Modeling Neurological Disorders in a Dish

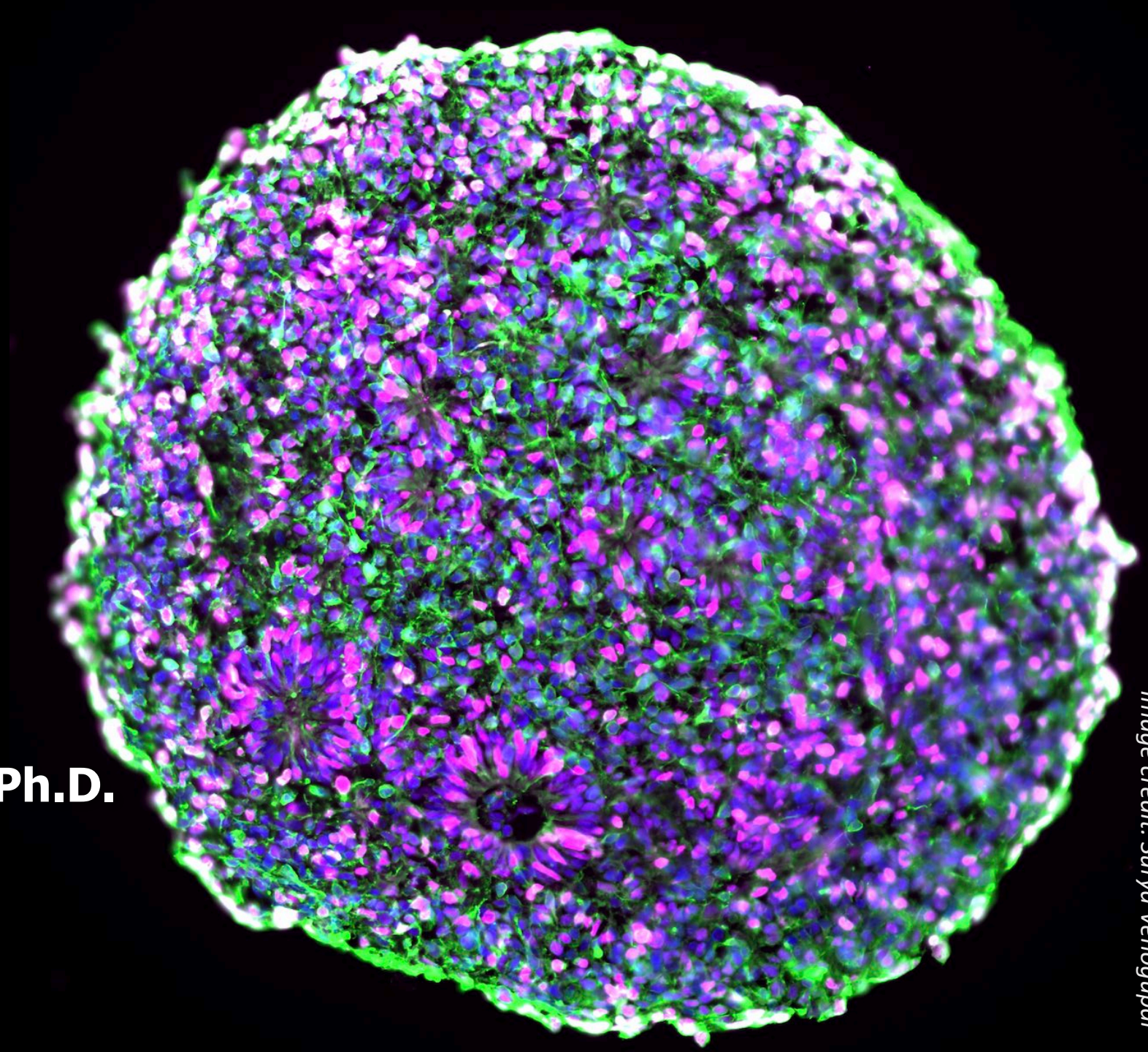

Image credit: Surya Venogupal

Angels Almenar-Queralt, Ph.D.

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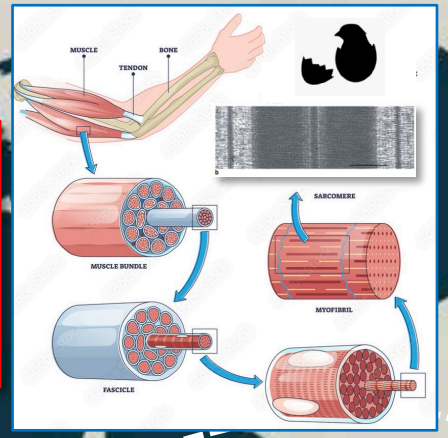
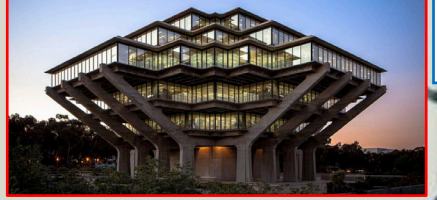
University of California, San Diego
Dept. Pediatrics

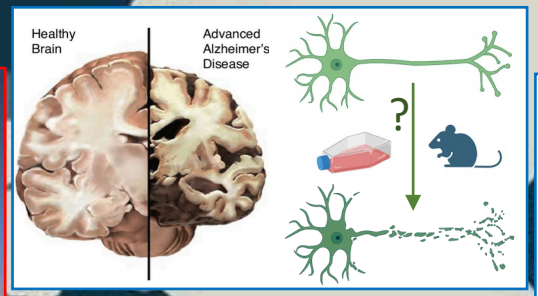
Ph.D. Cell Biology (Dr. Fowler Lab)
The Scripps Research Institute,
La Jolla, CA

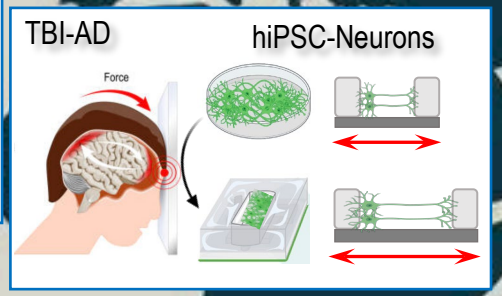


B.S. Biology,
Universitat de Barcelona, Spain

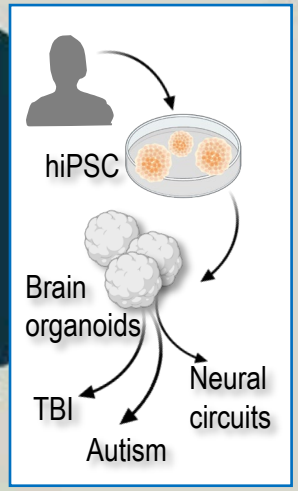
Postdoc (Dr. Goldstein Lab)
University California, San Diego
(UCSD)







Sanford Consortium for Regenerative Medicine
Project Scientist (Dr. Muotri Lab) UCSD



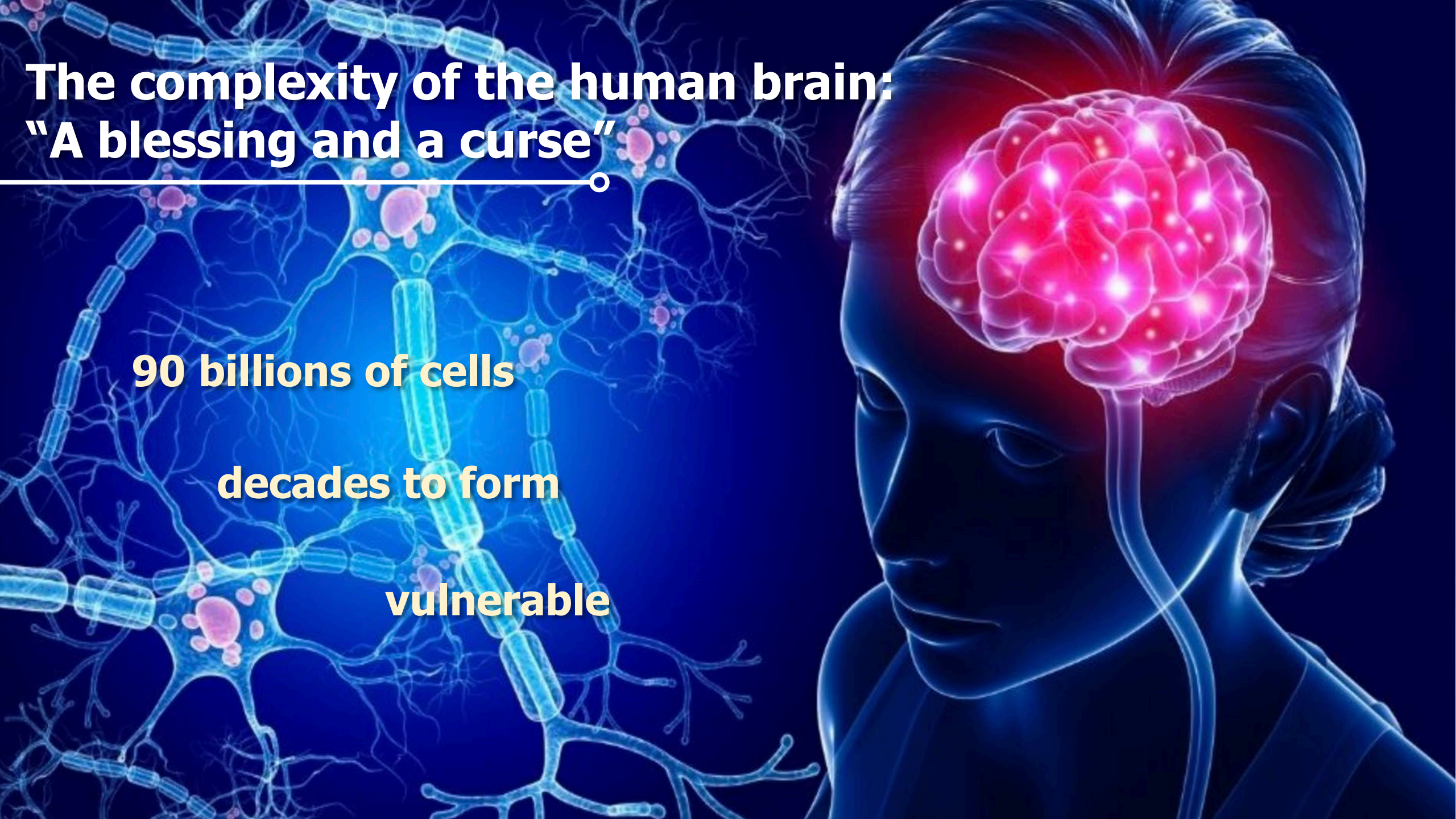
A stem cell neurobiologist dedicated to understand the mechanisms underlying neuronal dysfunction to guide therapy development for incurable neurological disorders.

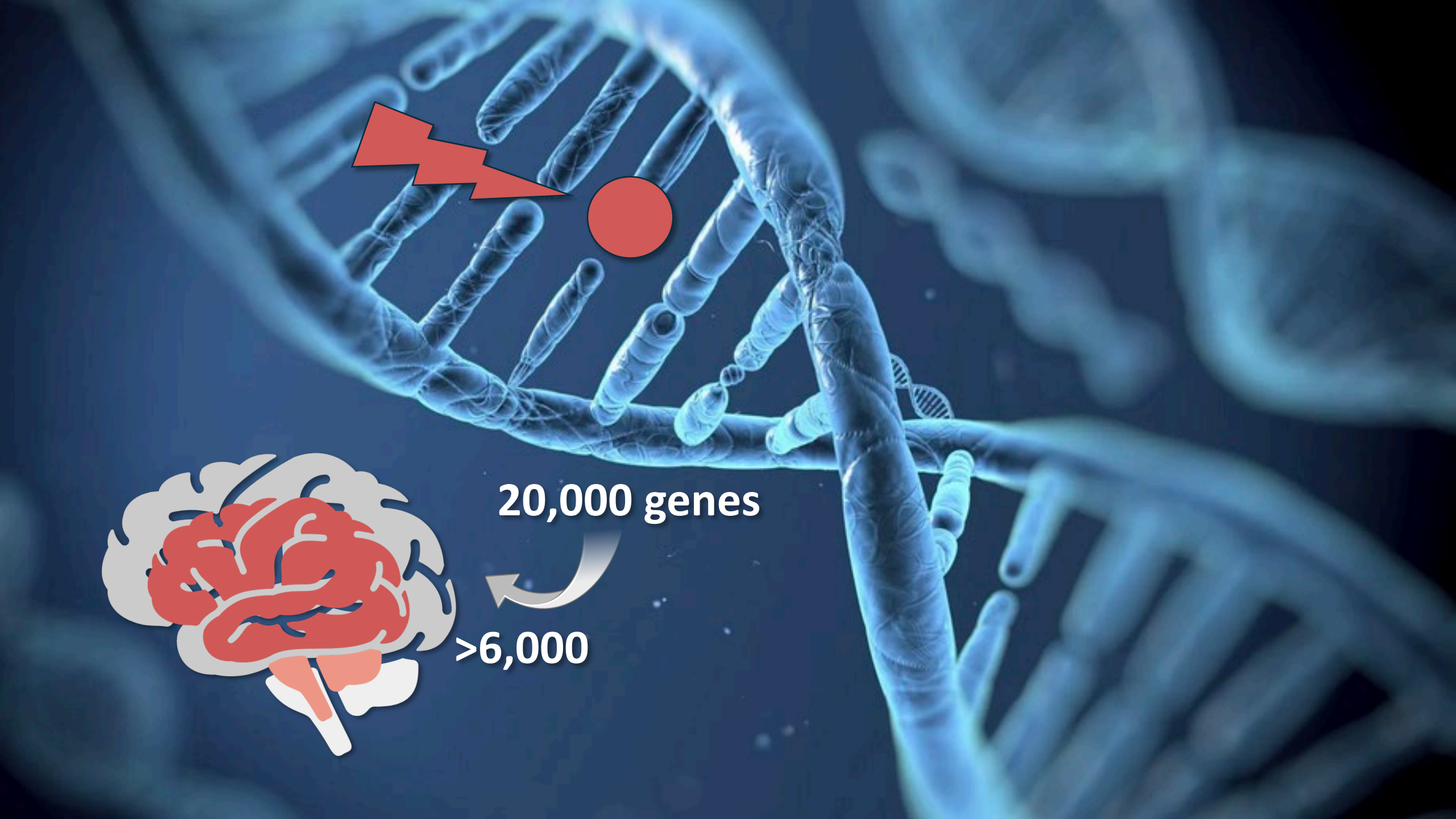
The complexity of the human brain: "A blessing and a curse"

90 billions of cells

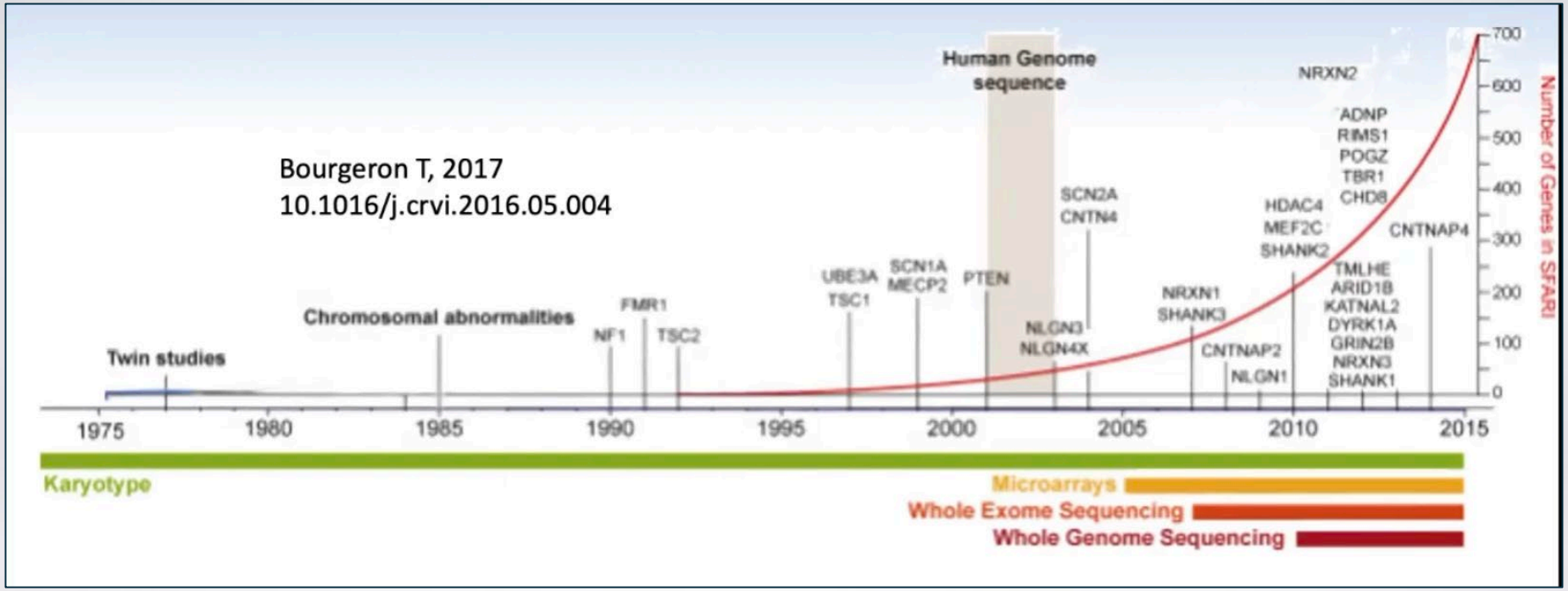
decades to form

vulnerable



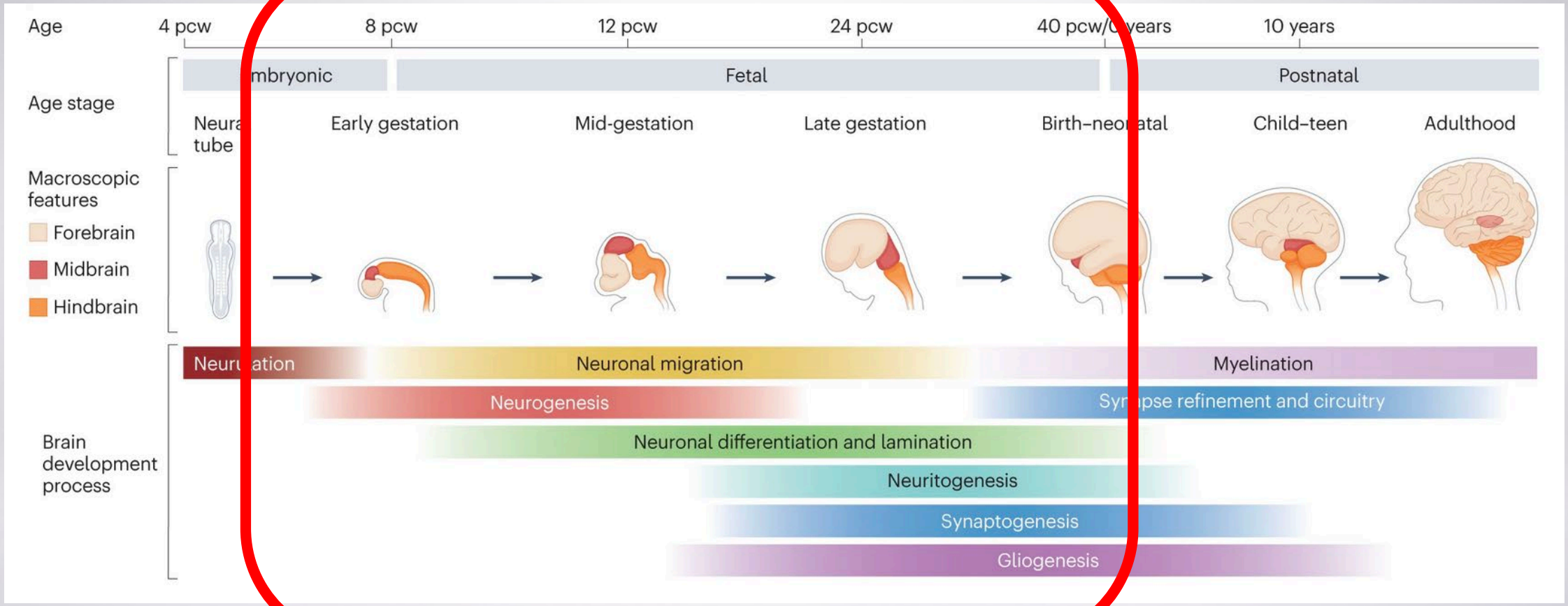

20,000 genes
>6,000

Rapid discovery of genes linked to disease



Linked to autism

When and Where do Autism Genes Act?



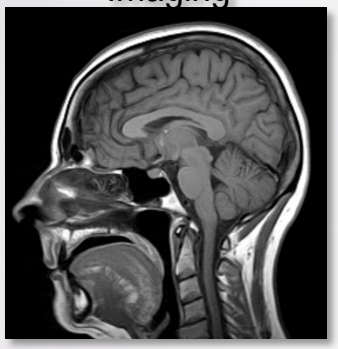
Adapted from Zhou et al, Nature Review Genetics 2023

Developing brain is inaccessible

Postmortem tissue

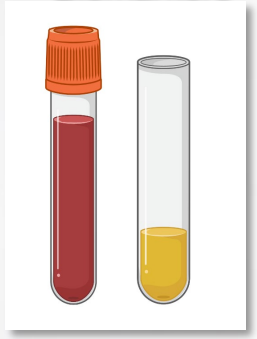
Snapshots

Imaging



Low Resolution

Biomarkers



Indirect

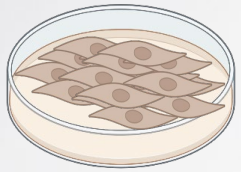
Reverse engineering the human brain

Dr. Yamanaka

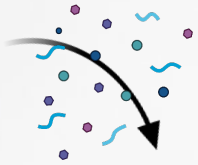
2006 reprogramming

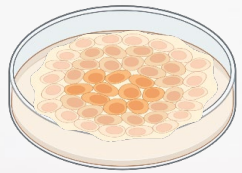
2012 Nobel Prize

skin biopsy

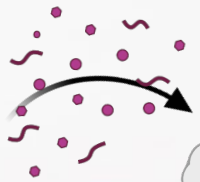


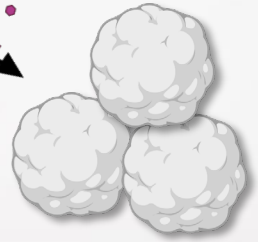
fibroblasts





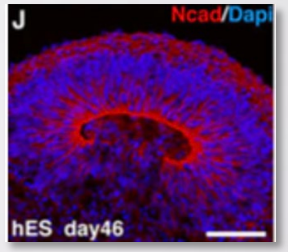
Induced Pluripotent Stem Cells (hiPSC)



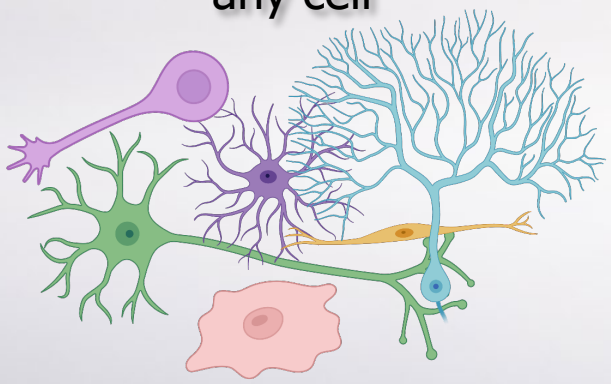


cortical organoids

Dr. Sasai (2008)

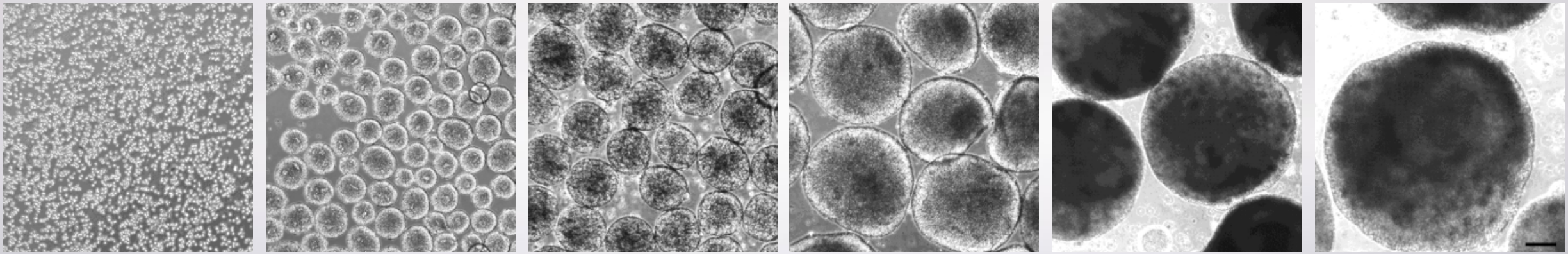


any cell

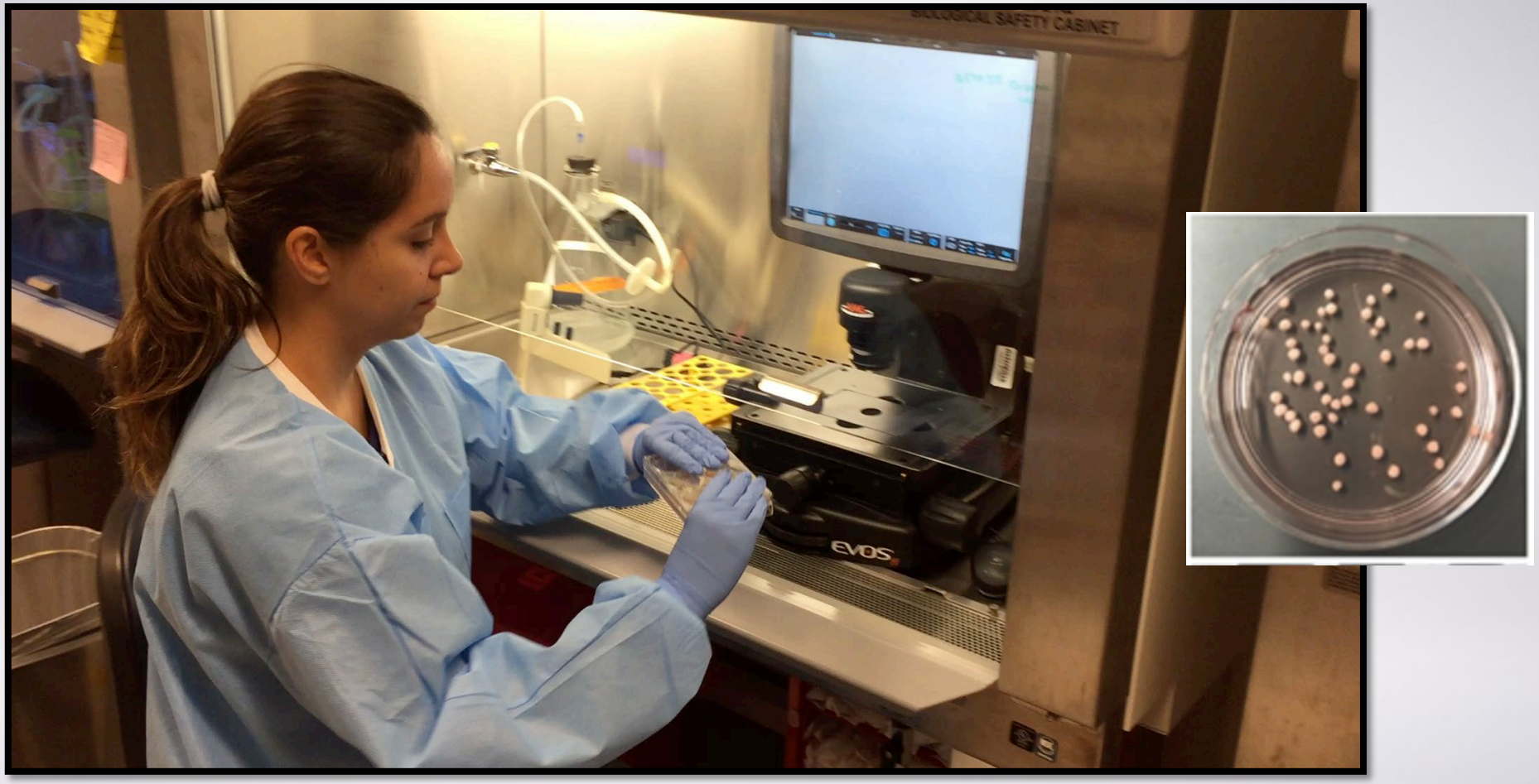


Muotri lab cortical organoid recipe

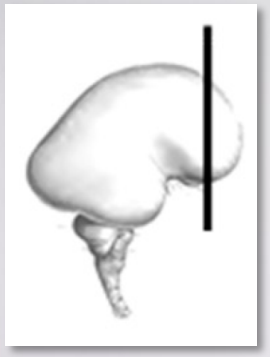
Dissociated iPSC	Neural induction	NPC proliferation		Neural differentiation	Neural maturation
iDEAL Media	Media1	Media2	Media2	Media 3	Media2
2 days	7 days	7 days	7 days	7 days	months

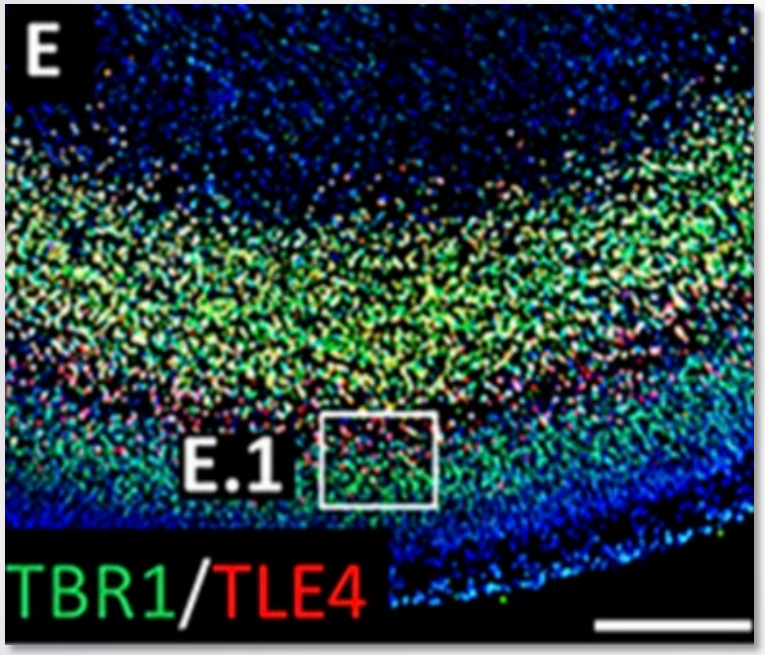


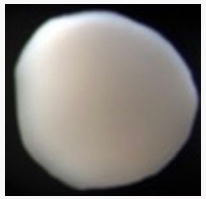
Meet the brain cortical organoids

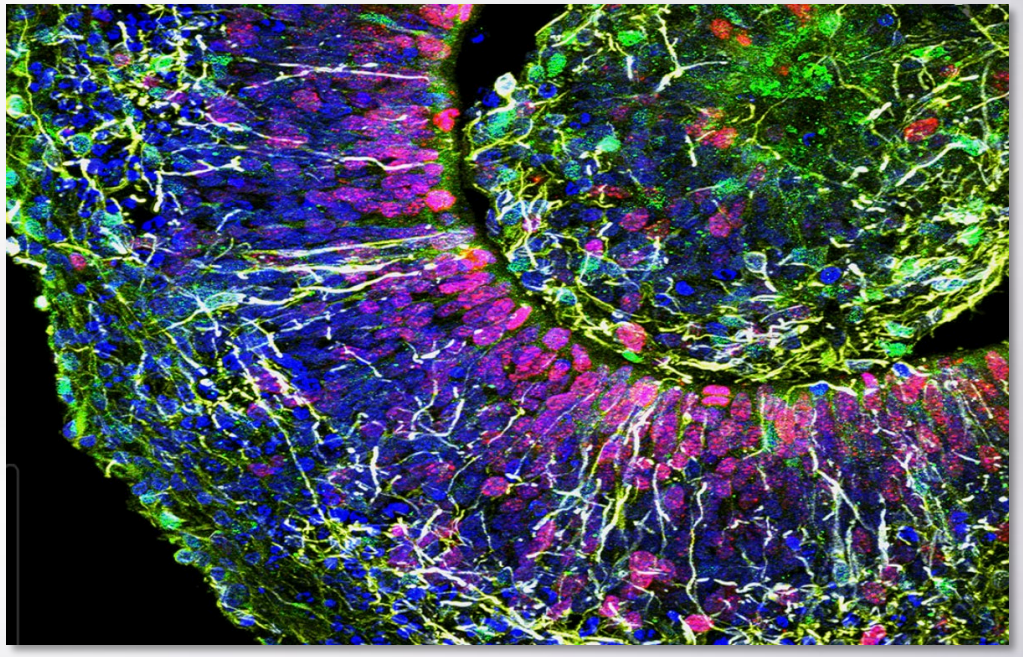


Miniaturizing the human fetal brain cortex









Trujillo 2019

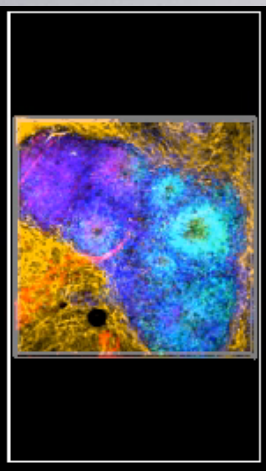
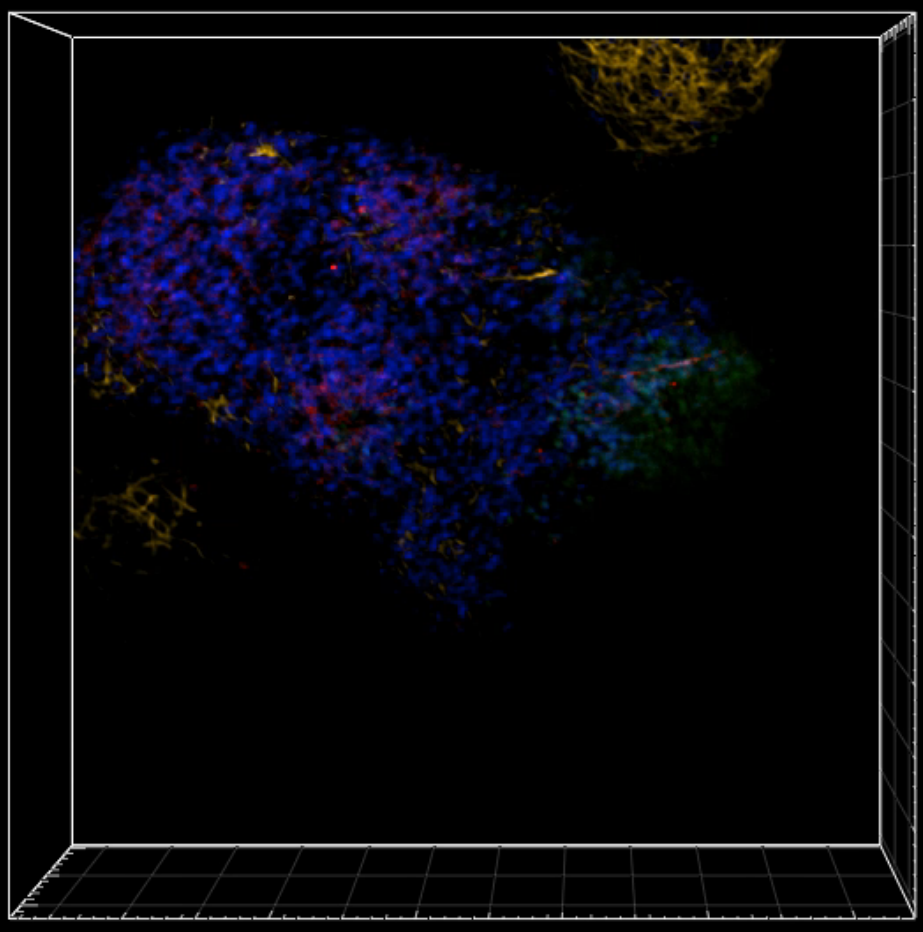


Image credit: Surya Venogupal



Firing Organoids

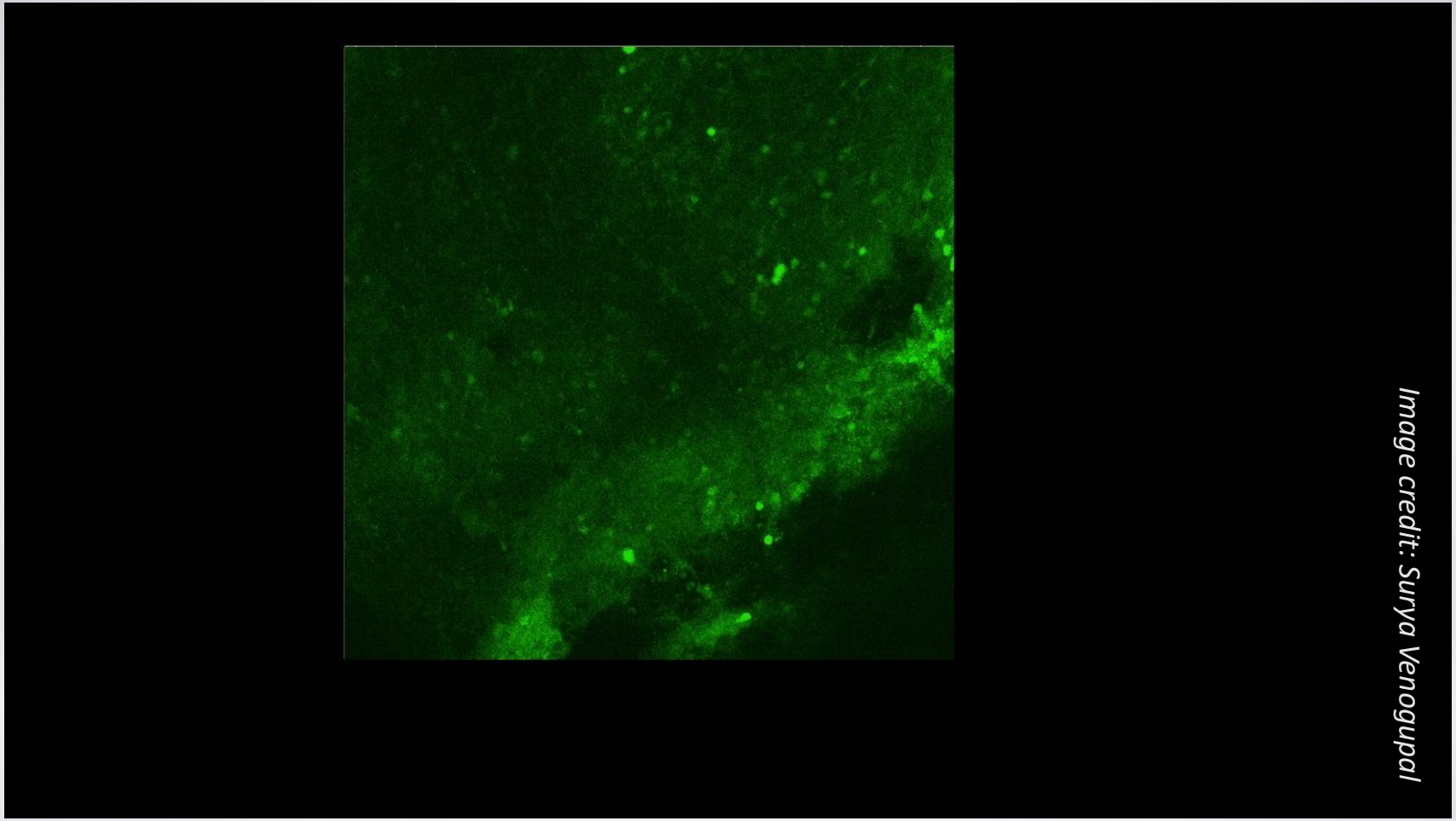
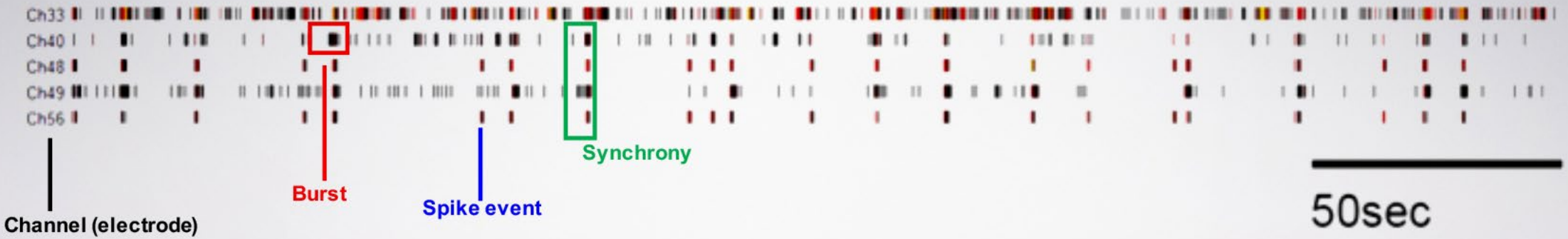
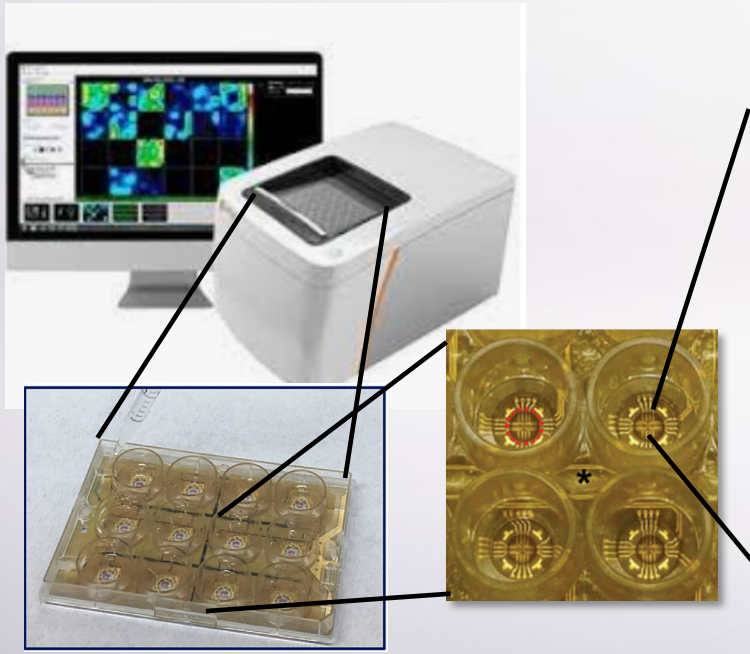


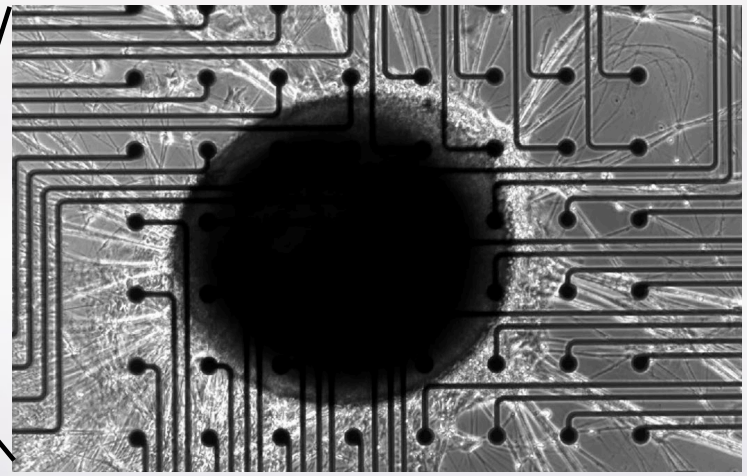
Image credit: Surya Venogupal

Measuring neuronal activity

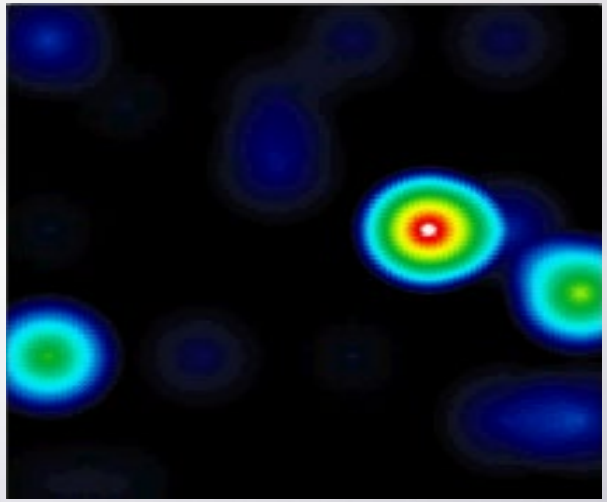
Raster Plot







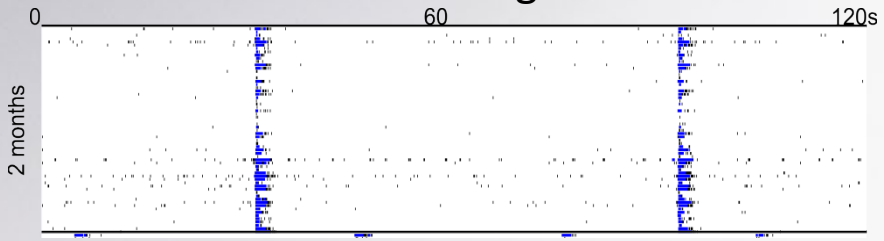
150 um



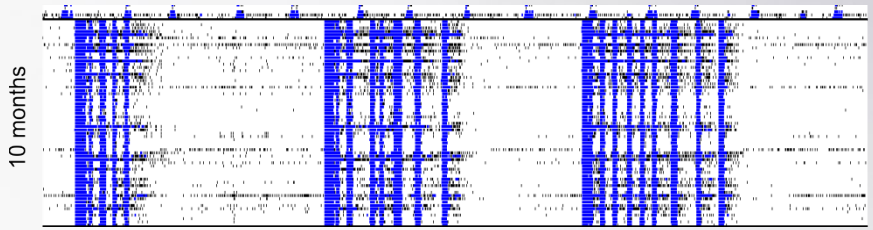
Activity Map

Increased network complexity over time

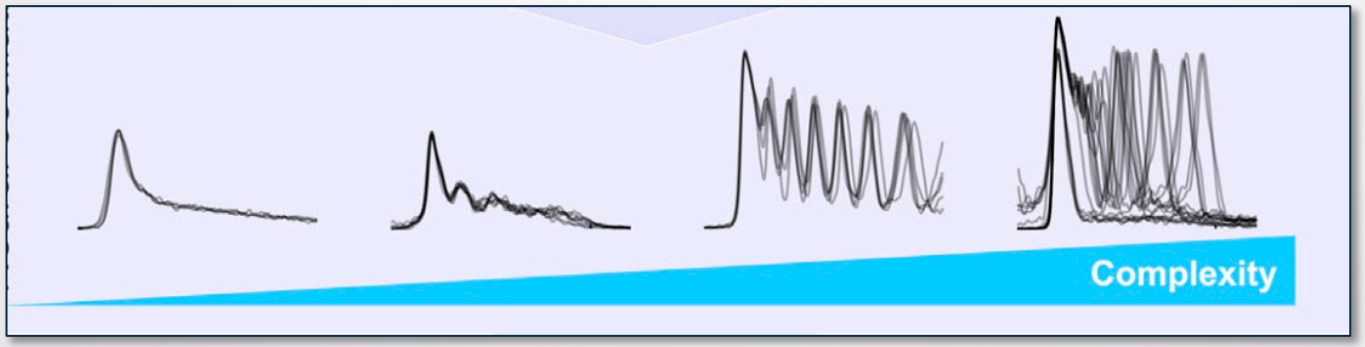
2-month-old organoids



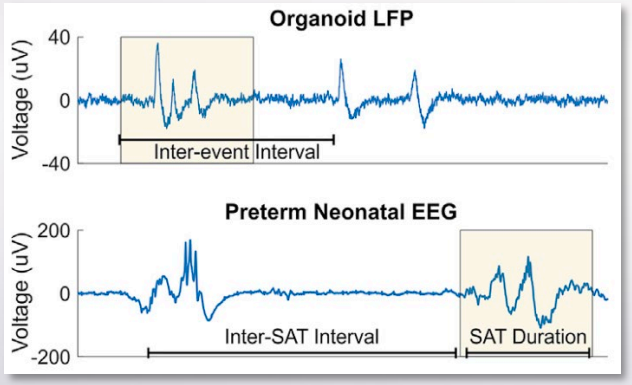
10-month-old organoids



sparse activity



higher complexity

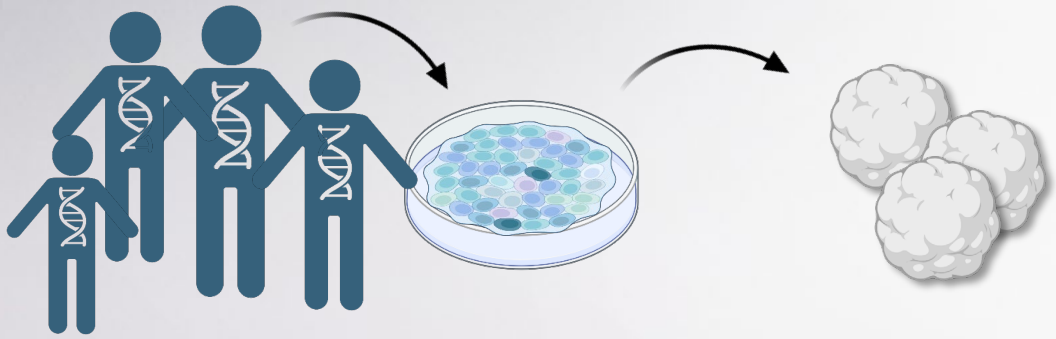


Trujillo 2019

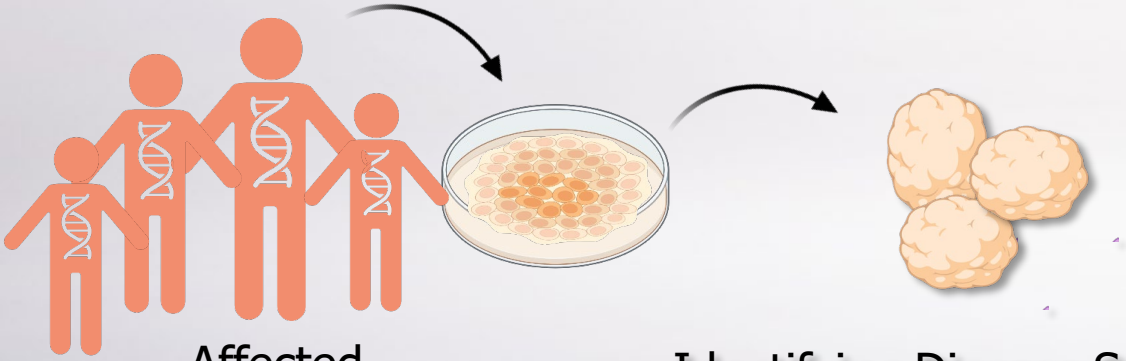
Limitations

*Lack postnatal-brain features
*Lack microglia and blood vessels
*No Blood Brain Barrier
*Isolated from other organs
*Variability

Seeking for neuronal phenotypes



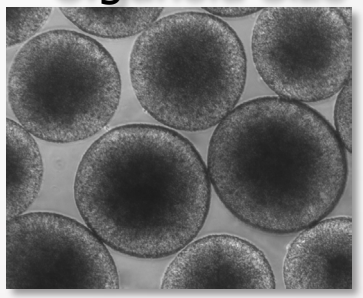
Neurotypical



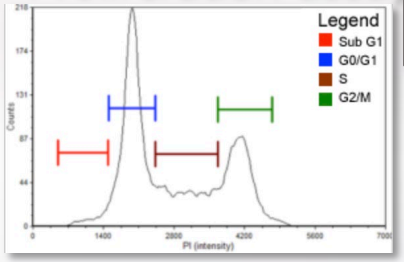
Affected

Identifying Disease-Specific Endophenotypes

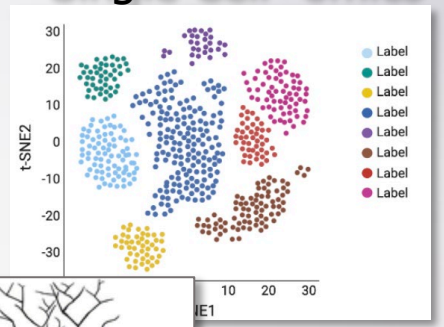
Organoid Size

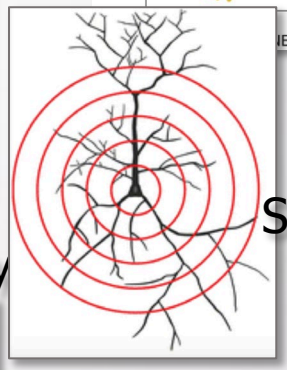


Proliferation assay

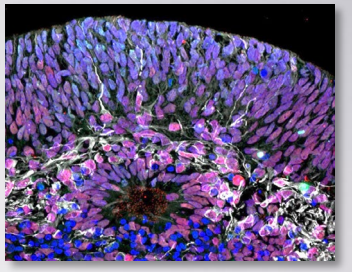


Single Cell -omics



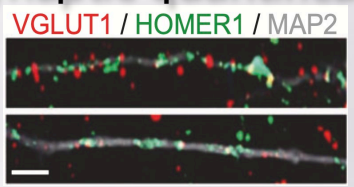


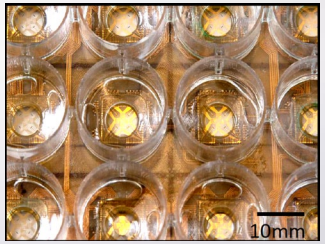
Morphology

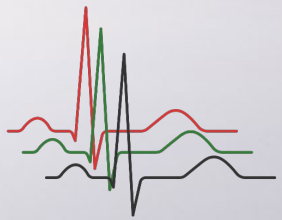


Cytoarchitecture

Synaptic quantification







Neuronal Activity

Personalizing therapies

Neurotypical

Affected

Genome Editing

Goal: Restoring physiological function

Small molecules

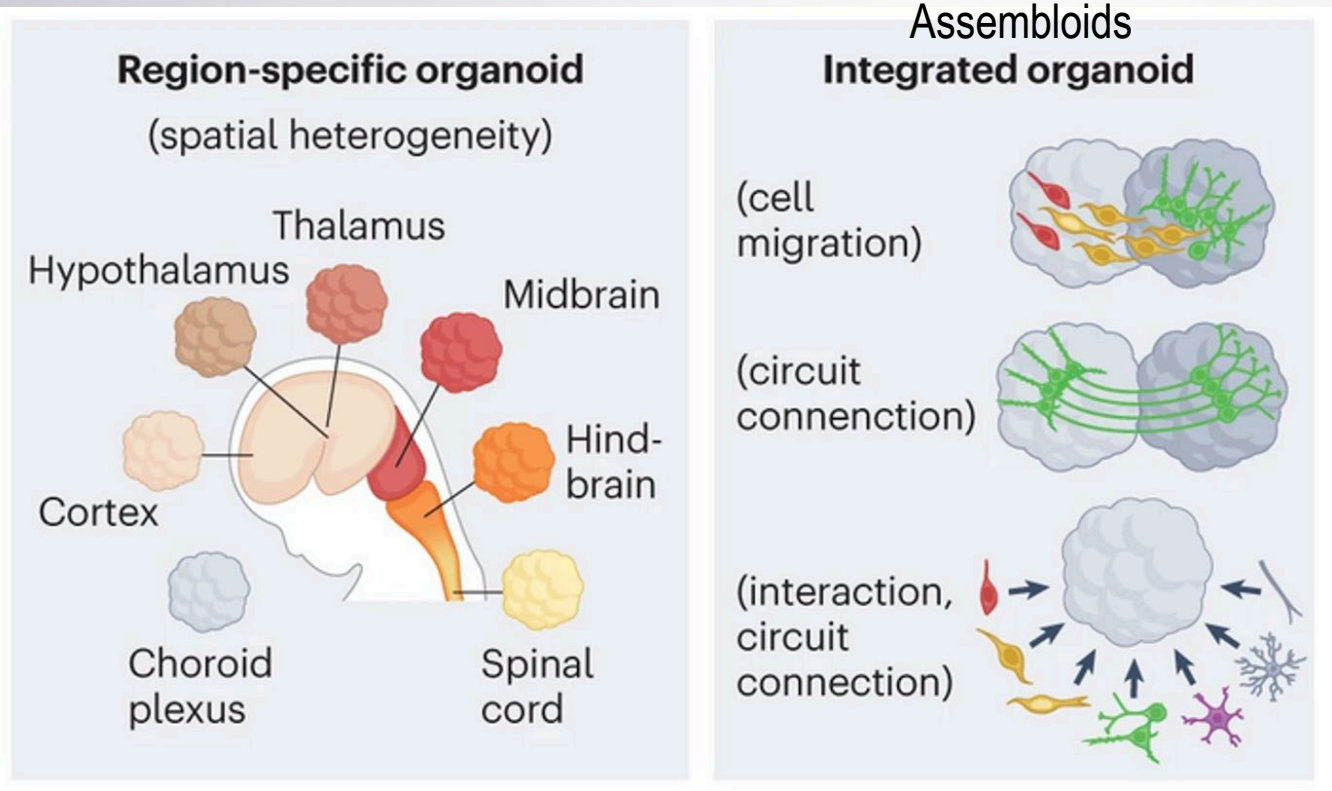
Gene Therapy

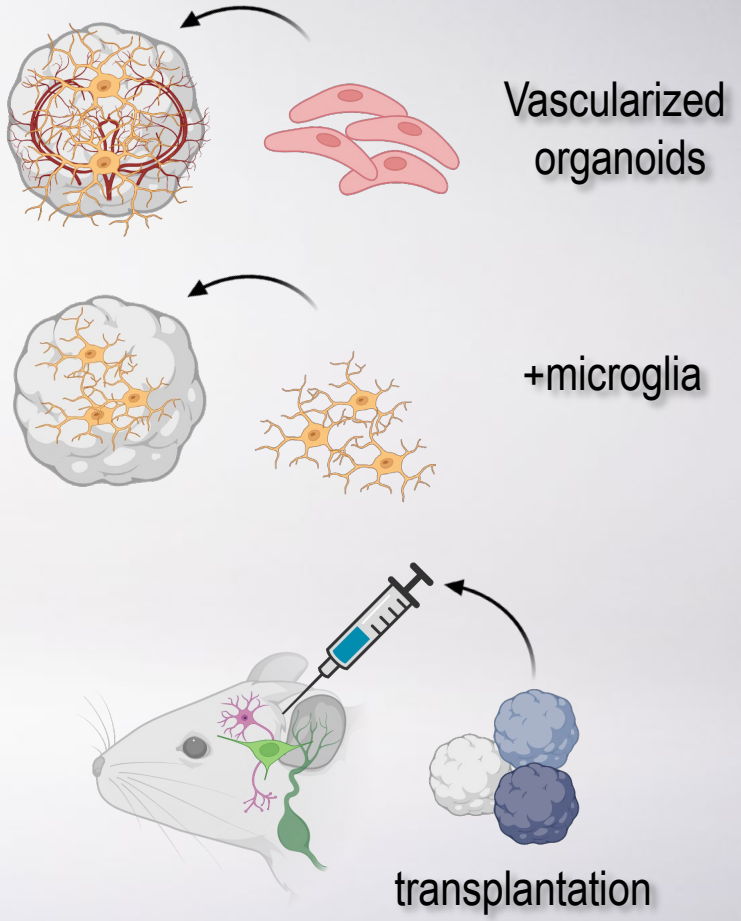
Adeno-associated virus

Lentivirus

ASOs

Increasing protocol complexity

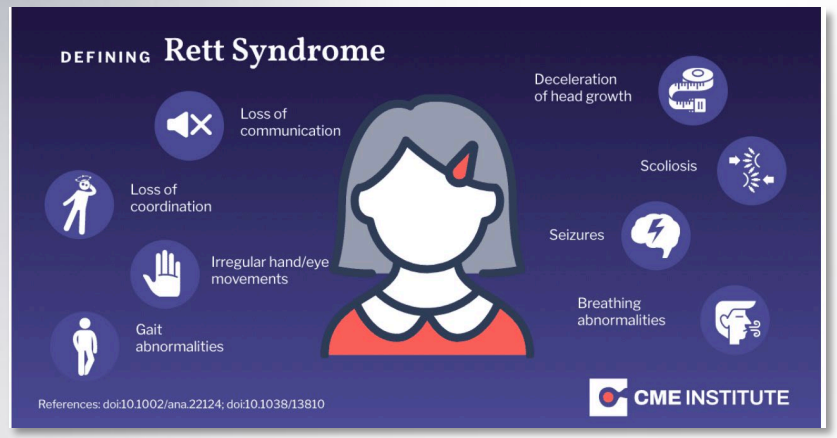




Modified from Kelley and Pasca 2022; Zhou et al., 2023

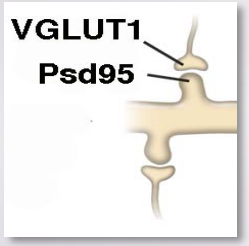
Rett syndrome

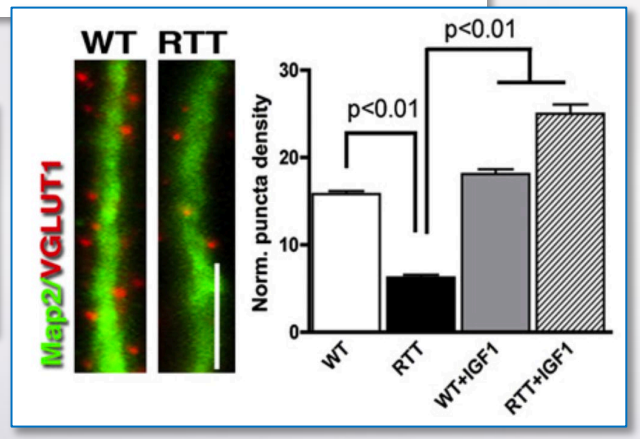
Rare (1:10:000) females
Milestones regression
Severe disabilities



A Model for Neural Development and Treatment of Rett Syndrome Using Human Induced Pluripotent Stem Cells — **Cell 2010**

Maria C.N. Marchetto,[1,5] Cassiano Carromeu,[2,5] Allan Acab,[2] Diana Yu,[1] Gene W. Yeo,[3] Yangling Mu,[1] Gong Chen,[4] Fred H. Gage,[1] and Alysson R. Muotri[2,*]
[1]The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA
[2]University of California San Diego, School of Medicine, Department of Pediatrics, Rady Children's Hospital San Diego, Department of Cellular and Molecular Medicine, Stem Cell Program, 9500 Gilman Drive, La Jolla, CA 92093, USA
[3]University of California San Diego, School of Medicine, Department of Cellular & Molecular Medicine, Stem Cell Program, 9500 Gilman Drive, La Jolla, CA 92093, USA
[4]Pennylvania State University, Department of Biology. 201 Life Science Building, University Park, PA 6802, USA
[5]These authors contributed equally to the work
*Correspondence: muotri@ucsd.edu
DOI 10.1016/j.cell.2010.10.016





Insulin Growth Like Factor 1 (IFG-1)

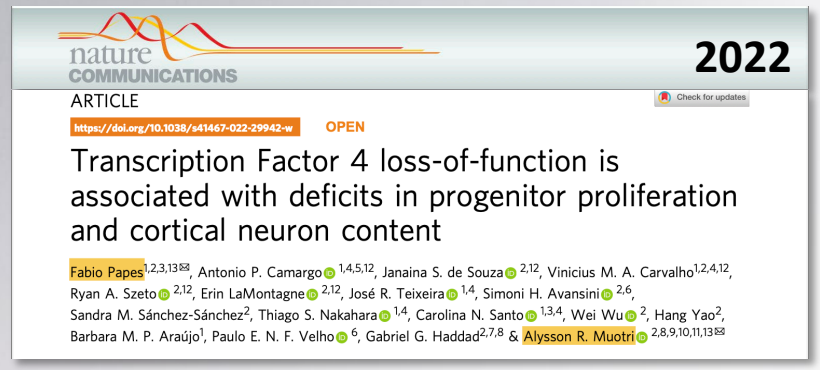
March 2023

ACADIA® Pharmaceuticals

FDA APPROVES TROFINETIDE
The first-ever treatment for Rett Syndrome

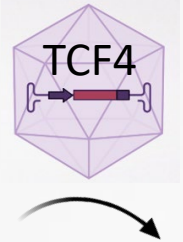
Trofinetide = Modified IGF-1
Decrease neuroinflammation
And supports neuronal synapses

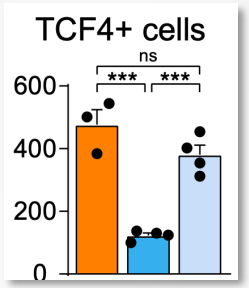
Pitt-Hopkins syndrome – TCF4 deficiency

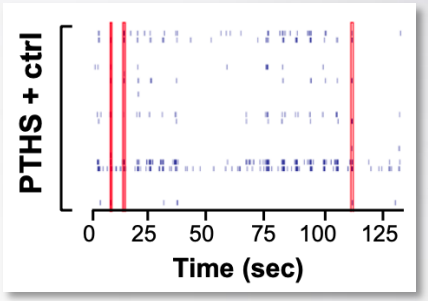


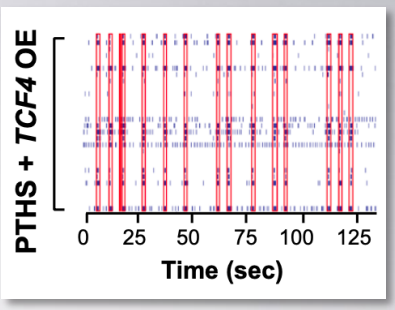
Rare genetic condition
Intellectual disability
Impaired speech
Breathing difficulty

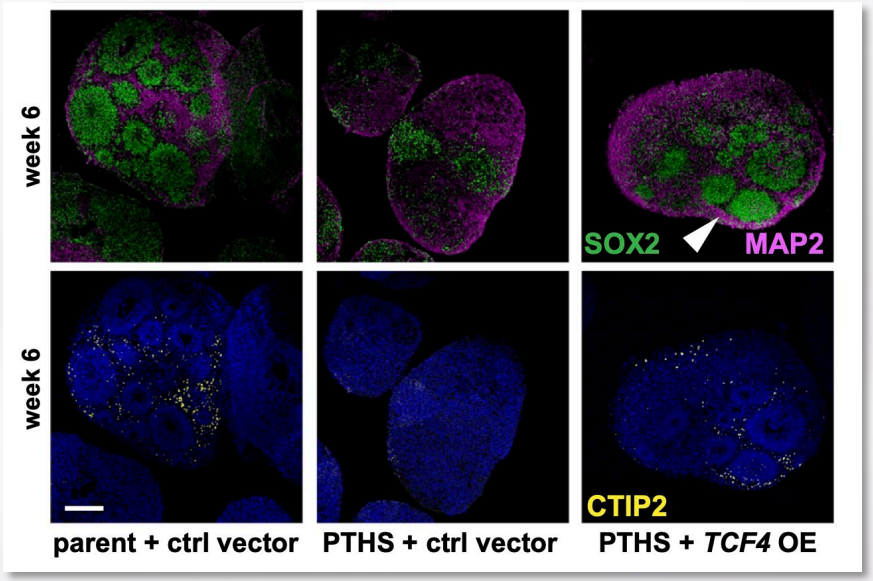
Adenovirus











Rescued phenotypes

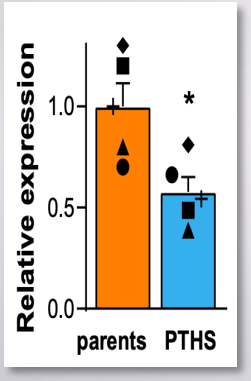
CIRM
$4 Million

AAV9-base TCF4 replacement approach

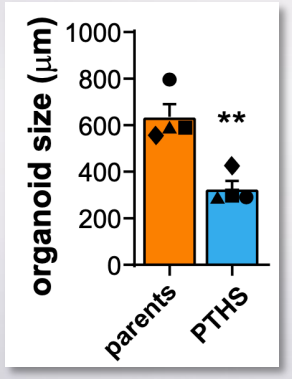
MAHZI therapeutics

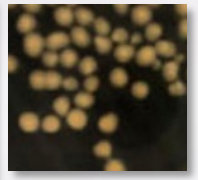
Only a few years

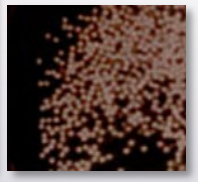
Lower TCF4



Smaller Organoids







CDKL5 deficiency disorder (CDD)

Rare (1:40,000)
Early onset seizures
Impaired cognition,
Speech, motor function

Molecular Psychiatry
https://doi.org/10.1038/s41380-021-01104-2

2021

ARTICLE

Altered network and rescue of human neurons derived from individuals with early-onset genetic epilepsy

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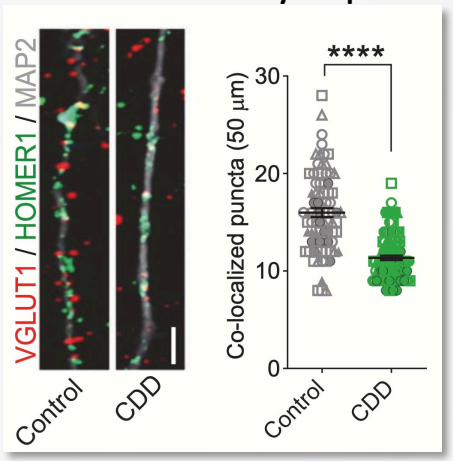
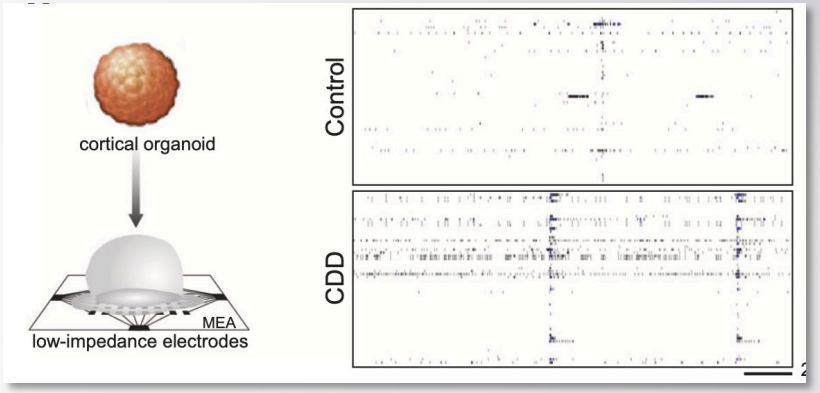
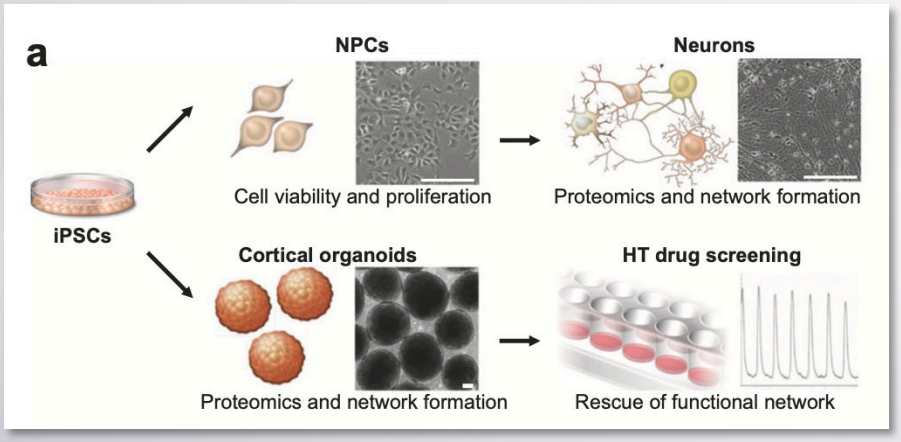
Reduced synapses

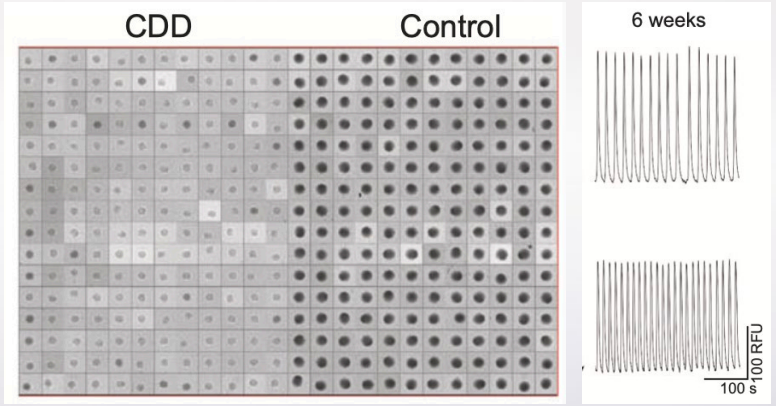


Human neurons

Hyperexcitability



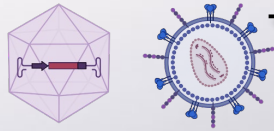




Small molecules

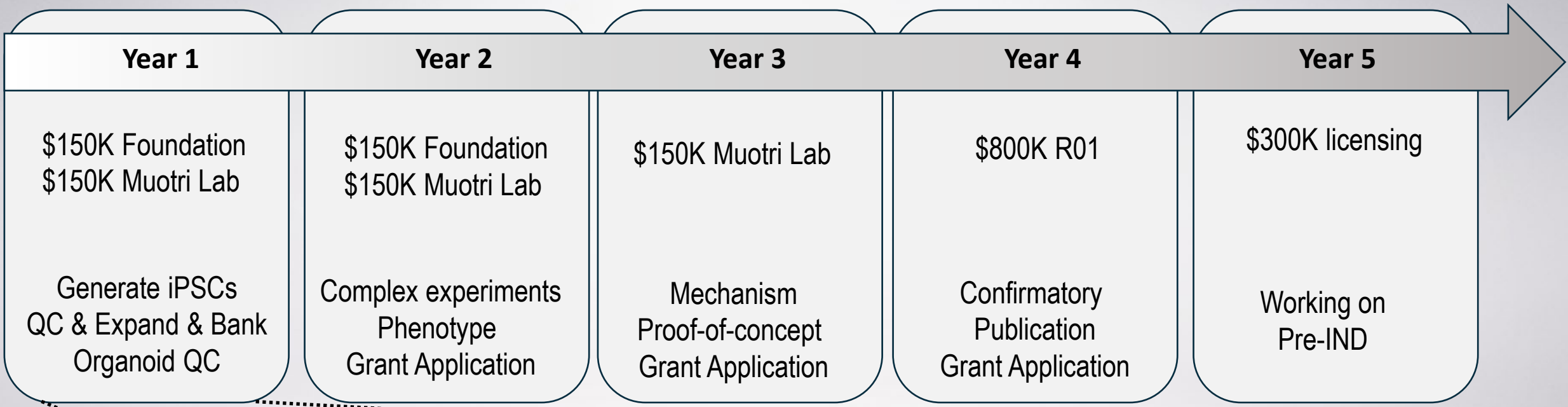
ultragenyx

Gene Therapy



ASOs

Cost? Timeline?



$500 to culture patient-skin fibroblasts
$10-20K to reprogram, QC, and establish one iPSC line
$15K to differentiate one iPSC line
$20K CRISPR-editing/line
+ SALARIES 50% technician/100% postdoc

The Muotri Lab