

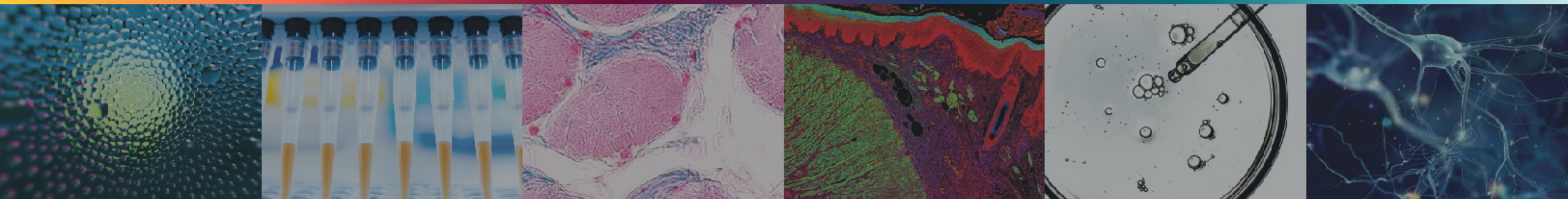


THE FRONT ROW  
at Scripps Research

# Editing genes to tackle neurological conditions

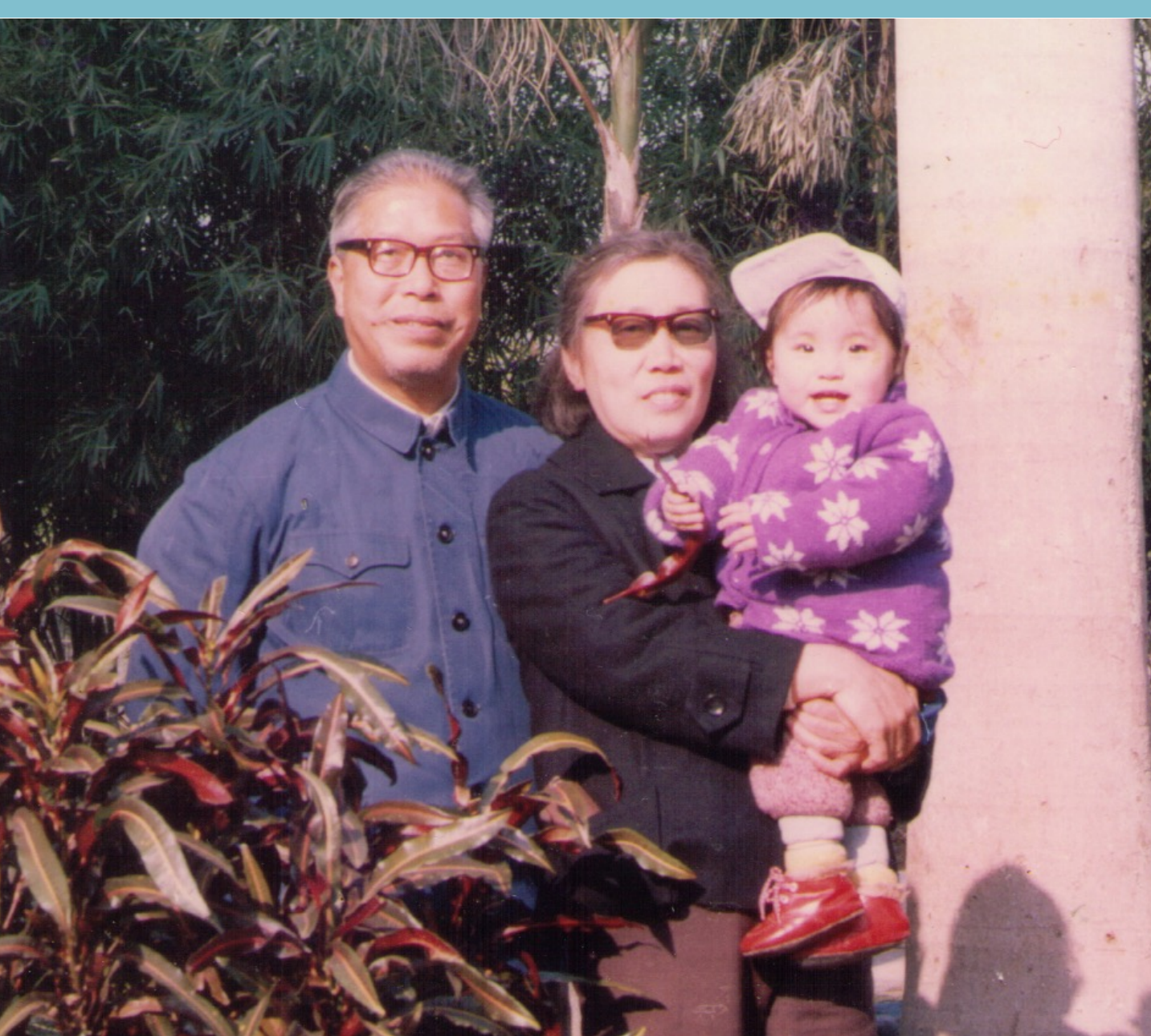
**Xin Jin, Ph.D.**

Department of Neuroscience, Dorris Neuroscience Center  
Scripps Research



# Xiamen, Fujian





II. Lvs. undivided or irregularly lobed, ovate or elliptic.  
 L. Wings of the samara acutely angled; lvs. pubescent along the nerves beneath.

M. Lf. margins irregularly sharply and doubly serrate, 4-10cm. the long. dull green.

A. ginnala



MM. Lf. margins entire or irregularly lobed, 2-6cm. long, glossy above, often glaucous beneath

A. oliverianum

A. nikoense  
 花 1/194

LL. Wings of the samara obtusely angled or nearly horizontal; lvs. ov to oblong, subcordate at base, abruptly pointed at tip, 3-7cm. long. margins remotely serrate near and below apex or nearly entire. A. cordatum



DD. Lvs. 7-9-lobed; segments sharply serrate; wings of the samara obtusely angle

A. sinense

A. sinopurpurea

N. Petiole and peduncles glabrous or nearly so:

\* A. theiferum Fang nom tantum 柔荑 (花 1/144) p. 8

A. ginnala sensu Auct. non Maxim.  
 (花 1/174)

花 1/185 青阳. 贵池. 木宁. 皖生. 全椒. 宁国. 太平. 此西.

ovary and lvs. glabrous.

A. palmatum

MN. Petioles and peduncles



A. truncatum

花 1/175. 4



# Plant biology and taxonomy

## Classification by their form, or their function?

II. Lvs. undivided or irregularly lobed, ovate or elliptic.

L. Wings of the samara acutely angled; lvs. pubescent along the nerves beneath.

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贵州. 志. 1:1185 贵阳. 贵地. 木. 志. 1:1185 全. 志. 1:1185 贵. 州. 志. 1:1185

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A. palmatum

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A. truncatum

A. sinense

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A. buergerianum

A. nikoense 1975.4



# Xin Jin, Ph.D.

B.Sc. Chemistry, 2010

Massachusetts Institute of Technology

Ph.D. Biology, 2016

HHMI International Predoctoral Fellow

The Rockefeller University

Junior Fellow, 2021

Society of Fellows

Harvard University



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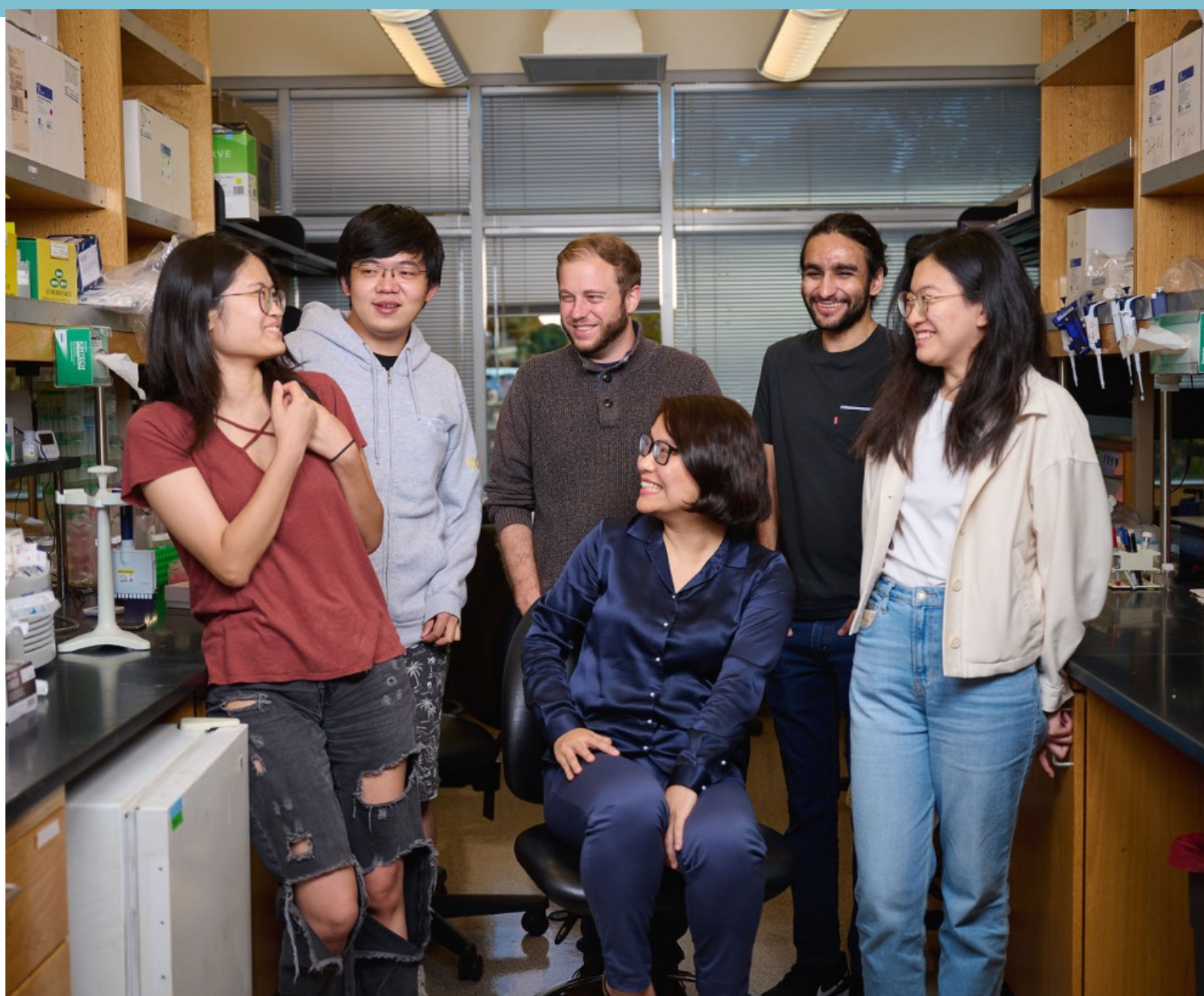
Junior Fellow, 2021

Society of Fellows

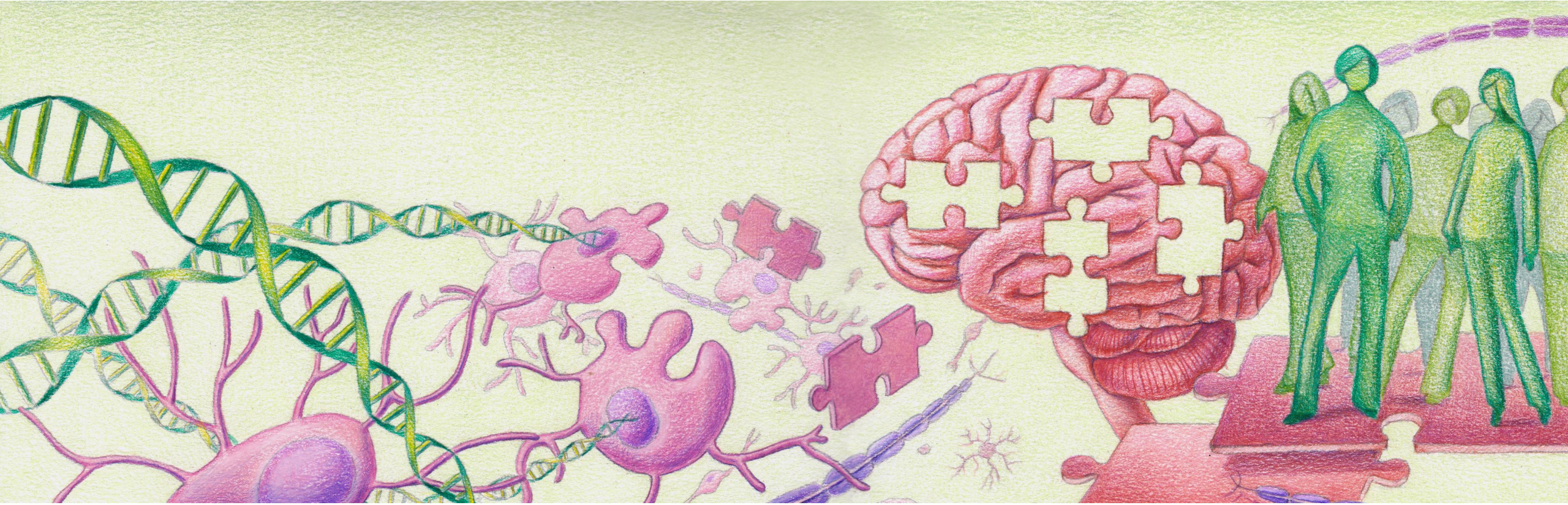
Harvard University

Assistant Professor, 2021-

Scripps Research



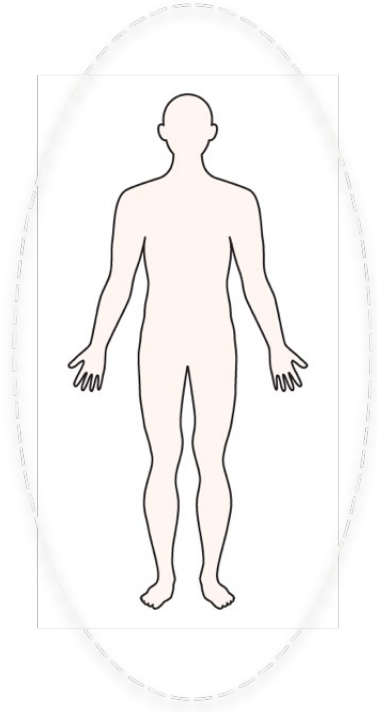
# From genomic variations to human diseases






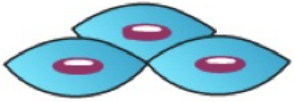
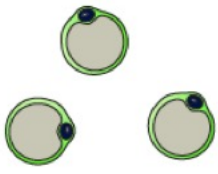

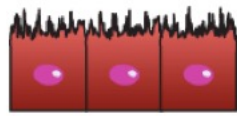
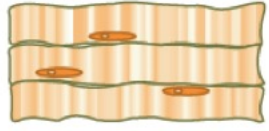

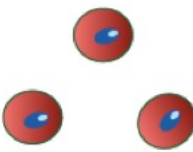
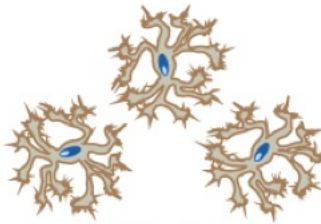
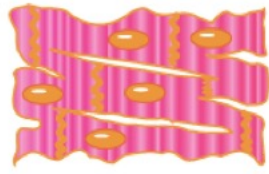
Classify brain cell functions, *one cell at a time.*



# Cells are our basic units



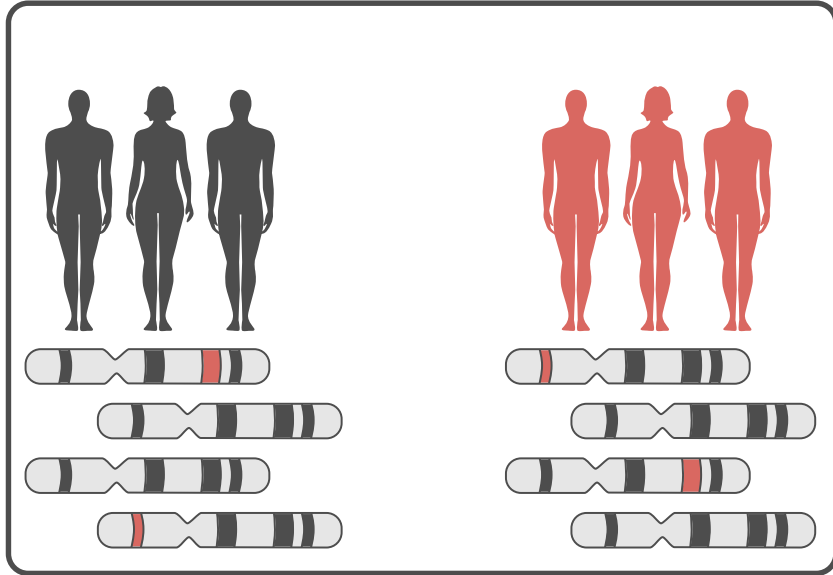
Diverse cells are classified by their location, morphologies, function, molecules

Skin Cells	Immune Cells	Brain Cells	Muscle Cells
 Fibroblasts	 Megakaryocytes	 Neurons	 Smooth Muscle
 Adipocytes	 Dendritic Cells	 Ependymal Cells	 Skeletal Muscle
 Epithelial Cells	 T Cells	 Astrocytes	 Cardiac Muscle





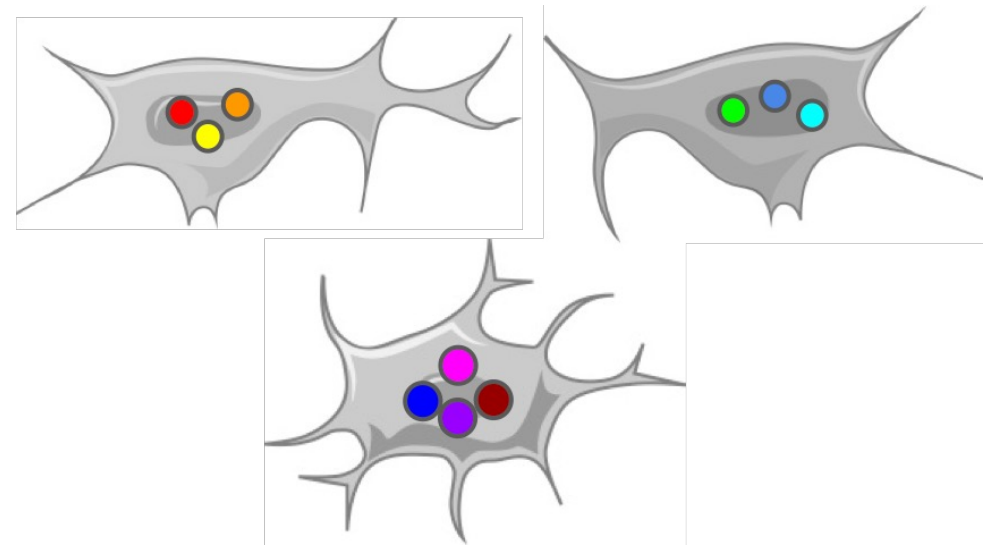
# Disease risks and resilience in our genome



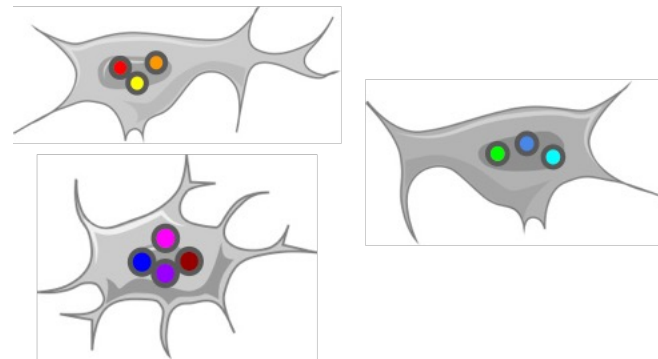
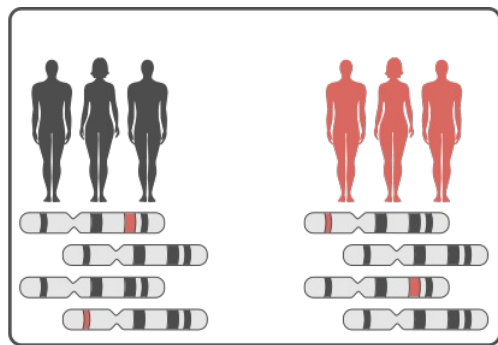
Risk variants:



# Cell type-specific actions of risk genes



*Neuropsychiatric conditions, neurodevelopmental disorders, neurodegeneration, aging, etc*



**Many risk genes**

**Many cell types**

We build *in vivo* Perturb-seq:  
systematically and scalably dissect genome functions,  
*one cell at a time.*



# Long lists of genetic variants in neuropsychiatric illnesses



**25,000+** autism/neurodevelopmental delay: whole exome sequencing

Stephan Sanders, Mike Talkowski, Joseph Buxbaum, Kathryn Roeder, Bernie Devlin, Mark Daly and teams



2012

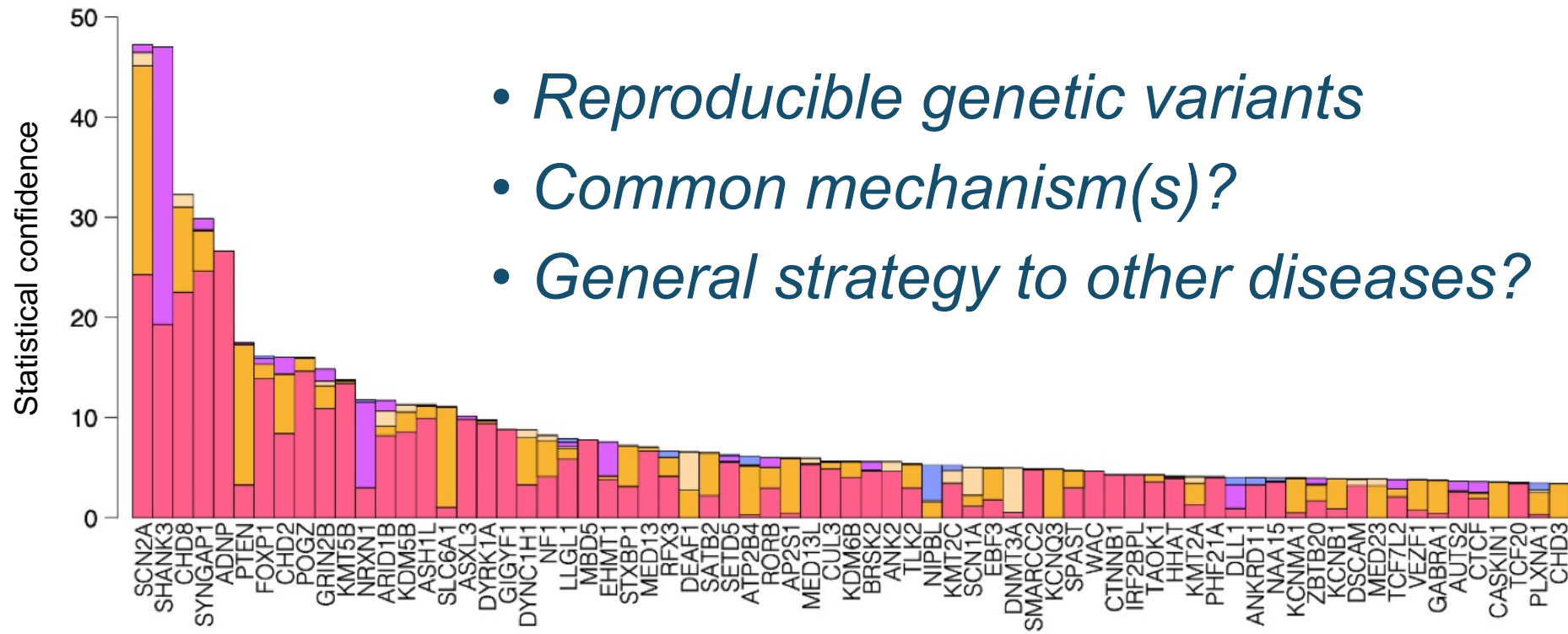
<10 genes

2020

101 genes  
FDR<0.2

2022

255 genes  
FDR<0.1    71 genes  
FDR<0.001



- *Reproducible genetic variants*
- *Common mechanism(s)?*
- *General strategy to other diseases?*

71 risk genes in autism and developmental delay

25,000+ autism/neurodevelopmental delay: whole exome sequencing

Stephan Sanders, Mike Talkowski, Joseph Buxbaum, Kathryn Roeder, Bernie Devlin, Mark Daly and teams



# Perturb-seq: a systems genetic approach towards disease gene functions

CRISPR gene editing



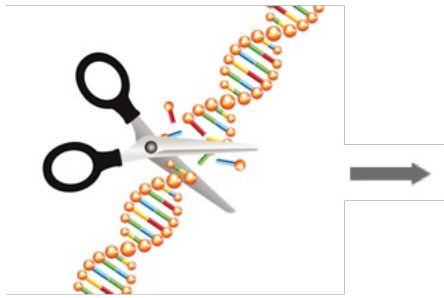
Jin et al Science 2020



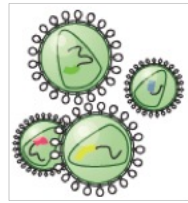
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# Perturb-seq: a systems genetic approach towards disease gene functions

CRISPR gene editing



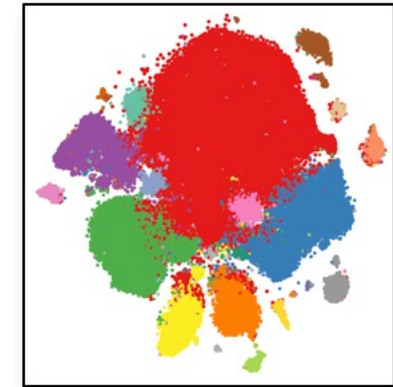
Viral delivery



*In vivo* genetic perturbation



High resolution, single-cell analysis



## 2020: *in vivo* Perturb-seq

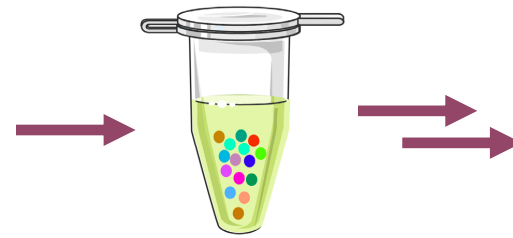
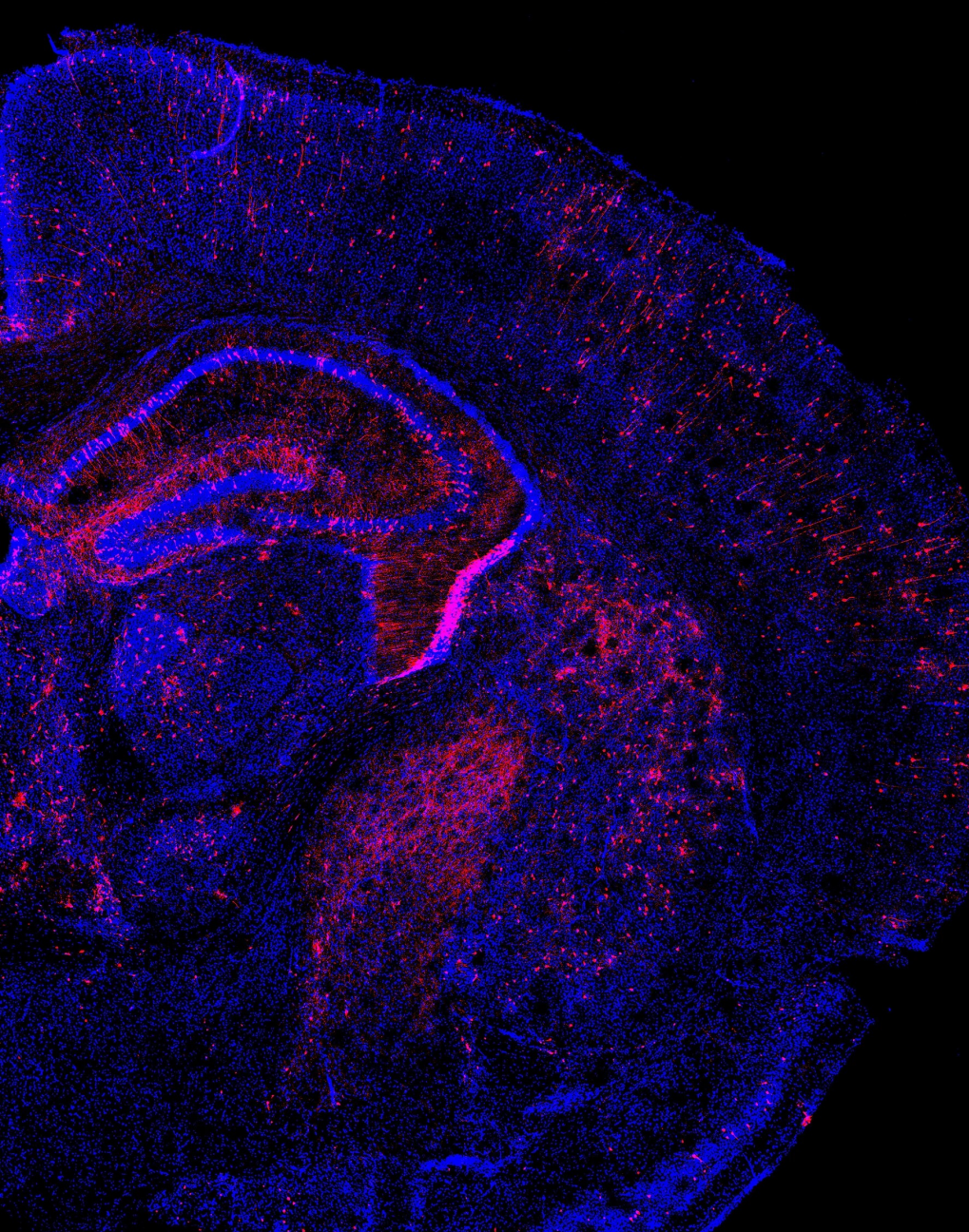
Reveals convergent cell type networks impacted by autism risk genes

Jin et al Science 2020

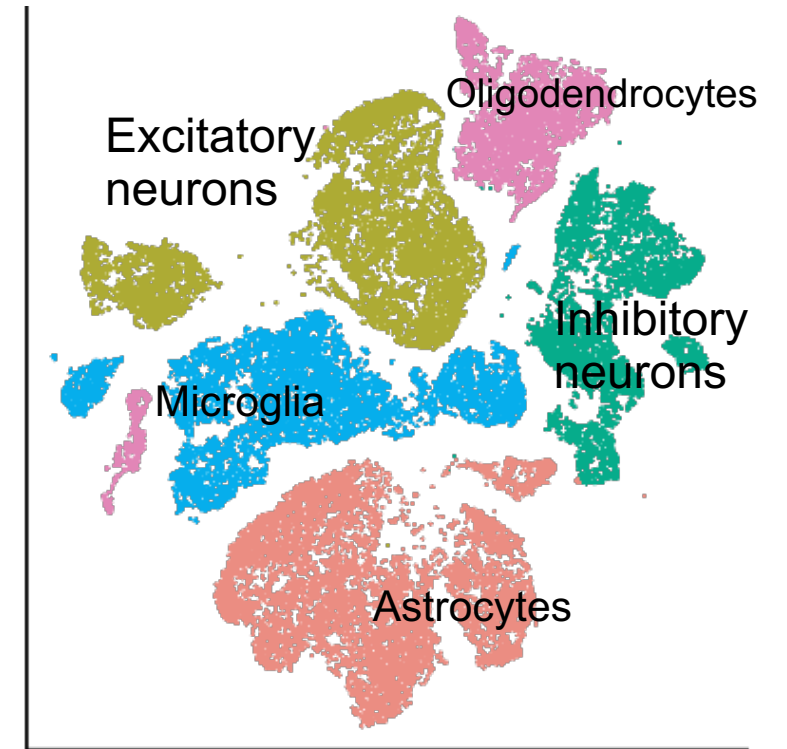


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# High-resolution phenotypic readout of cell subtype and cell state



## Major cell types from cortex

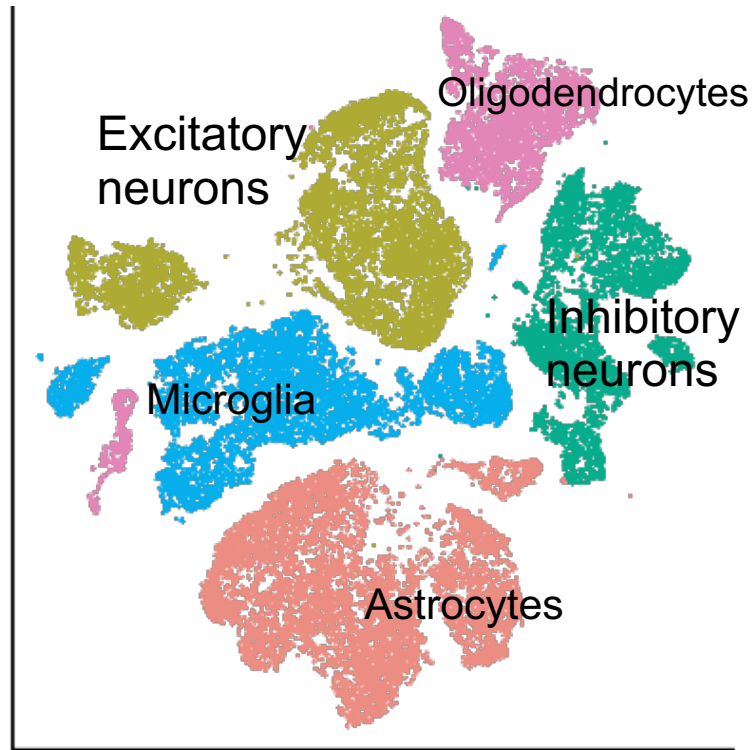


Analyzed 35 risk gene perturbation function with 46,770 cells

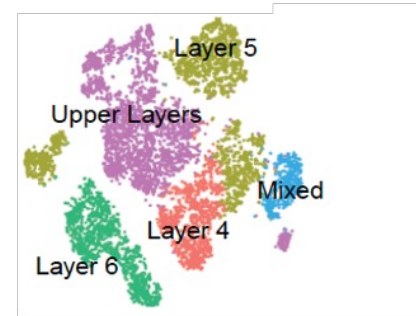


# High-resolution phenotypic readout of cell subtype and cell state

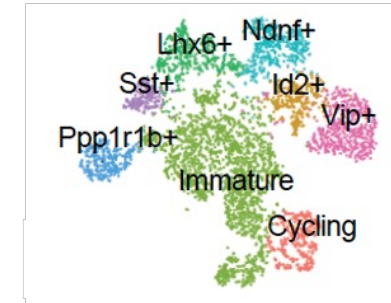
## Major cell types from cortex



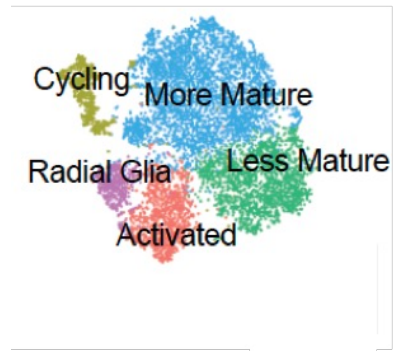
## Excitatory projection neurons



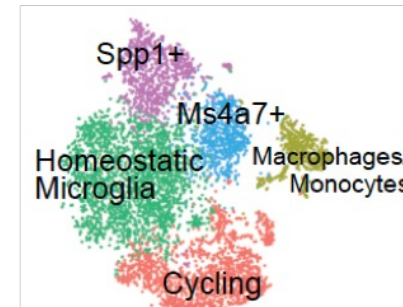
## Inhibitory neurons



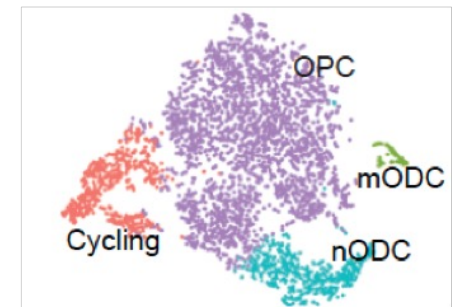
## Astrocytes



## Microglia



## Oligodendrocytes



Jin et al Science 2020

Analyzed 46,770 cells with 35 risk gene perturbation



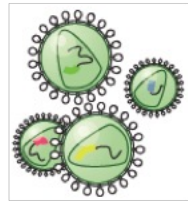


# A systems genetic approach to map gene functions in human disease

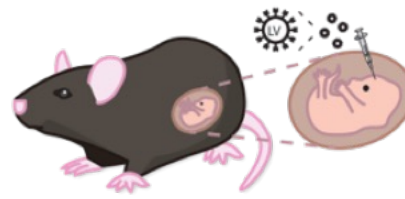
CRISPR gene editing



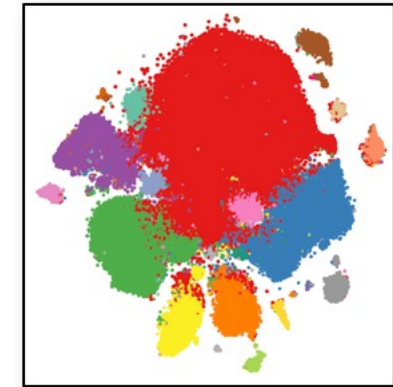
Viral delivery



*In vivo* genetic perturbation



High resolution, single-cell analysis



**2020: *in vivo* Perturb-seq**

Reveals convergent cell type networks impacted by autism risk genes

Jin et al Science 2020

**2023: massively parallel Perturb-seq**

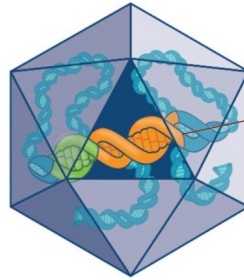
Analyzing over 30,000 individual cells within a single experiment

Zheng et al BioRxiv 2023, in revision

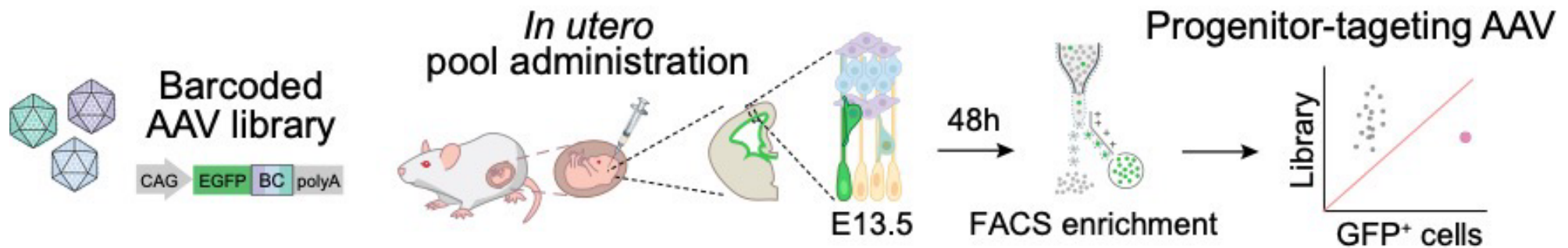


# Identification of optimal vectors to expand the scale and expression

Adeno Associated Viral (AAV) vectors



*Gene cargo  
(e.g. CRISPR reagents)*



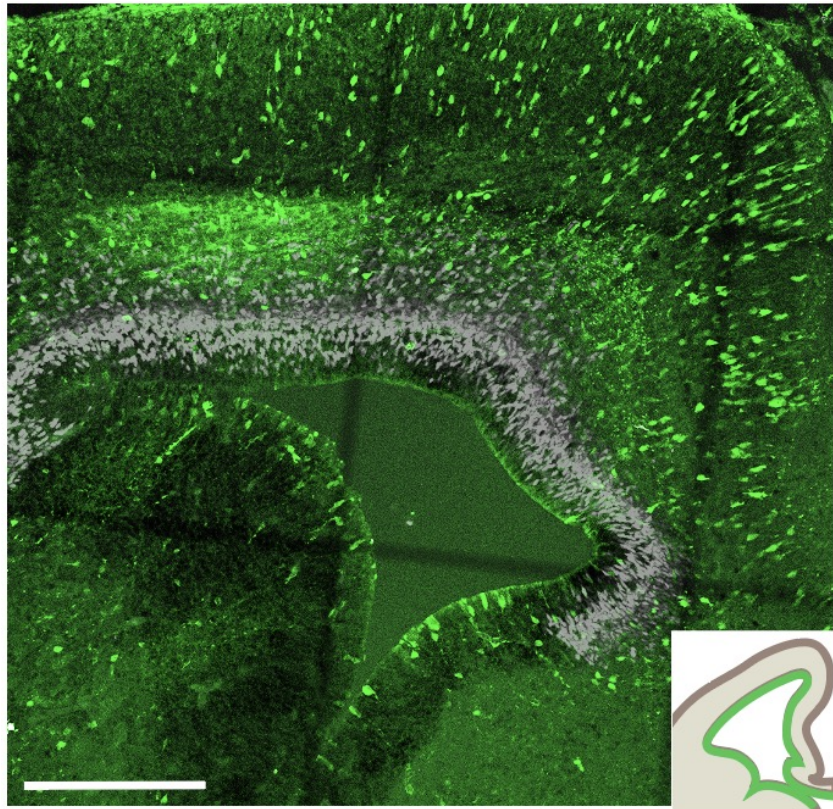
Testing 86 AAV vectors including:  
AAV1, AAV2, AAV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12 & AAV13

Collaboration with Joshua Levin (Broad), Xiangmin Xu (UCI)

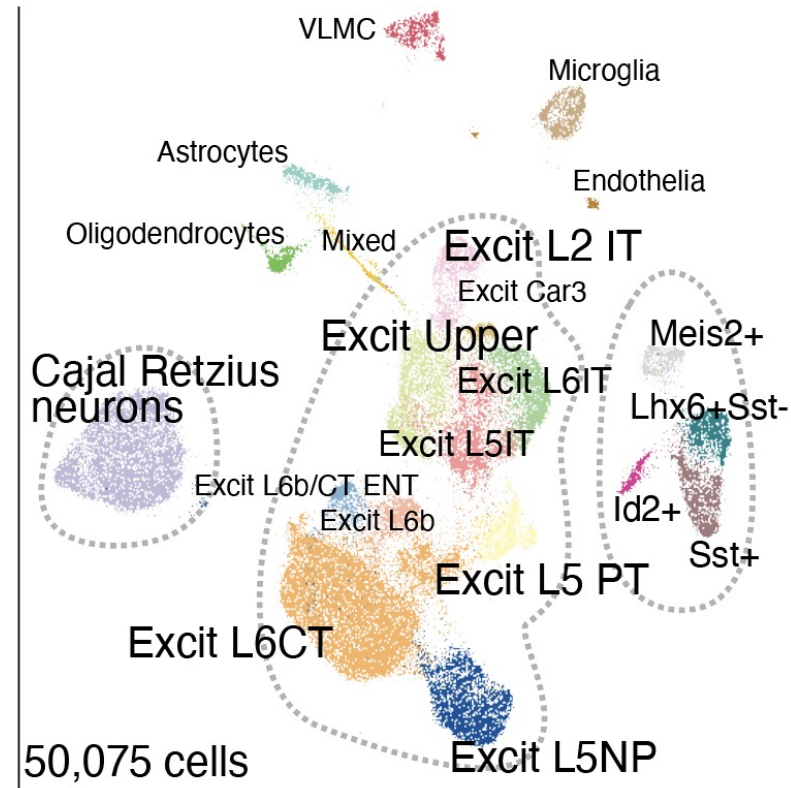


# An accelerated platform to achieve massively parallel Perturb-seq

48 hours after AAV injection



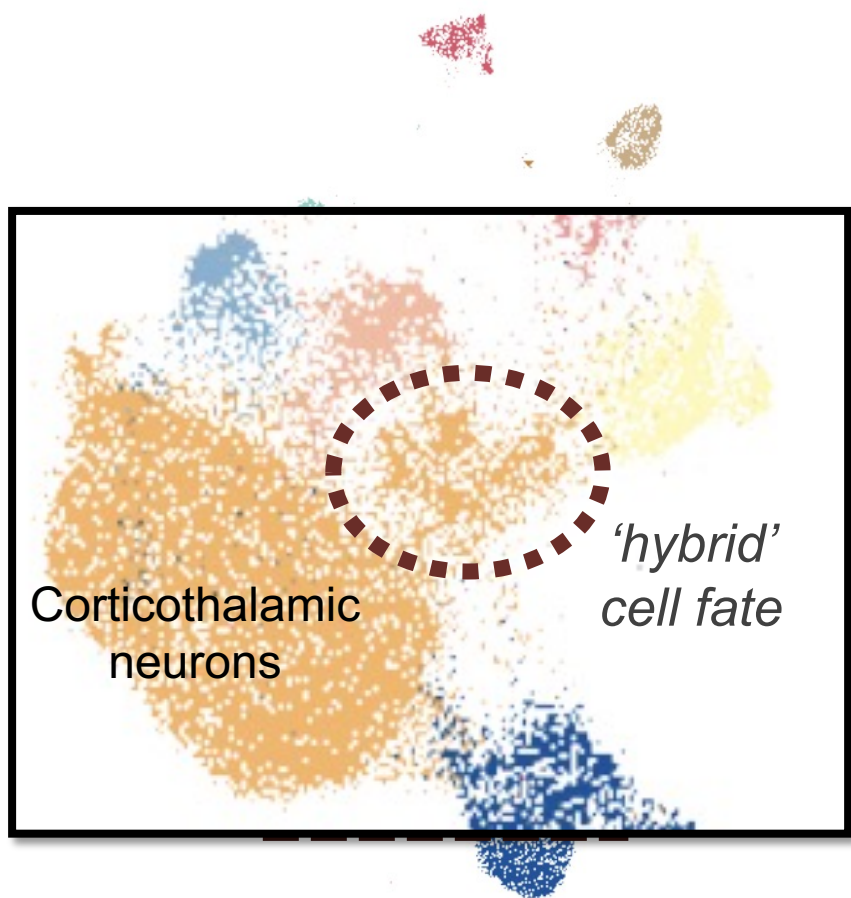
Analysis of > 30,000 cells in one experiment



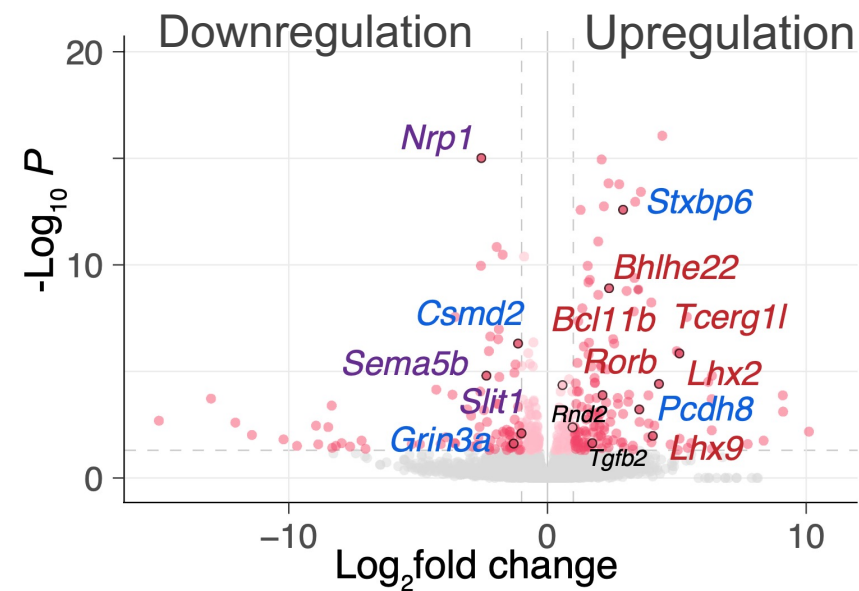
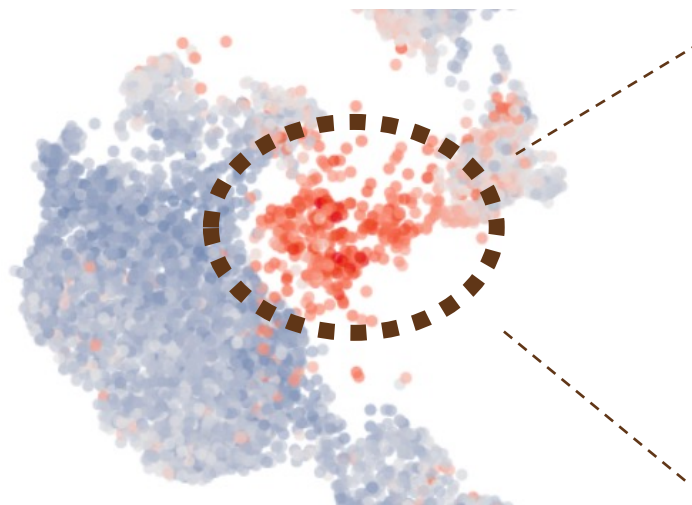
Collaboration with Joshua Levin (Broad), Xiangmin Xu (UCI)



# FOXG1 perturbation leads to hybrid states in distinct cell types



Perturbation of an autism risk gene *Foxg1*

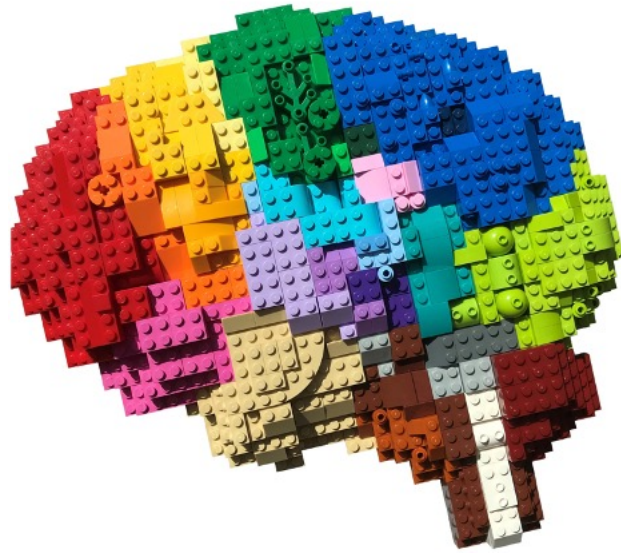


Collaboration with Joshua Levin (Broad), Xiangmin Xu (UCI)



# Functional genomics: scalable, *in vivo* screen with high-resolution readout

## The tissue we study



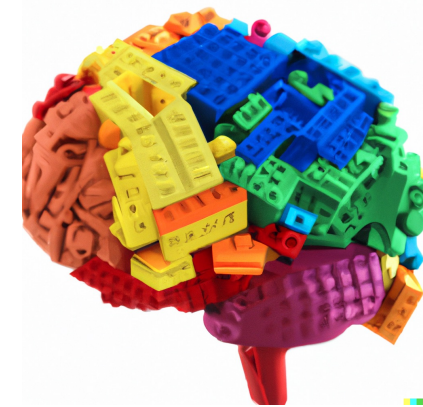
### Bulk analysis



### Single-cell analysis



### Tissue clearing and whole brain imaging



From Bo Xia and DALL-E



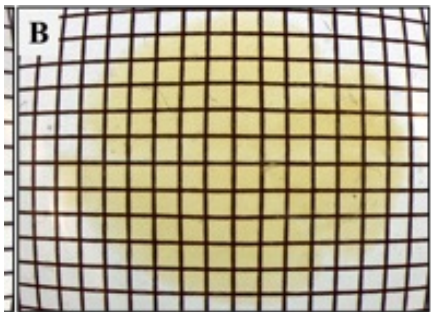
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Boli Wu  
Mark Pearson Endowed Graduate Fellow



# Perturb-map: cytoarchitecture changes in an intact brain

Tissue clearing



Collaboration with Zhuhao Wu (Weill Cornell)



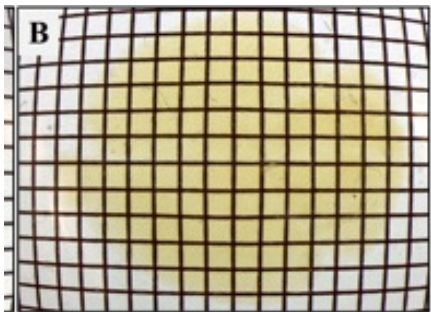
THE FRONT ROW  
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Boli Wu  
*Mark Pearson Endowed Graduate Fellow*

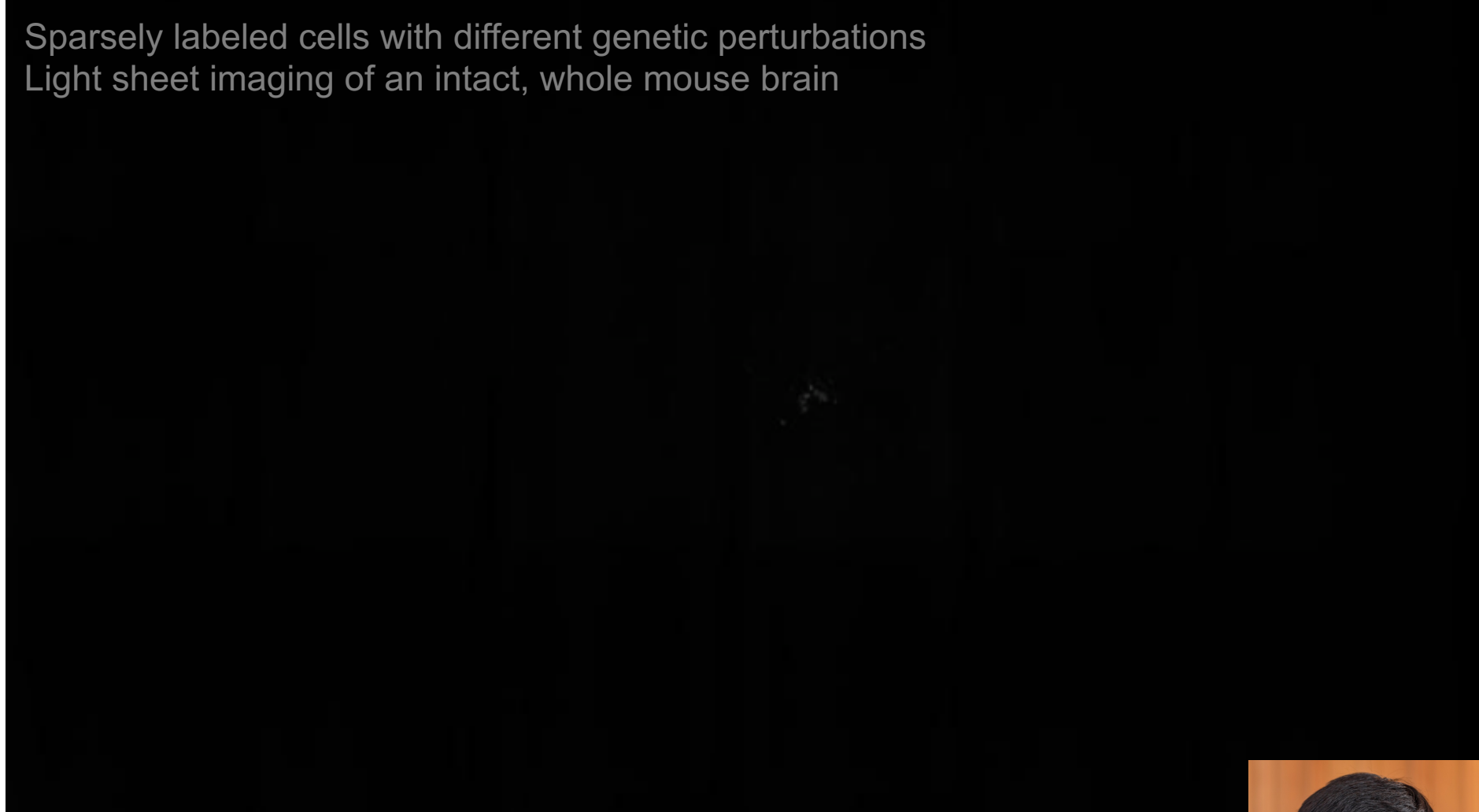


# Perturb-map: cytoarchitecture changes in an intact brain

Tissue clearing



Sparsely labeled cells with different genetic perturbations  
Light sheet imaging of an intact, whole mouse brain



Collaboration with Zhuhao Wu (Weill Cornell)

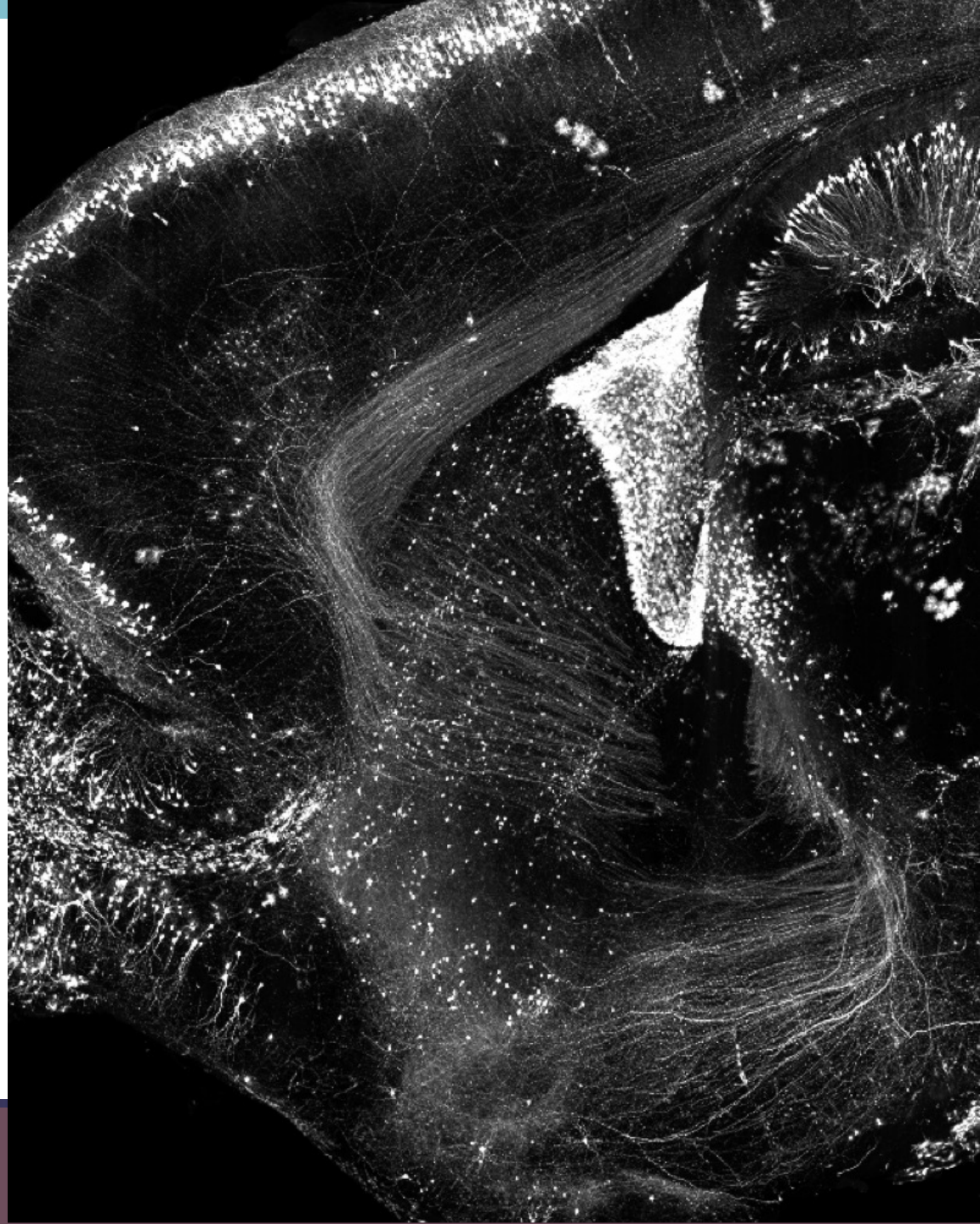
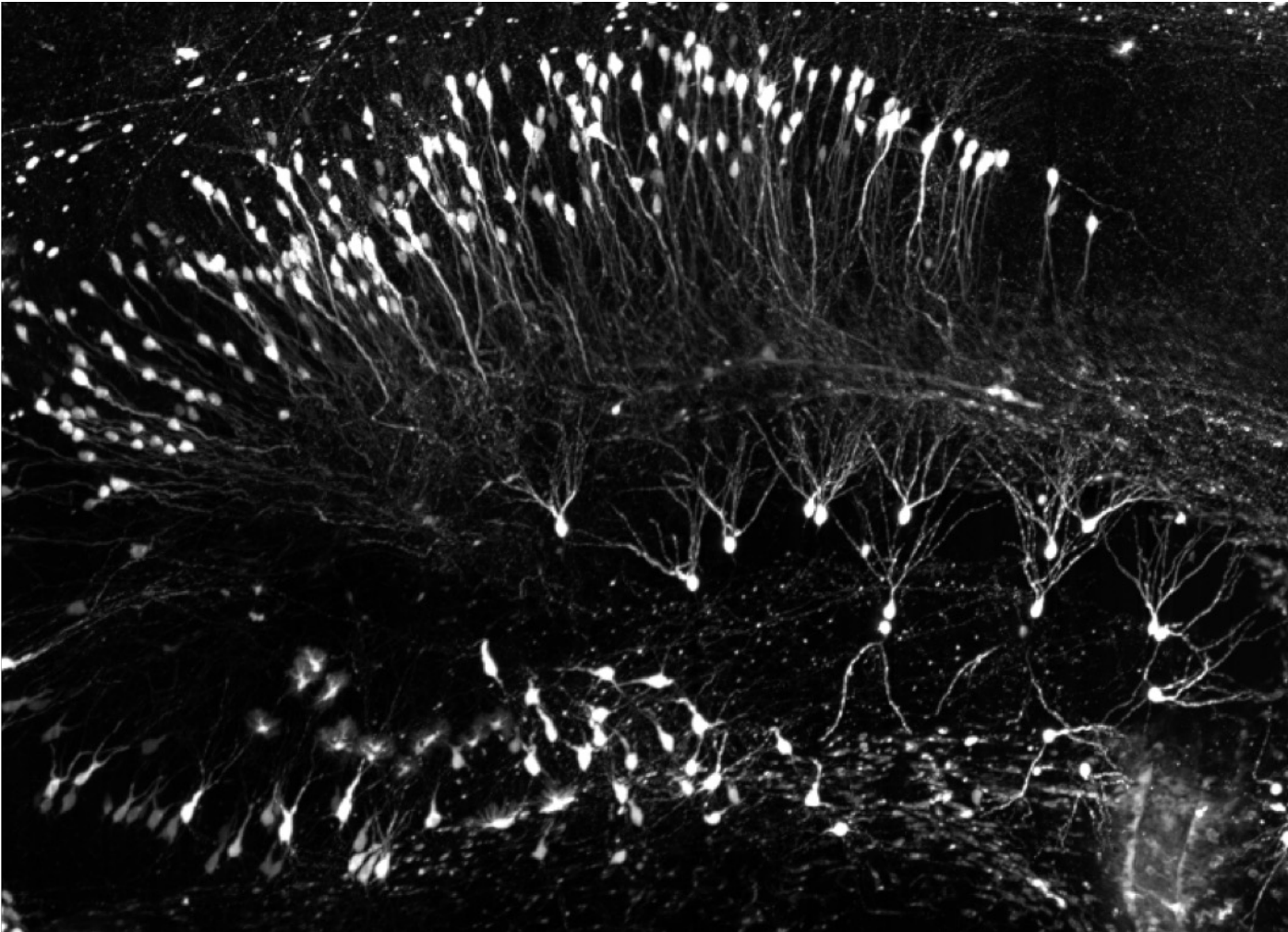


THE FRONT ROW  
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Mark Pearson Endowed Graduate Fellow

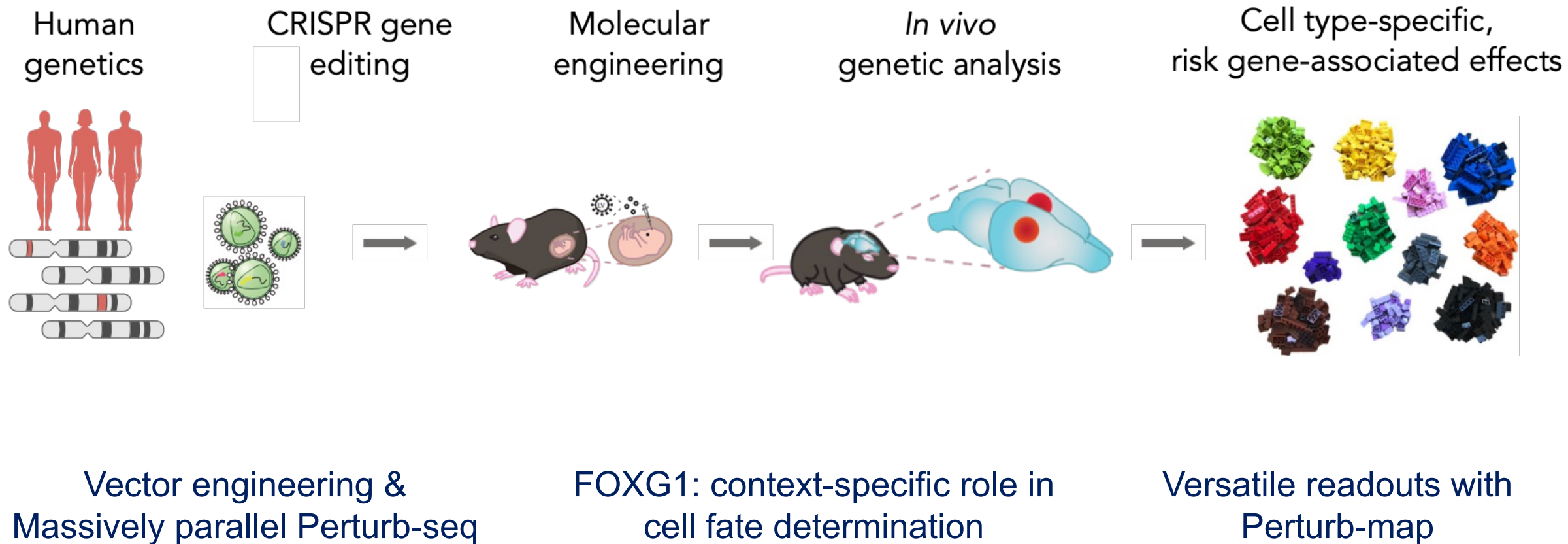


# Perturb-map: cytoarchitecture changes resulting from disease risk genes

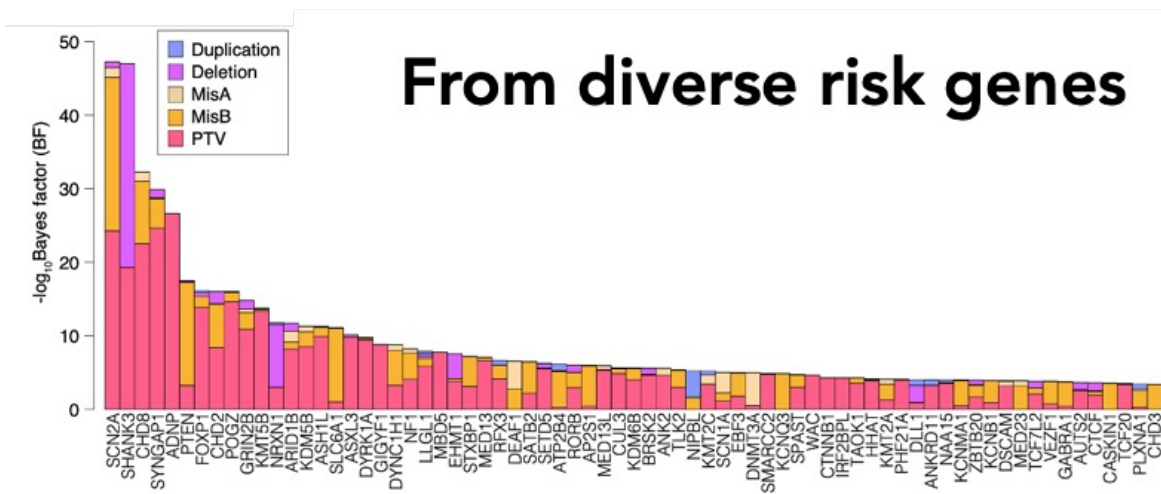
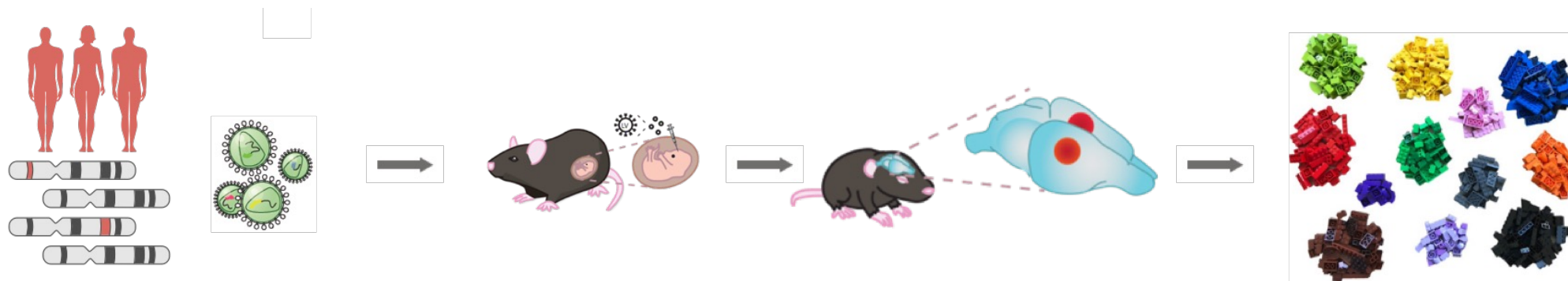




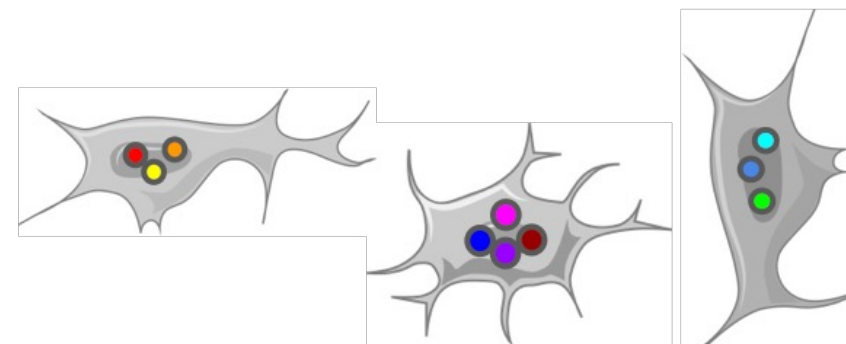
# Towards genomics-inspired therapeutics



# Towards genomics-inspired therapeutics



## To actionable drug targets

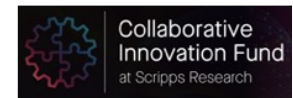
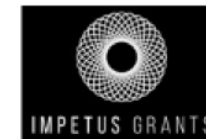
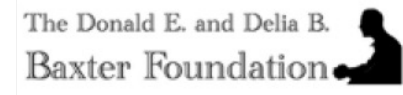




# Collaborators

Joshua Levin, Sean Simmons  
 Xiangmin Xu  
 Vadim Gladyshev  
 Stephan Sanders  
 Zhuhao Wu, Keerthi Rajamani  
 Carina Hanashima

Broad Institute  
 UC Irvine  
 Harvard Med School  
 UCSF/Oxford  
 Weill Cornell  
 Waseda University



**James Fickel**  
**Jed McCaleb**

R01HG012819

