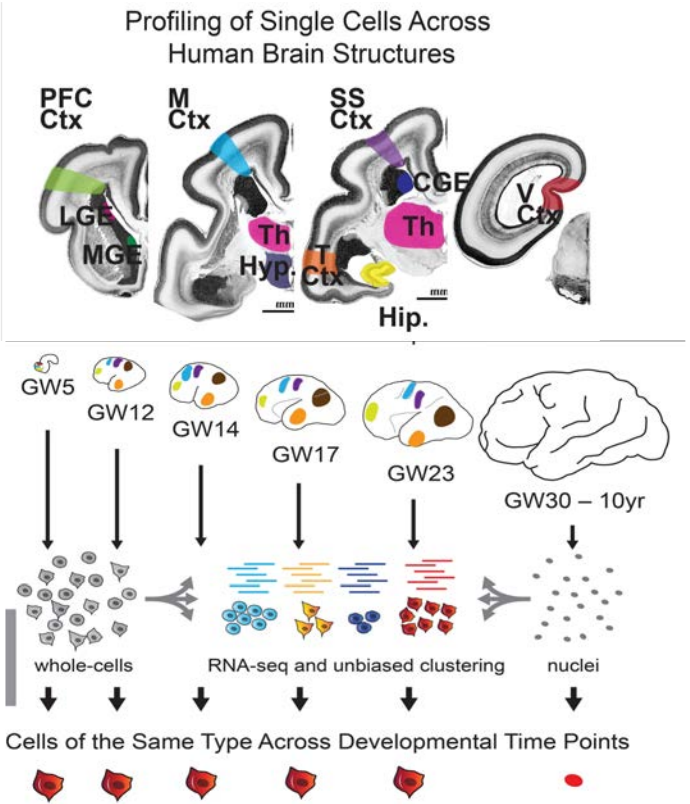




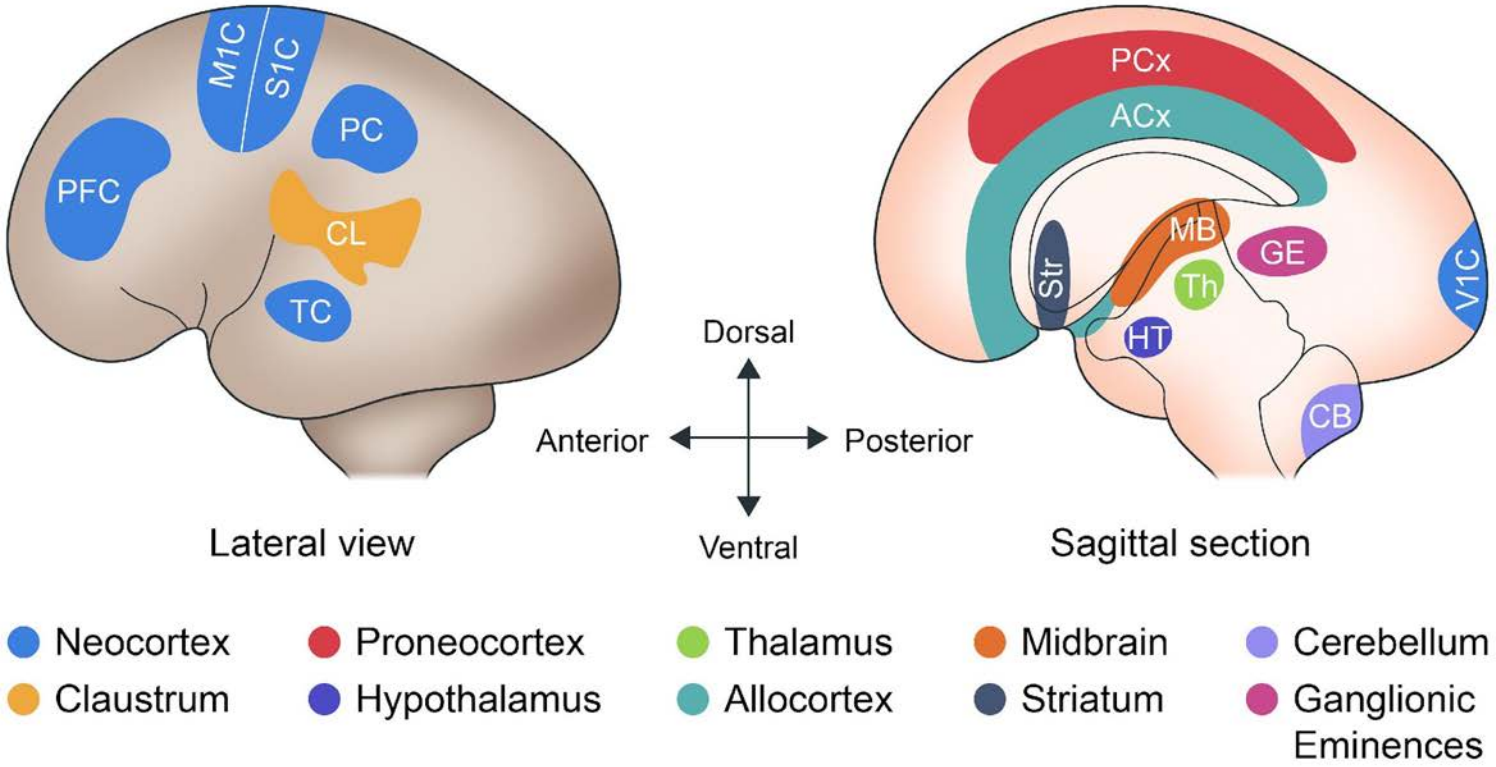


Bhaduri*, Andrews*, et al, *Nature* 2020

Developing Human Brain Cell Atlas

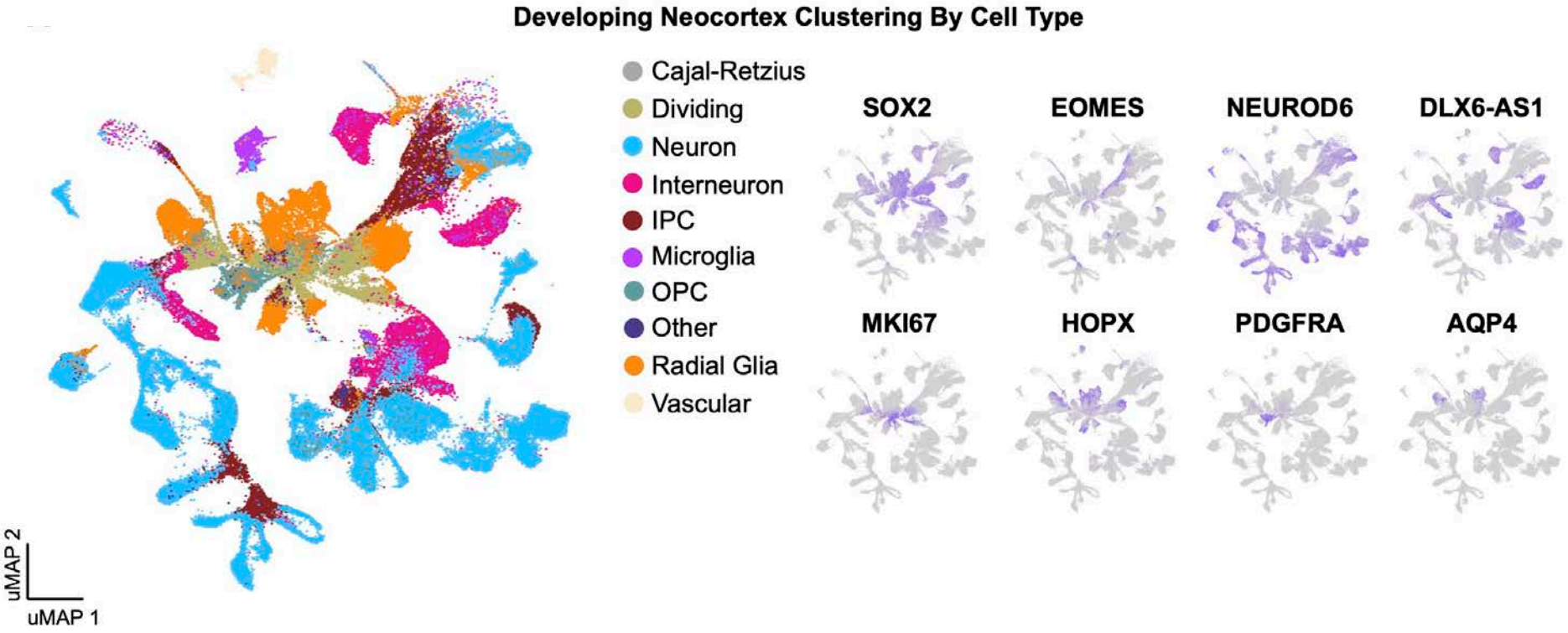


Atlas During Peak Stages of Neurogenesis



Bhaduri*, Sandoval Espinosa* et al. *Nature,* 2021

Neocortex Cell Types

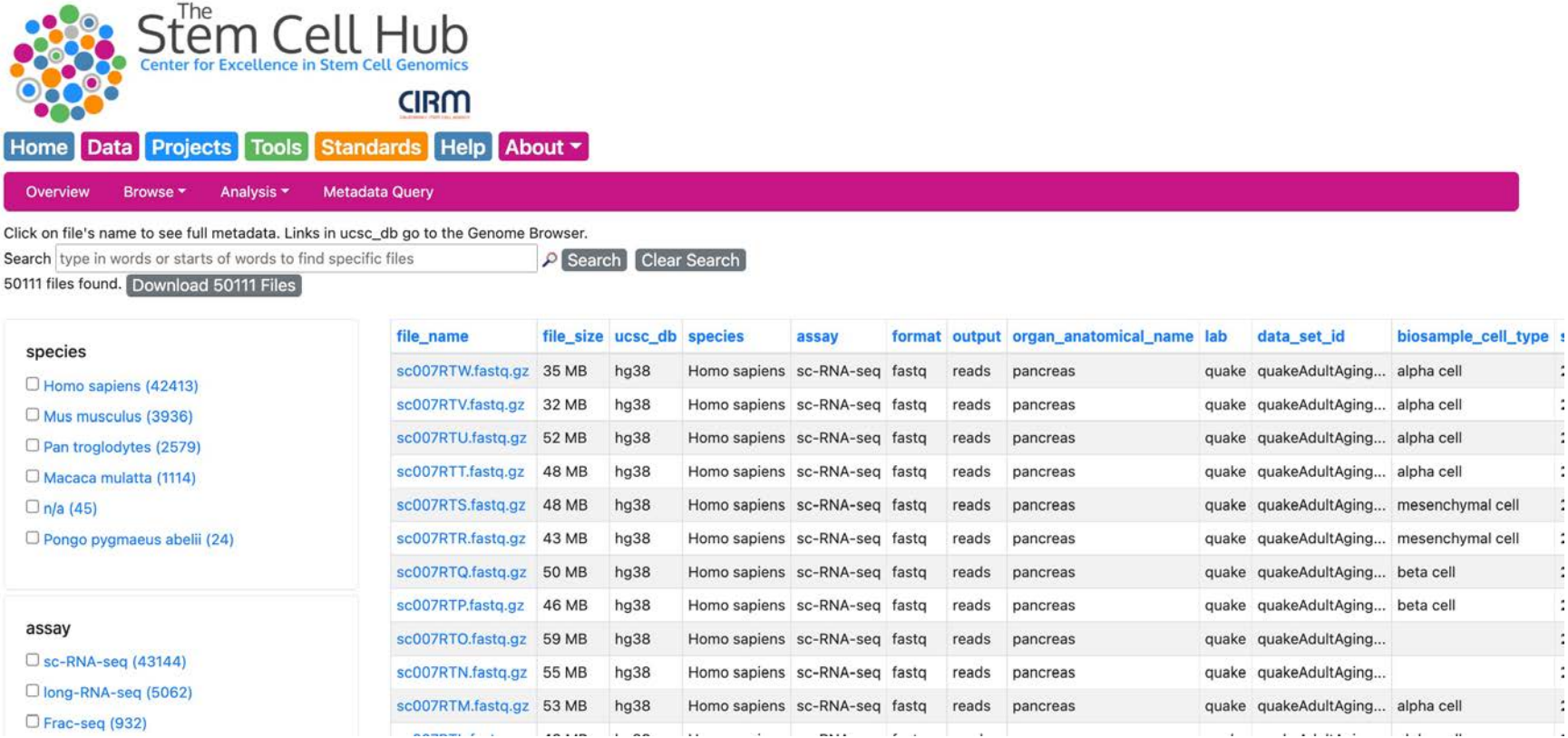


Bhaduri*, Sandoval Espinosa* et al. *Nature,* 2021

The Data Browser

Max Haeussler, UCSC

CIRM-funded data warehouse (cirm.ucsc.edu)



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sc007RTU.fastq.gz	52 MB	hg38	Homo sapiens	sc-RNA-seq	fastq	reads	pancreas	quake	quakeAdultAging...	alpha cell
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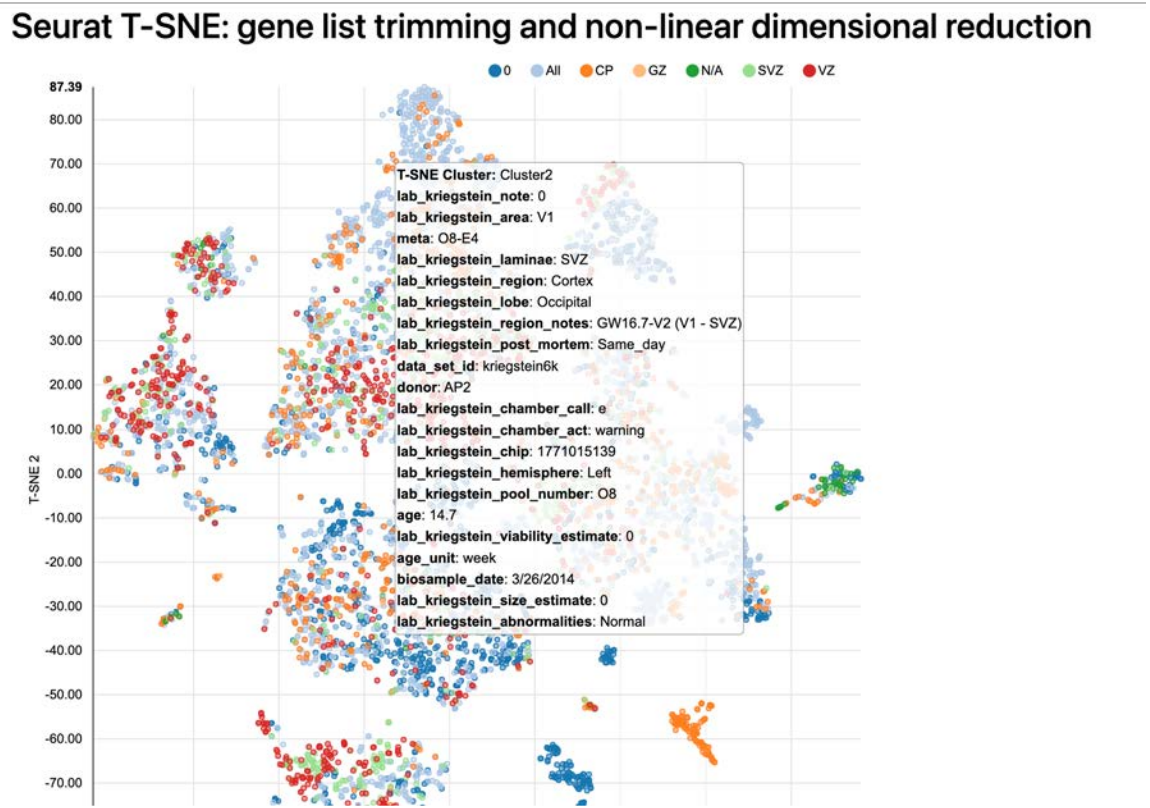
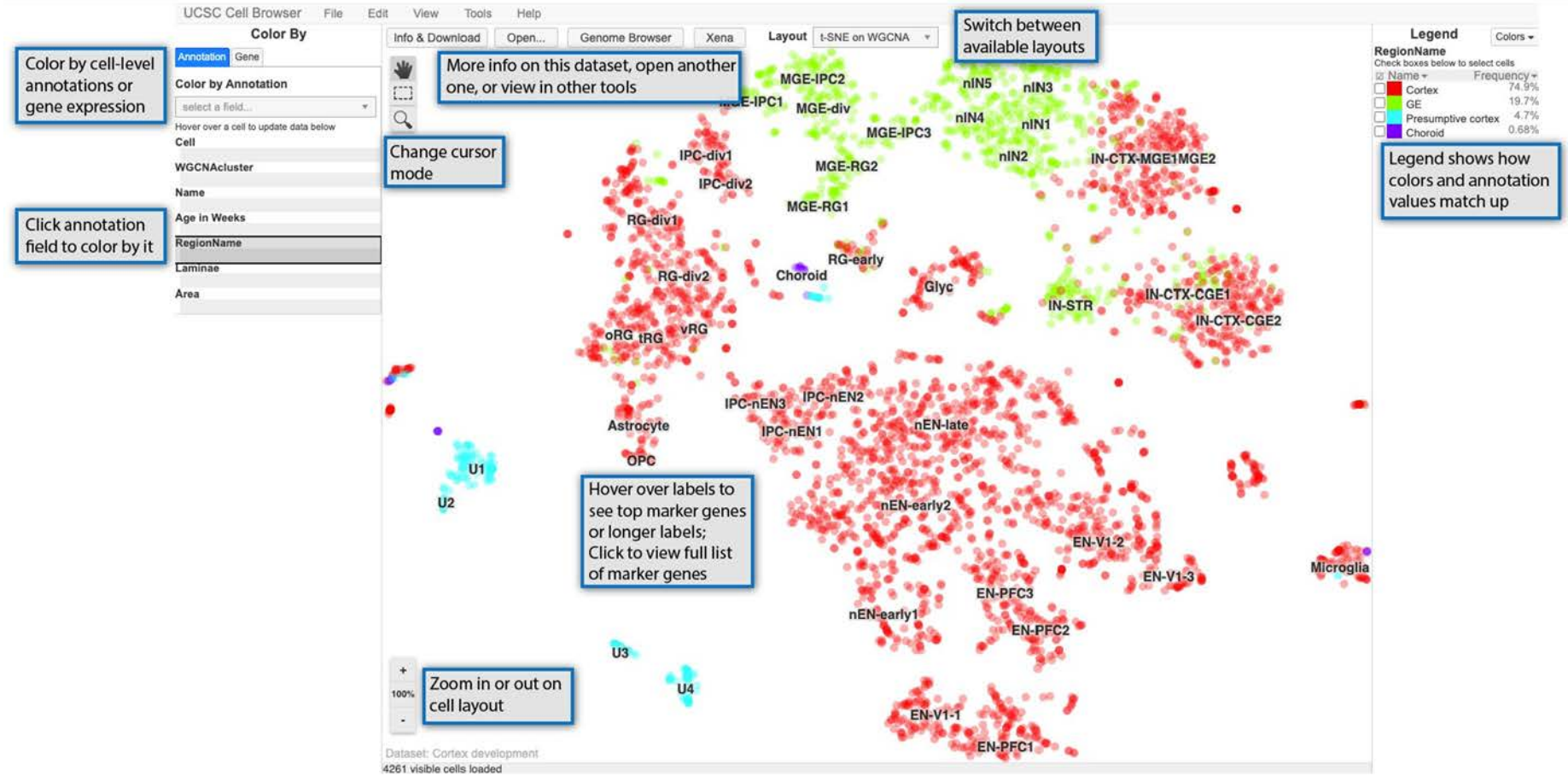
Initial data browser on UCSC CIRM Data Warehouse



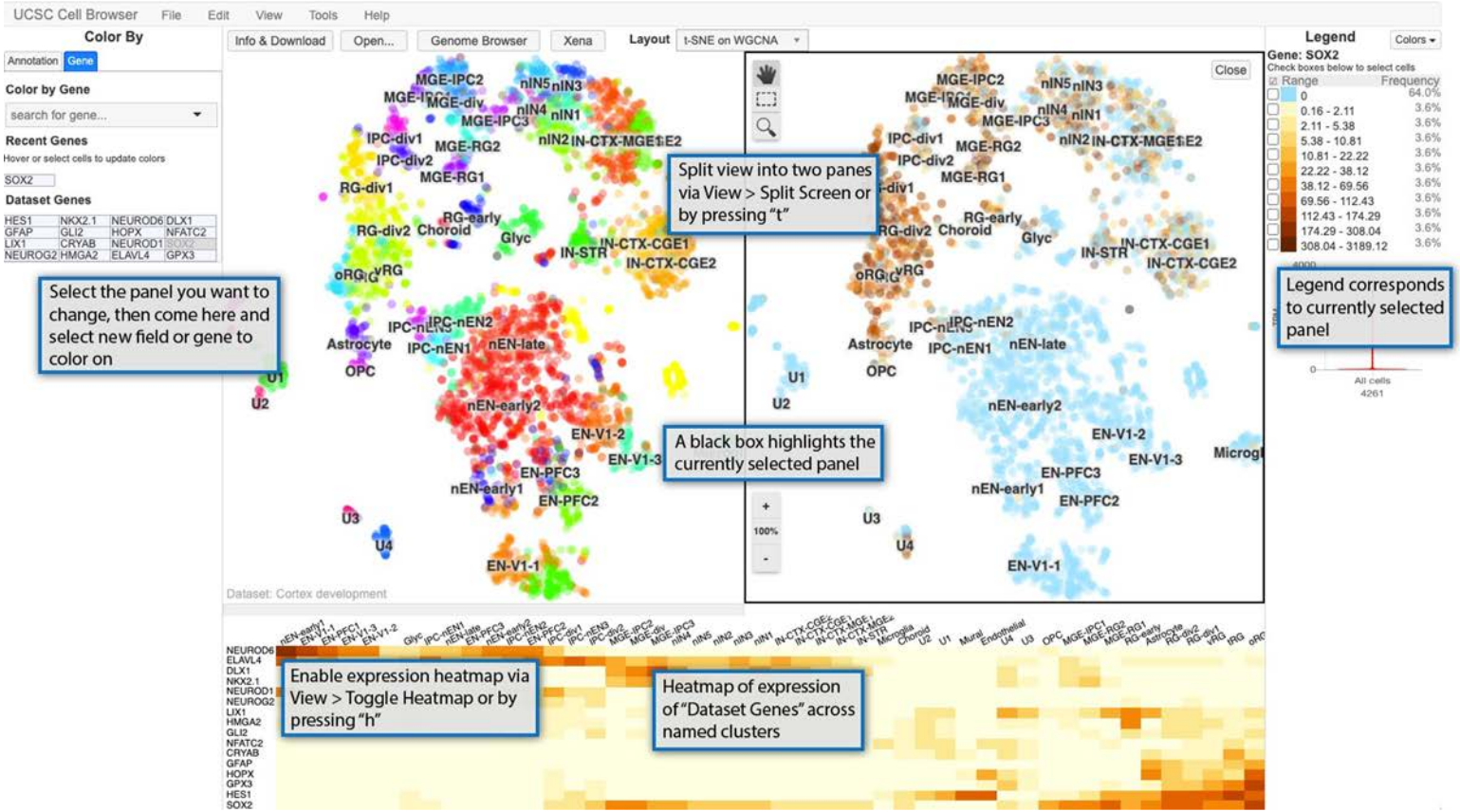
Post-2018: cortex-dev.cells.ucsc.edu



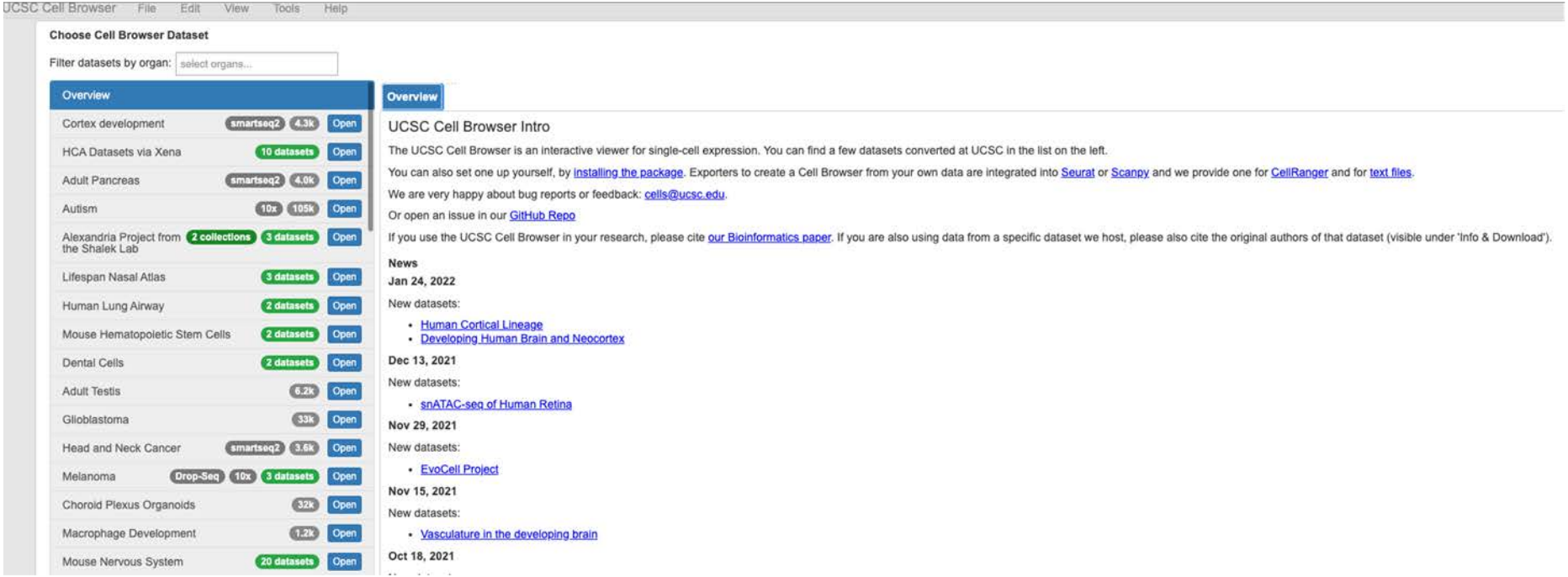
Features of the data browser

- No heavy server needed - cheap to run (end of CIRM data funding)
- Can be used for any single cell dataset - added non-CIRM datasets
- Uses lab-provided results, no analysis - easy to use
- One dataset, one URL - find mentions in Google Scholar
- Documentation at cellbrowser.readthedocs.org

Added features over time



More than 100 datasets



But Kriegstein-lab CIRM brain datasets still almost 25% of site's usage

Relatively popular website

- > 3000 monthly users as of Jan/Feb 2021
- Mentioned in 180 publications

Typical usage in papers

“We extracted genes that have been found to carry common and rare genetic variants detected in the most recent studies and analyzed the expression pattern of these genes in different cells in the developing human cortex using publicly available database (**http://cortex-dev.cells.ucsc.edu/**). “

Yang et al, Dev Dynamics 2019

The BrainSpan Atlas of the Developing Human Brain has an extensive collection of such data including transcriptomic and microarray atlases as well as an in situ hybridization resource (http://www.brainspan.org/). Single-cell transcriptomic resources are also available to query cell-type-specific gene expression in the developing human neocortex (e.g. ***https://cortex-dev.cells.ucsc.edu/***, http://solo.bmap.ucla.edu/shiny/webapp/).

Khakipoor et al, Brain Res 2020

Data from RNA sequencing of isolated single nuclei, performed on surgical specimens of healthy, non-affected lung tissue from 12 lung adenocarcinoma patients, were analysed for AR, TMPRSS2 and ACE2 expression using Eils Lab UCSC Cell browser (https://eils-lung.cells.ucsc.edu)

Leach et al, Nature Comm 2021

…and 178 other publications…

Why did this collaboration work?

- CIRM mandated data sharing
- Kriegstein group extremely successful single-cell lab
  - Cutting-edge domain knowledge available
- Kent group has been doing visualization for 20 years, no single cell at all
  - no competition
- Kent group: long-term staff, Kriegstein: mostly post-docs
  - Long-term IT staff is less cutting-edge than post-docs but expensive
  - 2-3x more expensive than postdocs, but covered by CIRM (-> Schmidt Foundation)
- CIRM had specific funding for data browsing (Stephen Lin encouraged)

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K99/R00 Pathway to Independence
L'Oreal For Women in Science Fellowship

CIRM
CALIFORNIA'S STEM CELL AGENCY

NIH National Institute of Neurological Disorders and Stroke

The BRAIN Initiative

For Women in Science
FONDATION L'ORÉAL
FOR WOMEN IN SCIENCE IN PARTNERSHIP WITH
L'ORÉAL USA
AAAS

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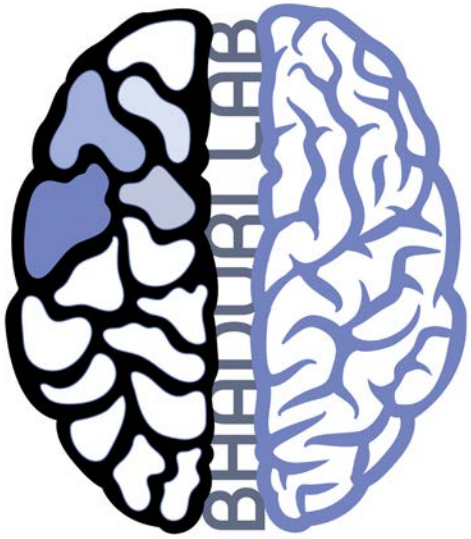

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NIH National Institute of Neurological Disorders and Stroke

Klingenstein Philanthropies

The BRAIN Initiative

UCLA Broad Stem Cell Research Center

UCLA Jonsson Comprehensive Cancer Center

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

The Margaret E. Early Medical Research Trust