A molecular and cellular paradigm for understanding human brain function and dysfunction

Ed Lein, Ph.D.
Investigator

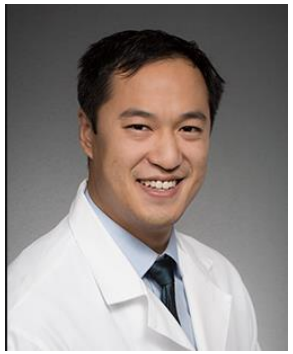
Alzheimer's Disease Centers Program Meeting
October 18, 2018

ALLEN INSTITUTE *for* BRAIN SCIENCE

Seattle neuropathologist and neurosurgeon collaborator network

University of Washington - Harborview

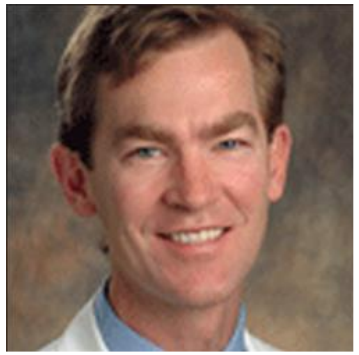
Jeff Ojemann
(Epilepsy)



Andrew Ko
(Epilepsy)

Dirk Keene

Swedish Hospital



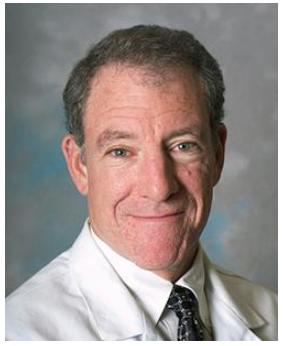
Charles Cobbs
(Tumor)

Ryder Gwinn
(Epilepsy)

University of Washington Medical Center

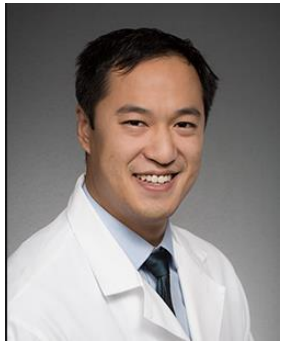
Rich Ellenbogen

Manny Ferreira



Dan Silbergeld

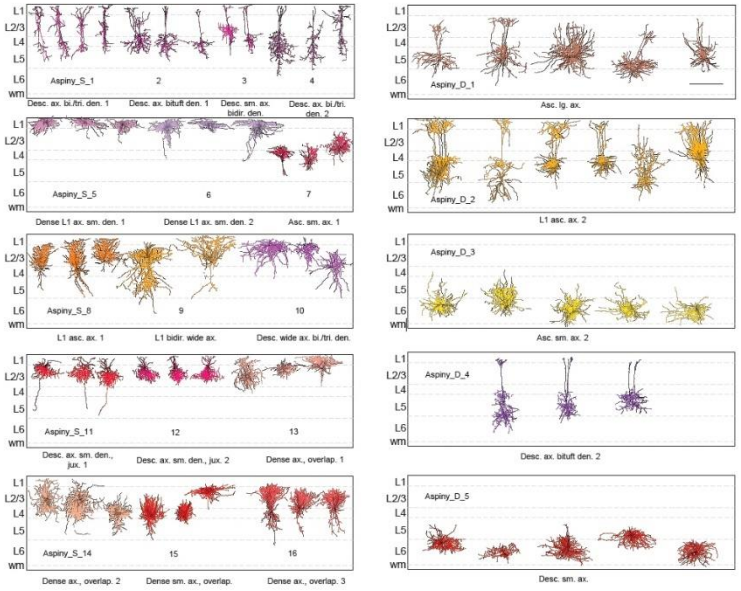
Jeff Ojemann

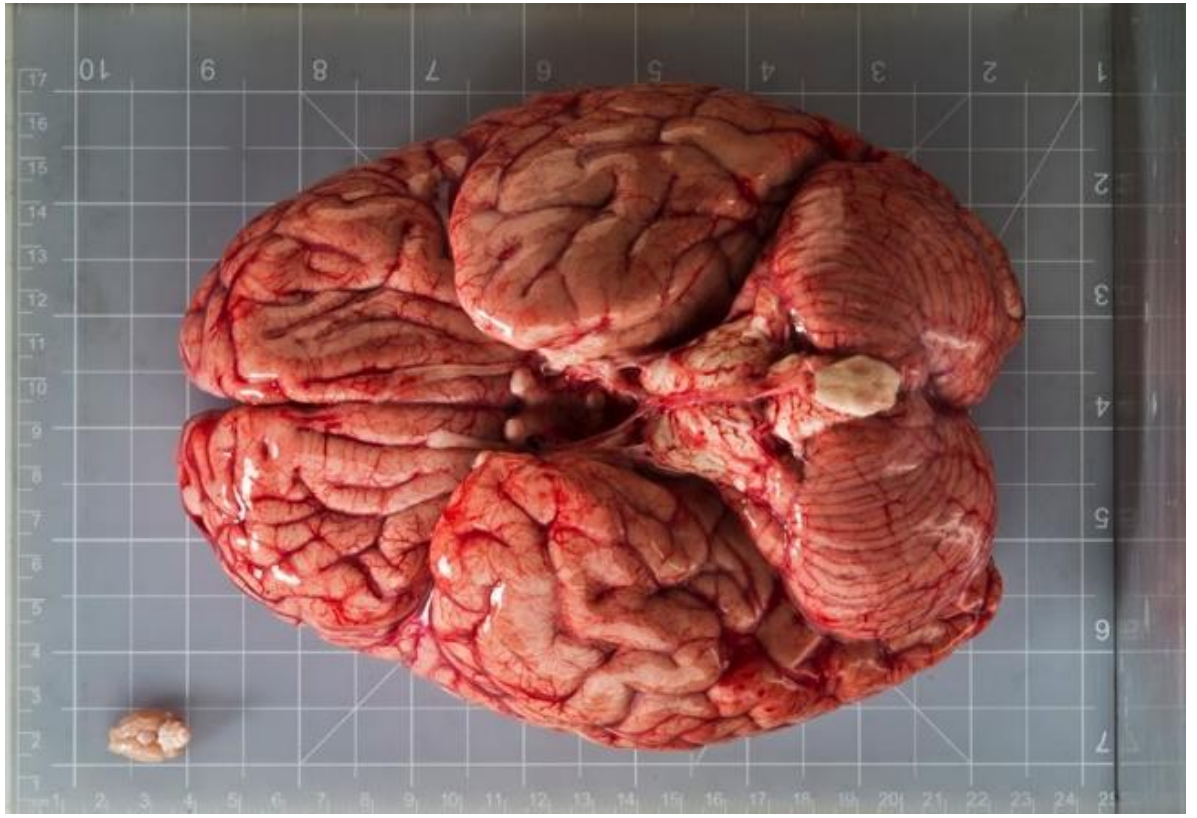


Andrew Ko

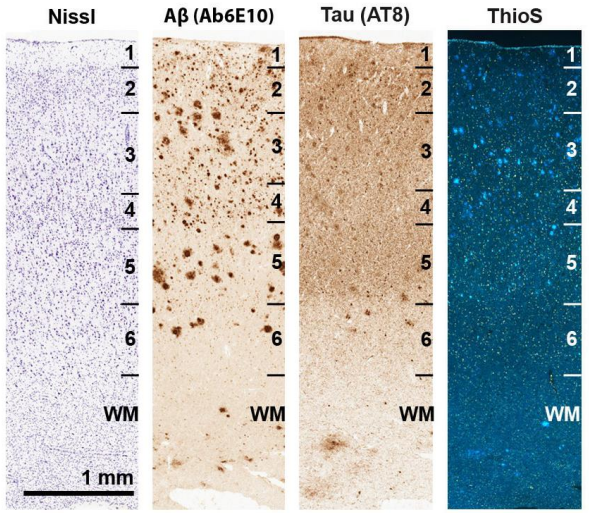
Translating advances in cellular-level analysis of the brain from model organisms to human brain, and to disease

Many cell types, many phenotypes





Brain regions, broad cell classes, markers of pathology

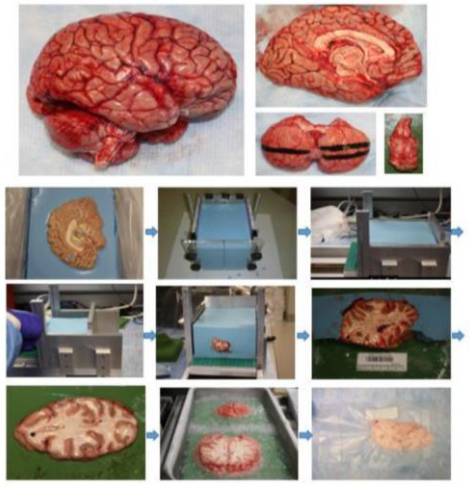


We should treat the brain like a complex cellular organ and understanding human brain dysfunction as cellular disease

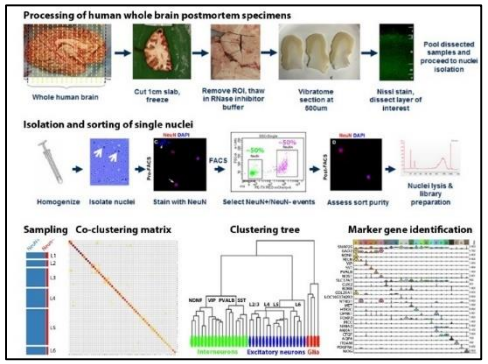
The advances of cellular analyses in model organisms are no longer inaccessible for studying human brain

Establishing the cellular and subcellular resolution tools of basic research to study the human brain

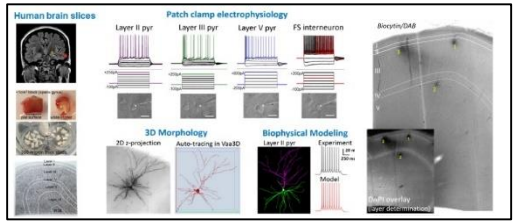
Optimized Human Tissue Preparation



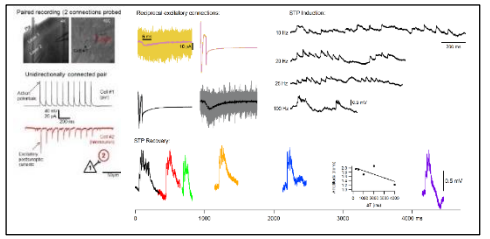
Human Single Nucleus Transcriptomics



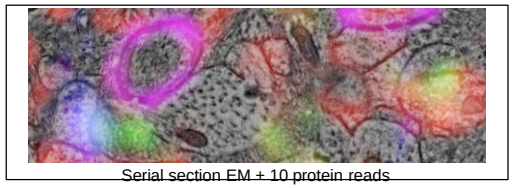
Human Slice Physiology and Morphology



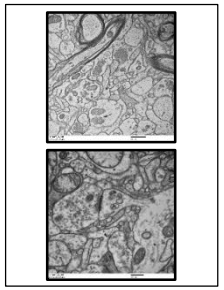
Human Synaptic Physiology



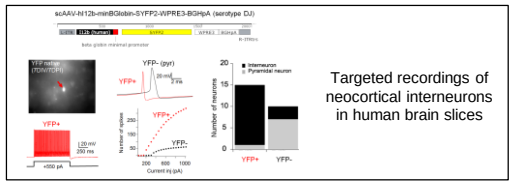
Human Array Tomography



Human large-scale Electron Microscopy

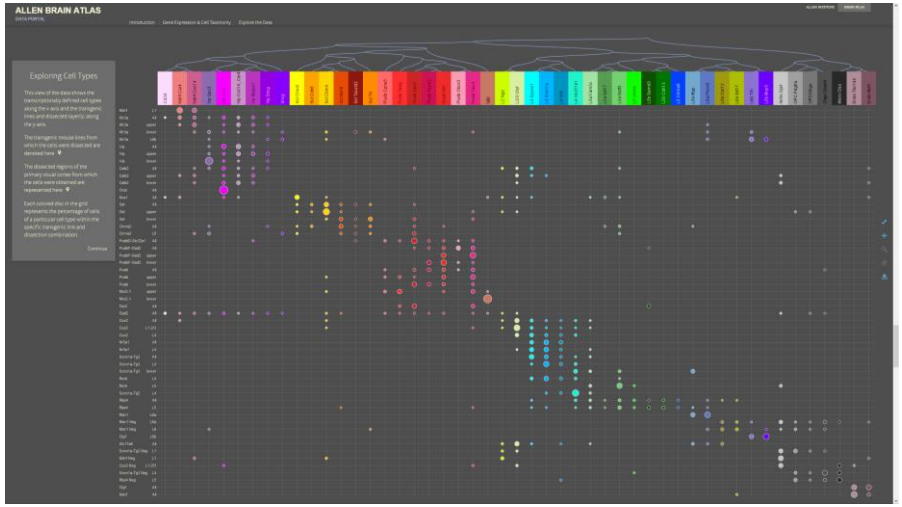


Human Viral Genetic Tools



A new era of cellular level analysis of brain driven by new technologies

Allen Cell Types Database



CellPress

Neuron

Perspective

The BRAIN Initiative Cell Census Consortium: Lessons Learned toward Generating a Comprehensive Brain Cell Atlas

Joseph R. Ecker,[1] Daniel H. Geschwind,[2] Arnold R. Kriegstein,[3] John Ngai,[4,*] Pavel Osten,[5] Damon Polioudakis,[2] Aviv Regev,[6] Nenad Sestan,[7] Ian R. Wickersham,[8] and Hongkui Zeng[9]
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https://doi.org/10.1016/j.neuron.2017.10.007

HUMAN CELL ATLAS

CSH Cold Spring Harbor Laboratory

bioRxiv beta
THE PREPRINT SERVER FOR BIOLOGY

New Results

The Human Cell Atlas

Aviv Regev, Sarah Teichmann, Eric S. Lander, Ido Amit, Christophe Benoist, Ewan Birney, Bernd Bodenmiller, Peter Campbell, Piero Carninci, Menna Clatworthy, Hans Clevers, Bart Deplancke, Ian Dunham, James Eberwine, Roland Eils, Wolfgang Enard, Andrew Farmer, Lars Fugger, Berthold Gottgens, Nir Hacohen, Muzlifah Haniffa, Martin Hemberg, Seung K. Kim, Paul Klenerman, Arnold Kriegstein, Ed Lein, Sten Linnarsson, Joakim Lundeberg, Partha Majumder, John Marioni, Miriam Merad, Musa Mhlanga, Martijn Nawijn, Mihai Netea, Garry Nolan, Dana Pe'er, Anthony Philipakis, Chris P. Ponting, Stephen R. Quake, Wolf Reik, Orit Rozenblatt-Rosen, Joshua R. Sanes, Rahul Satija, Ton Shumacher, Alex K. Shalek, Ehud Shapiro, Padmanee Sharma, Jay Shin, Oliver Stegle, Michael Stratton, Michael J. T. Stubbington, Alexander van Oudenaarden, Allon Wagner, Fiona M. Watt, Jonathan S. Weissman, Barbara Wold, Ramnik J. Xavier, Nir Yosef, Human Cell Atlas Meeting Participants
doi: https://doi.org/10.1101/121202

Changing sociology of neuroscience research: Consortium efforts to expand and accelerate cellular-level brain analyses

NIH BRAIN Initiative Cell Census Network

Data Center

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Associate Professor
Penn Image Computing and Science Laboratory

Mike Hawrylycz, PhD
Allen Institute for Brain Science

Maryann E. Martone, PhD
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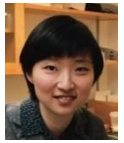
Lydia Ng, PhD
Allen Institute for Brain Science

Anthony Philippakis, M.D., Ph.D.
Chief Data Officer, Broad Institute of MIT and Harvard.

Mouse

Hongkui Zeng
AIBS

Lior Pachter
Caltech



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Human

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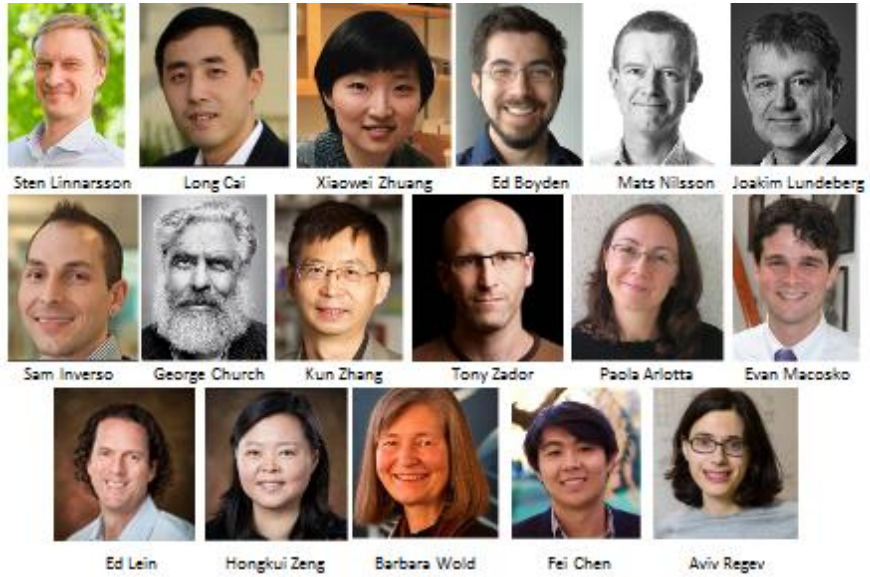
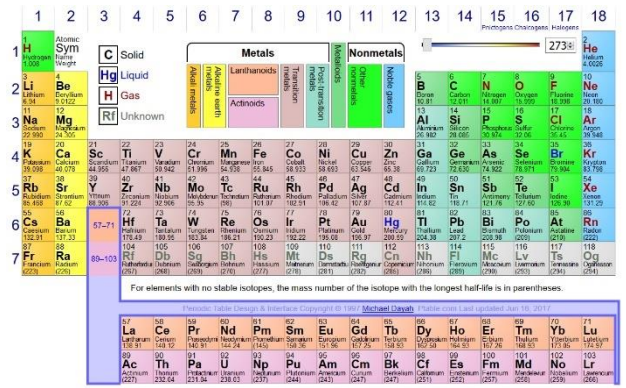
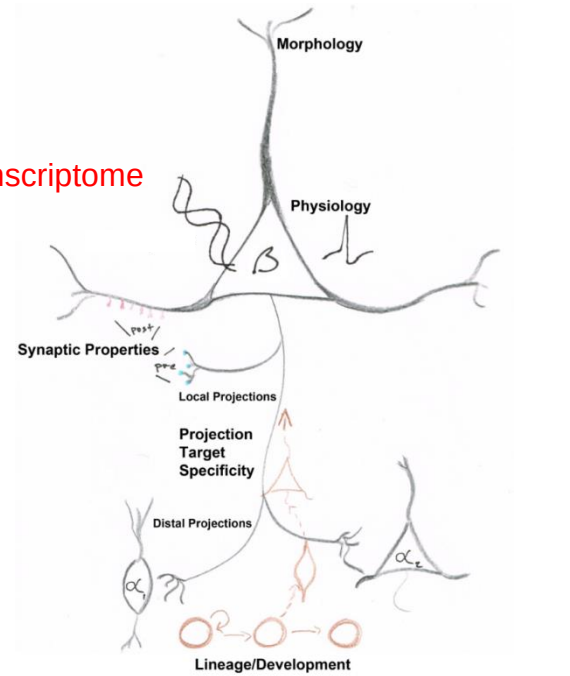
SpaceTx CZI/Human Cell Atlas

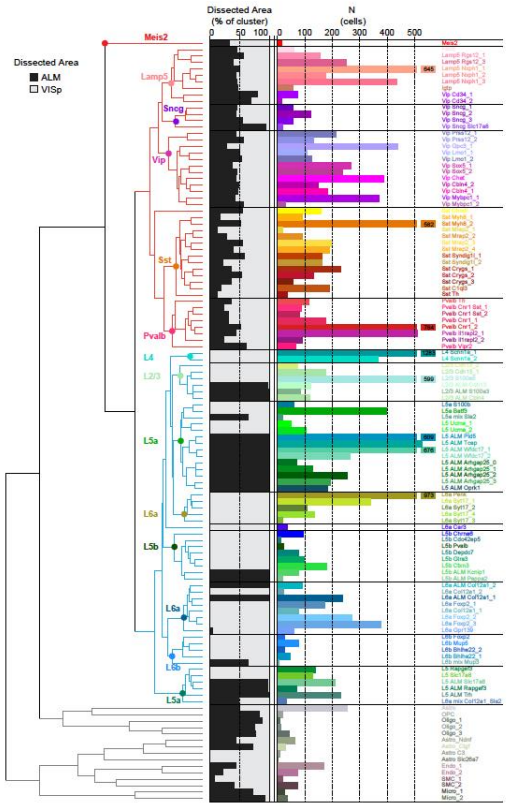


A genetically-based paradigm for classifying cell types in the brain bounds the problem of cellular diversity

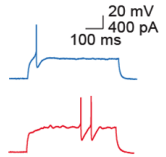




Transcriptome

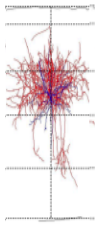


Physiology



Connectivity, function

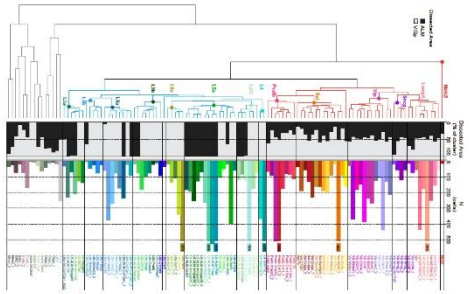
Anatomy



Gene expression in each cluster is also highly predictive of functional properties

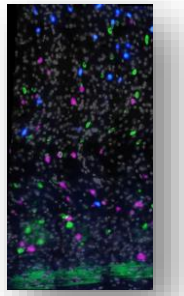
A transcriptomic classification presents a generalizable and pragmatic strategy to map and manipulate cell types in any species

Unbiased transcriptome-based cell type classification in different brain regions



Single cell transcriptomics

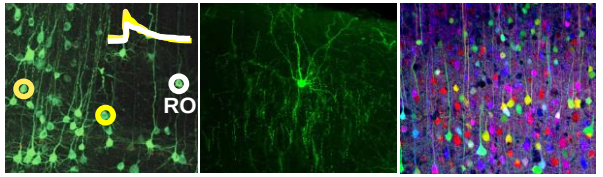
Spatial mapping in tissue sections



Spatial transcriptomics

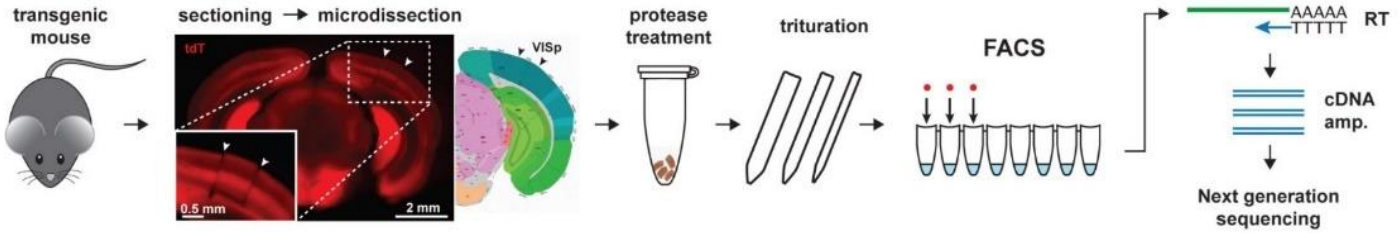
Analyze features of transcriptomic types

Multimodal analysis
Post-hoc spatial transcriptomics
Specific genetic tools



Patch-seq
smFISH
Cre lines, viruses

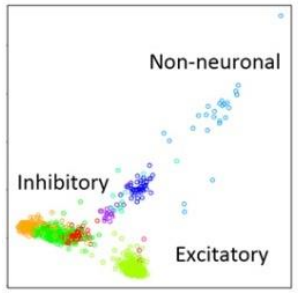
Single cell transcriptomics provides an unbiased molecular classification of cortical cell types



Transcriptomic data from 1679 whole cells

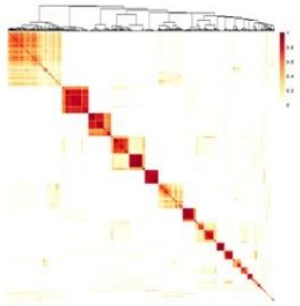
Unsupervised clustering

Iterative clustering



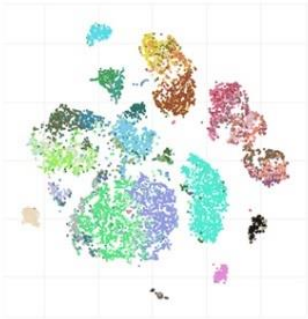
100 bootstrap iterations

Co-clustering robustness



1. Subsample 80% of nuclei
2. Repeat iterative clustering
3. Calculate co-clustering across iterations

Final clusters

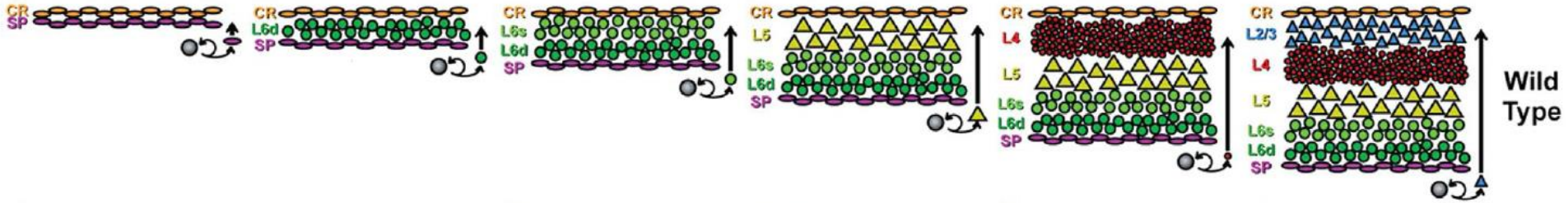


1. Hierarchically cluster co-clustering matrix
2. Maximize cluster cohesion and separation
3. Merge clusters lacking distinct markers
4. t-SNE visualization

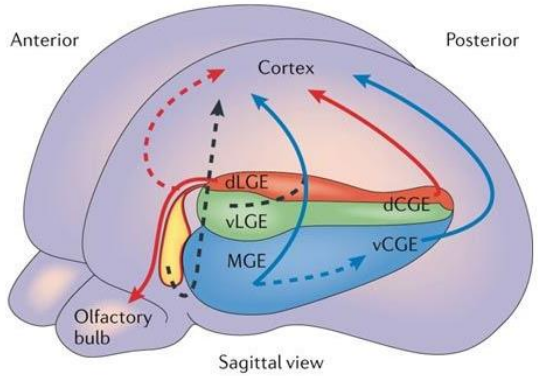
Tasic, Menon…Zeng (2015) Nature Neuroscience

Developmental biology helps interpret transcriptomic cellular diversity

Local generation of most excitatory neurons

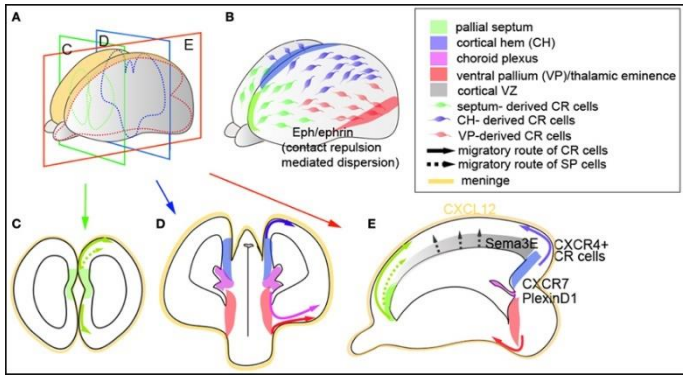


Boyle…Lein, JCN (2011)



Wonders and Anderson, 2006

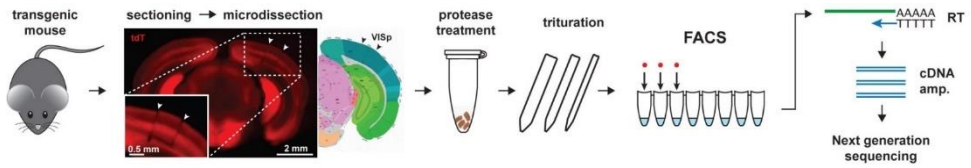
Migration of GABAergic interneurons from ganglionic eminences



Toma and Hamashima, 2015

Migration of Cajal Retzius cells and subplate cells (future layer 6b cells) from extracortical zones

Single cell transcriptomics provides an unbiased molecular classification of cortical cell types



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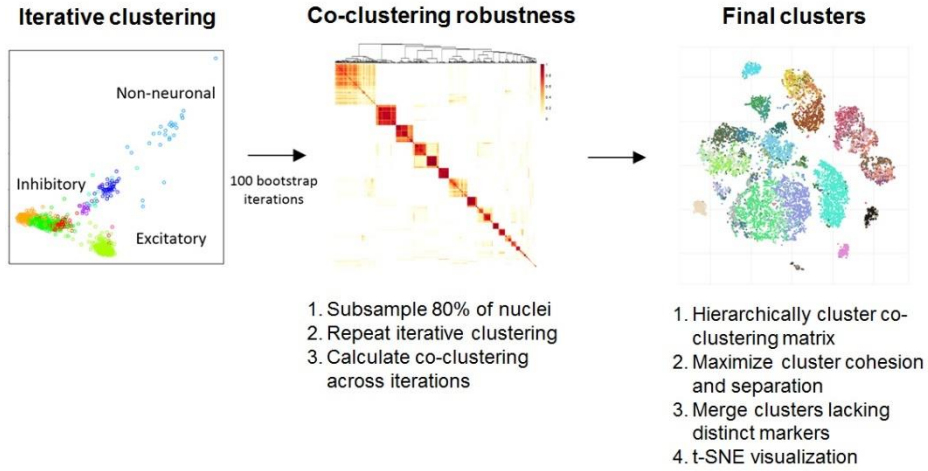
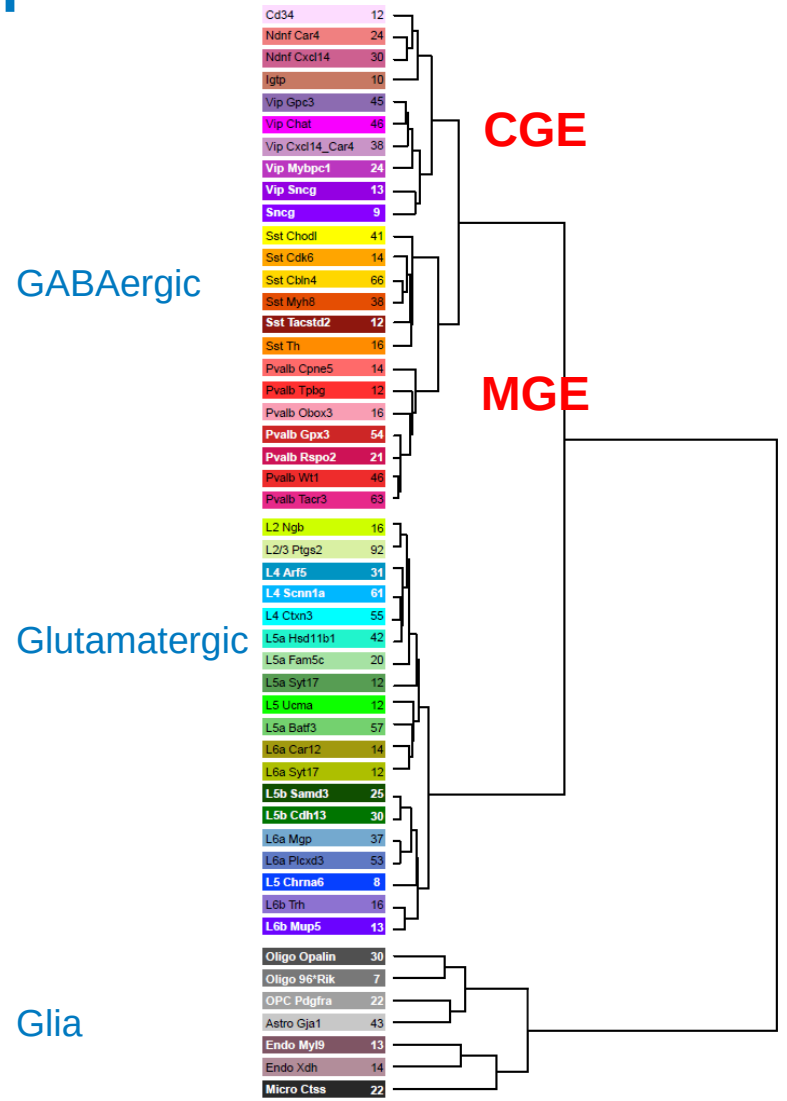


49 transcriptomic clusters

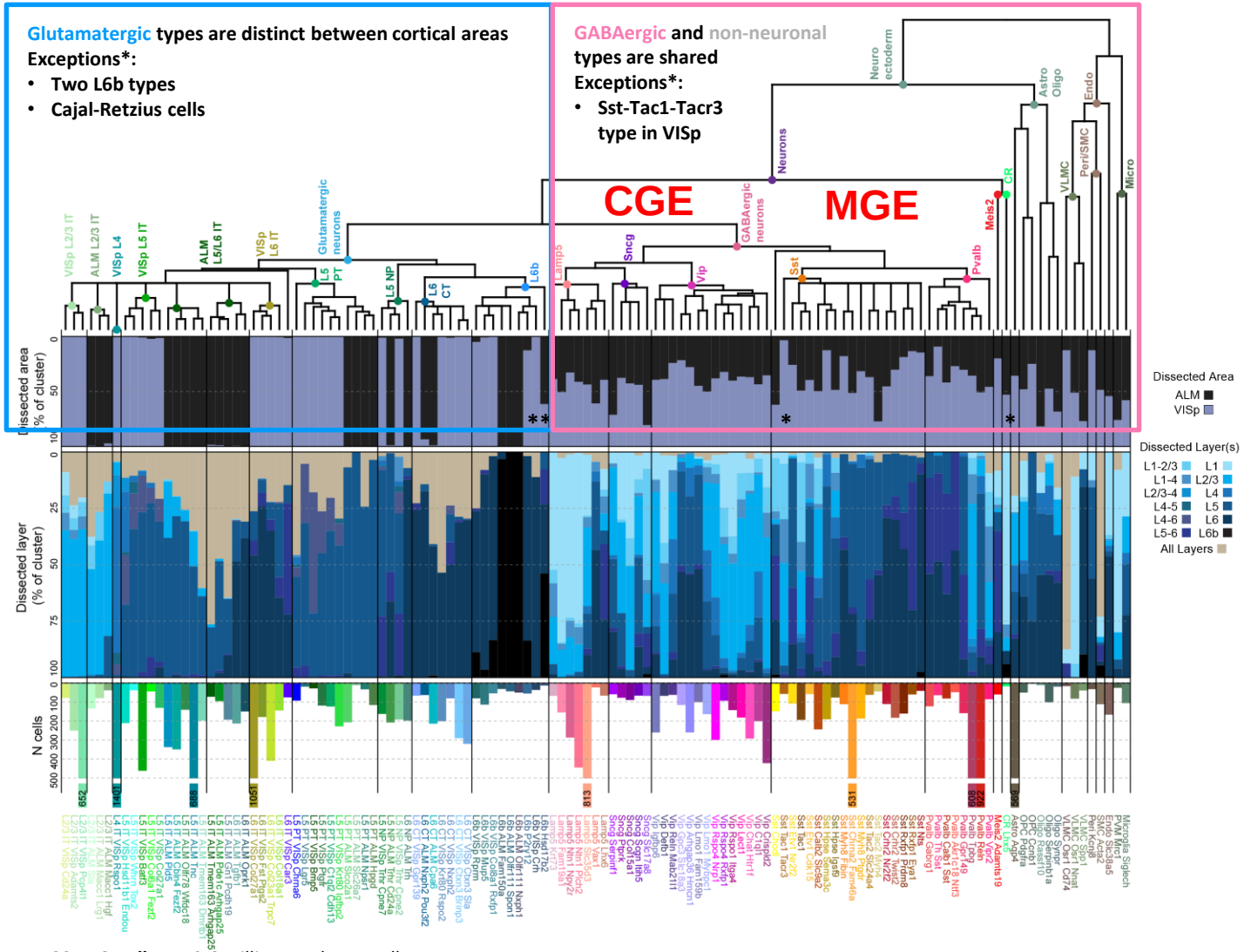


Tasic, Menon…Zeng (2015) Nature Neuroscience

Near-saturation coverage taxonomy of mouse cortex with scRNA-seq

10x # of cells, only 2x # of cell types

~100 cell types per cortical region



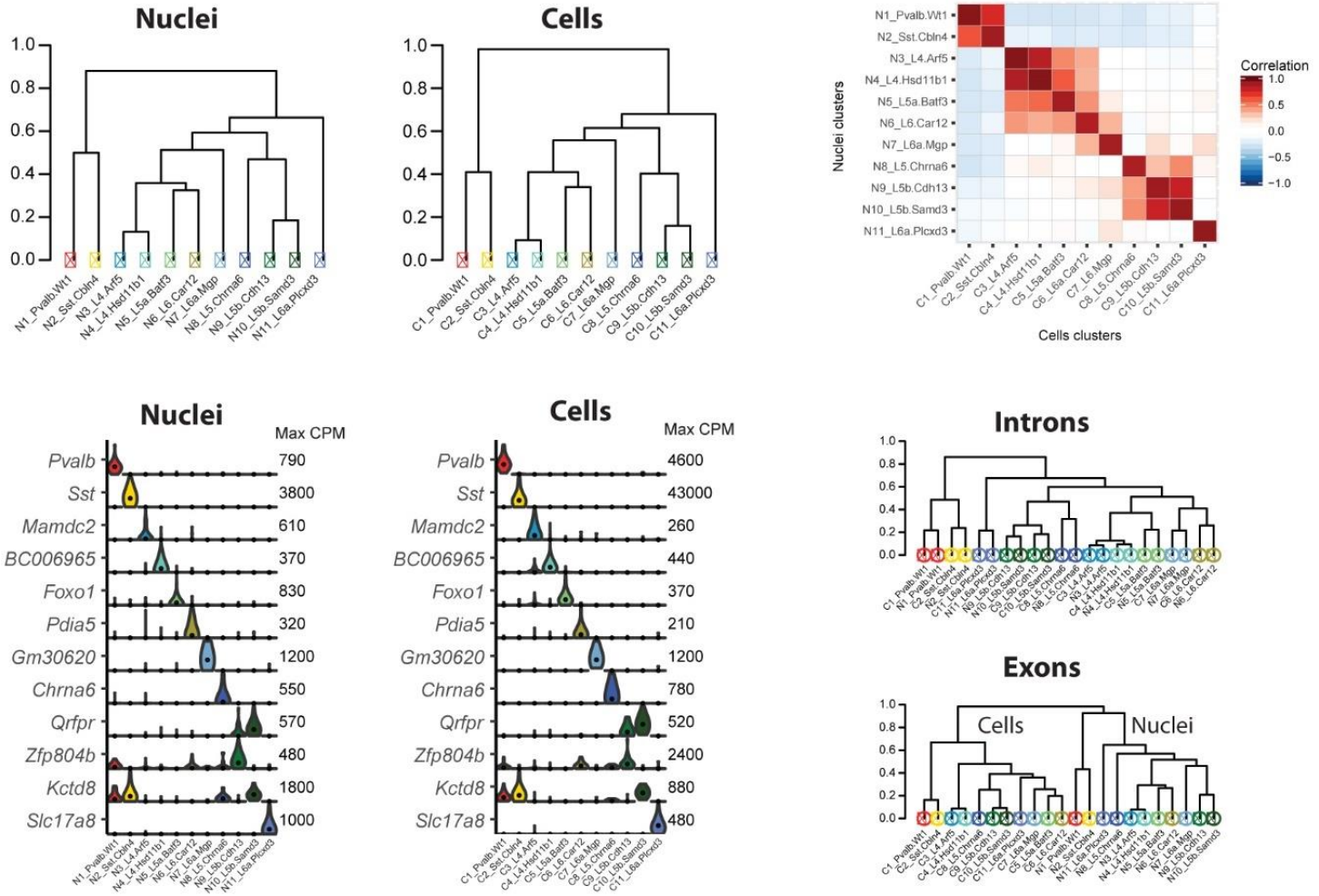
22,146 cells at ~2.6 million reads per cell
13,839, VISp
8,307, ALM

Primary visual cortex (V1) and Anterior lateral motor cortex (ALM)

Tasic, Yao, Smith, Graybuck…Koch, Zeng (BioRxiv)

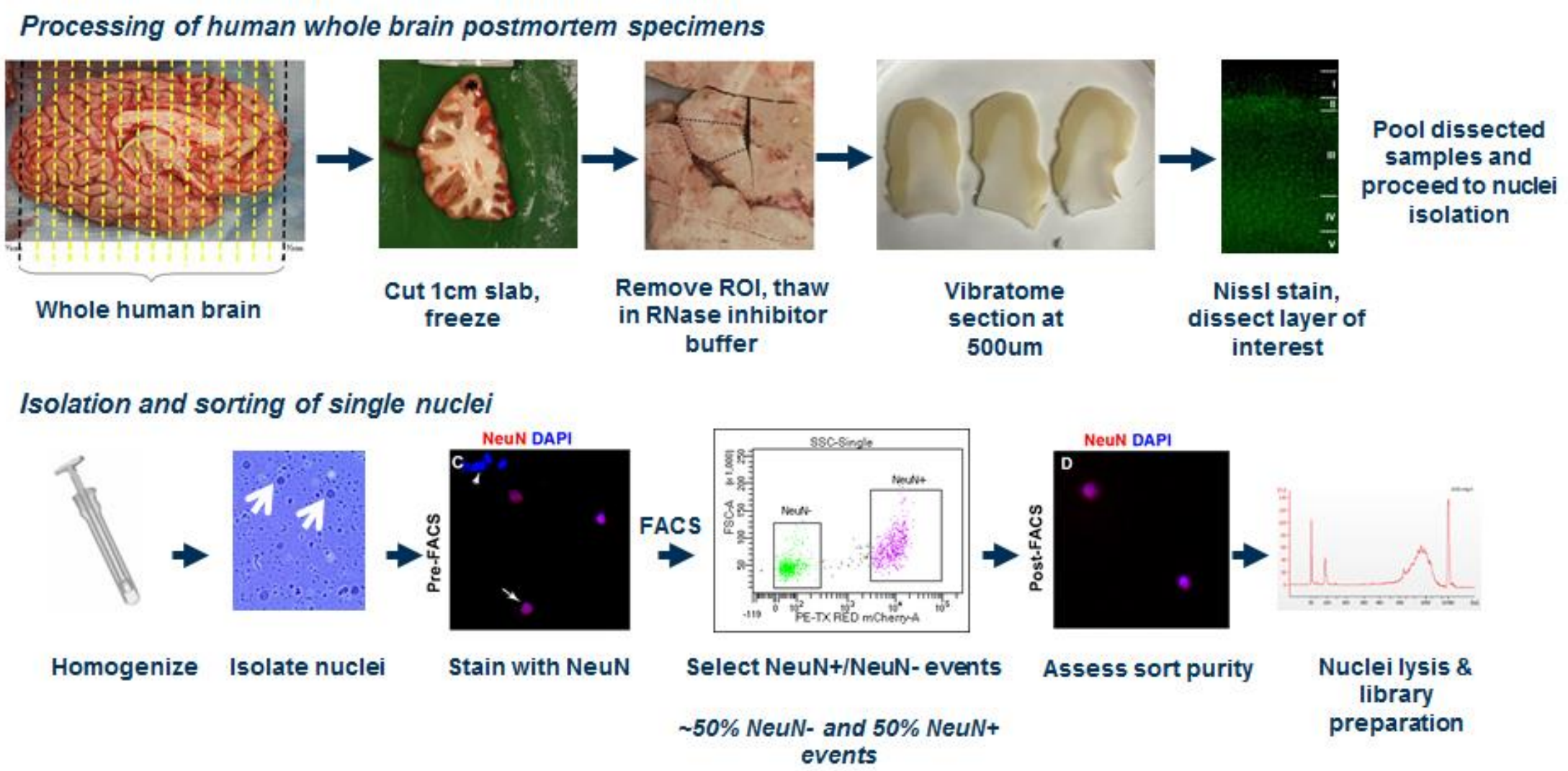
Similar results with single nucleus versus single cell RNA-seq

Mouse V1 layer 5 neurons, SMARTer v4 methodology



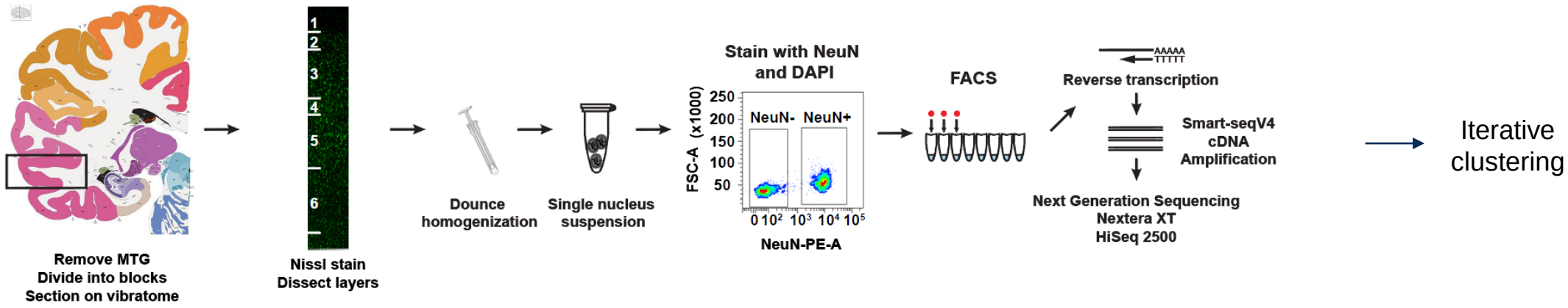
Trygve Bakken, Jeremy Miller, Rebecca Hodge, Bosiljka Tasic (BioRxiv)

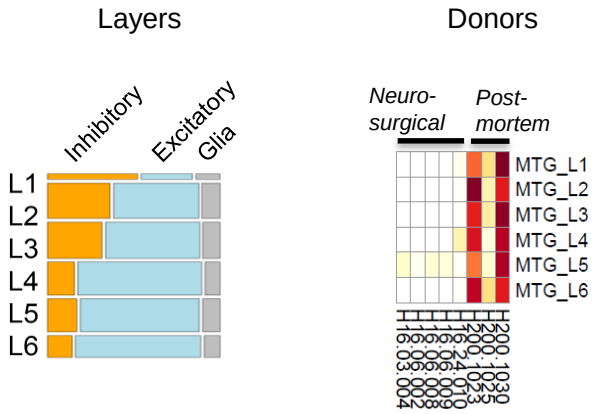
Human nuclei with intact RNA for RNA-seq analysis can be easily isolated from high quality frozen postmortem human brain specimens



Rebecca Hodge, Kim Smith

Building a foundational high resolution human cortical cell type taxonomy



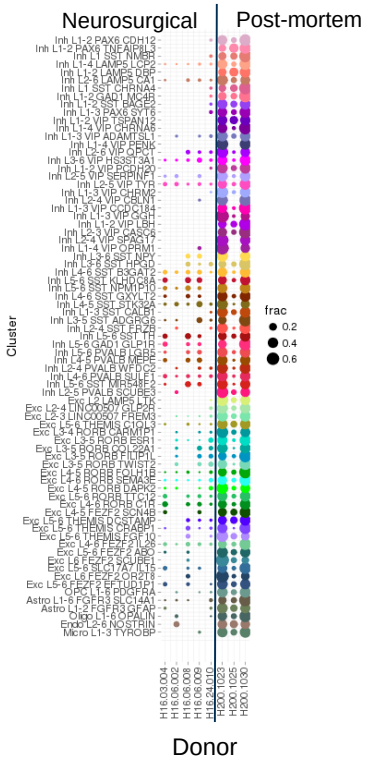


- Targeting types >0.5% frequency
- 15,928 single nuclei from middle temporal gyrus (MTG)
- Majority from 2 post-mortem donors
- **Included some neurosurgically-derived nuclei for comparison to postmortem**
- FAC-sorted for 90% neurons (NeuN+) and 10% glia (NeuN-)
- **2.5M reads, 8-10k genes detected per nucleus**

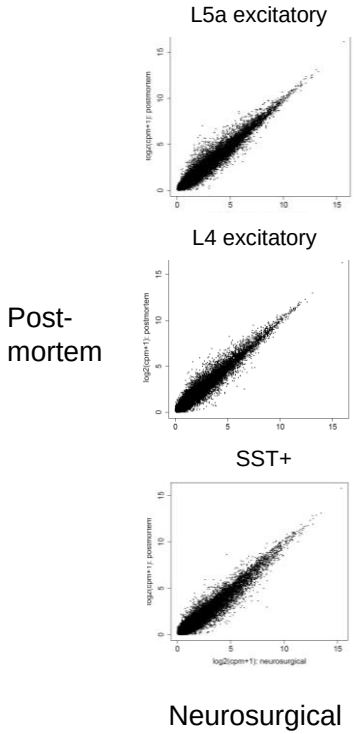
Similar results with postmortem and acute surgical cases

Nuclei from postmortem cortex and acute neurosurgical specimens cluster together, but there is a small but consistent expression signature of tissue source

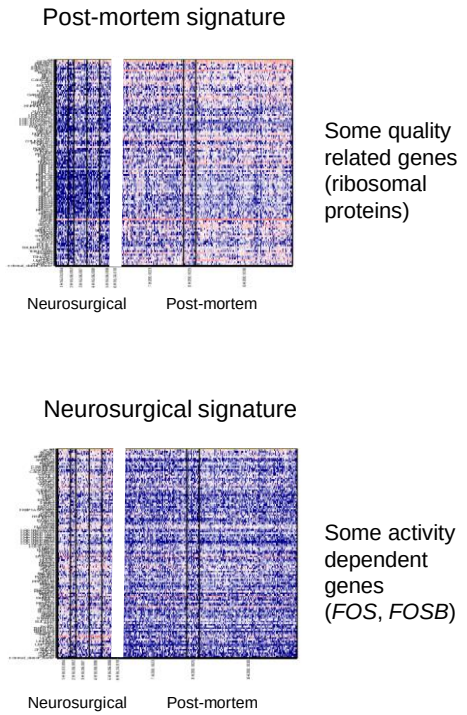
Co-clustering of nuclei from different tissue sources



Highly correlated expression within clusters



Weak expression signature of tissue source



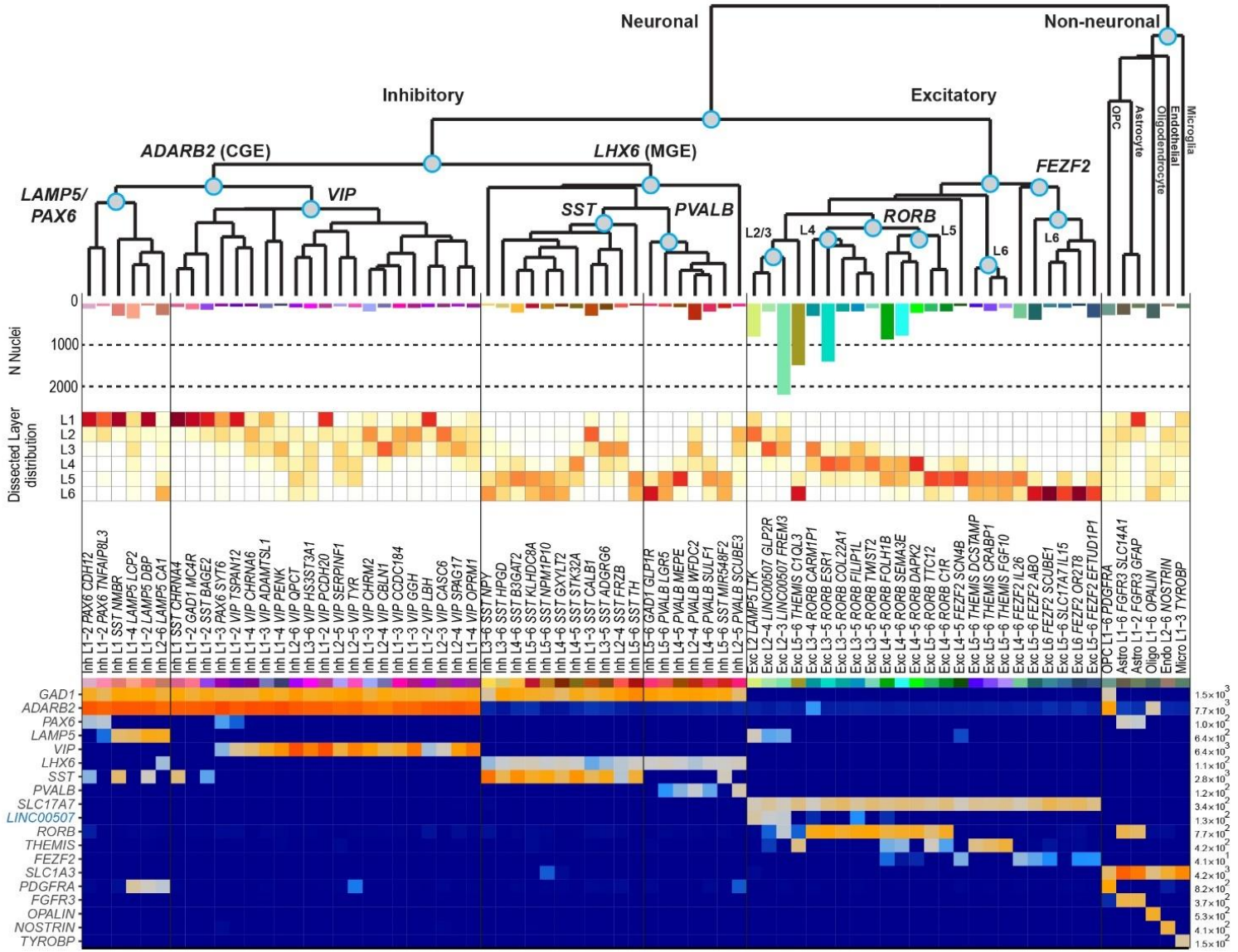
High resolution taxonomy of cell types in human middle temporal gyrus (MTG)

45 Inhibitory types

24 Excitatory types

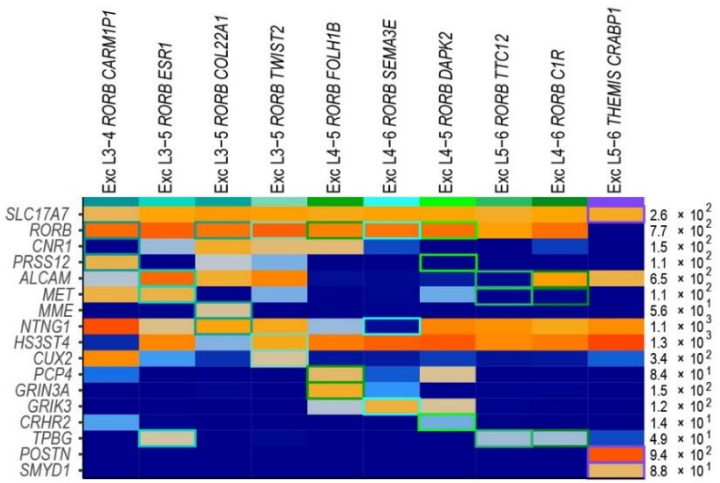
6 non-neuronal types

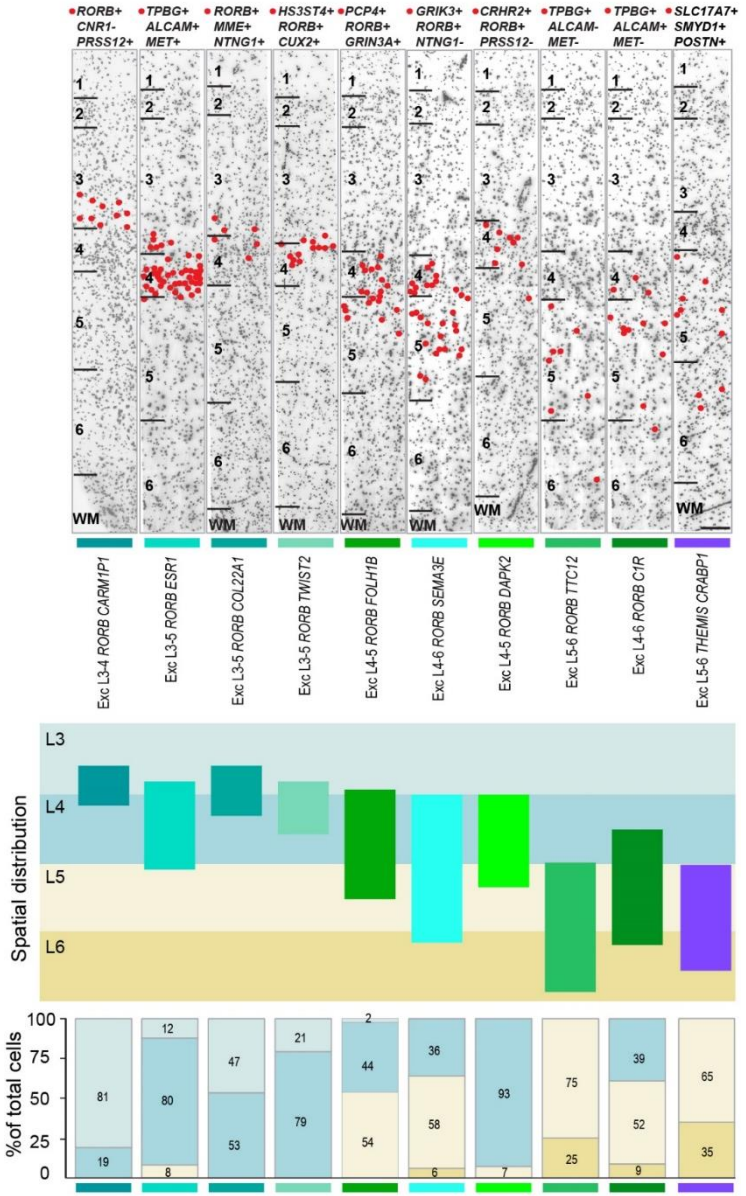
Most cell types are rare (especially GABAergic neurons)



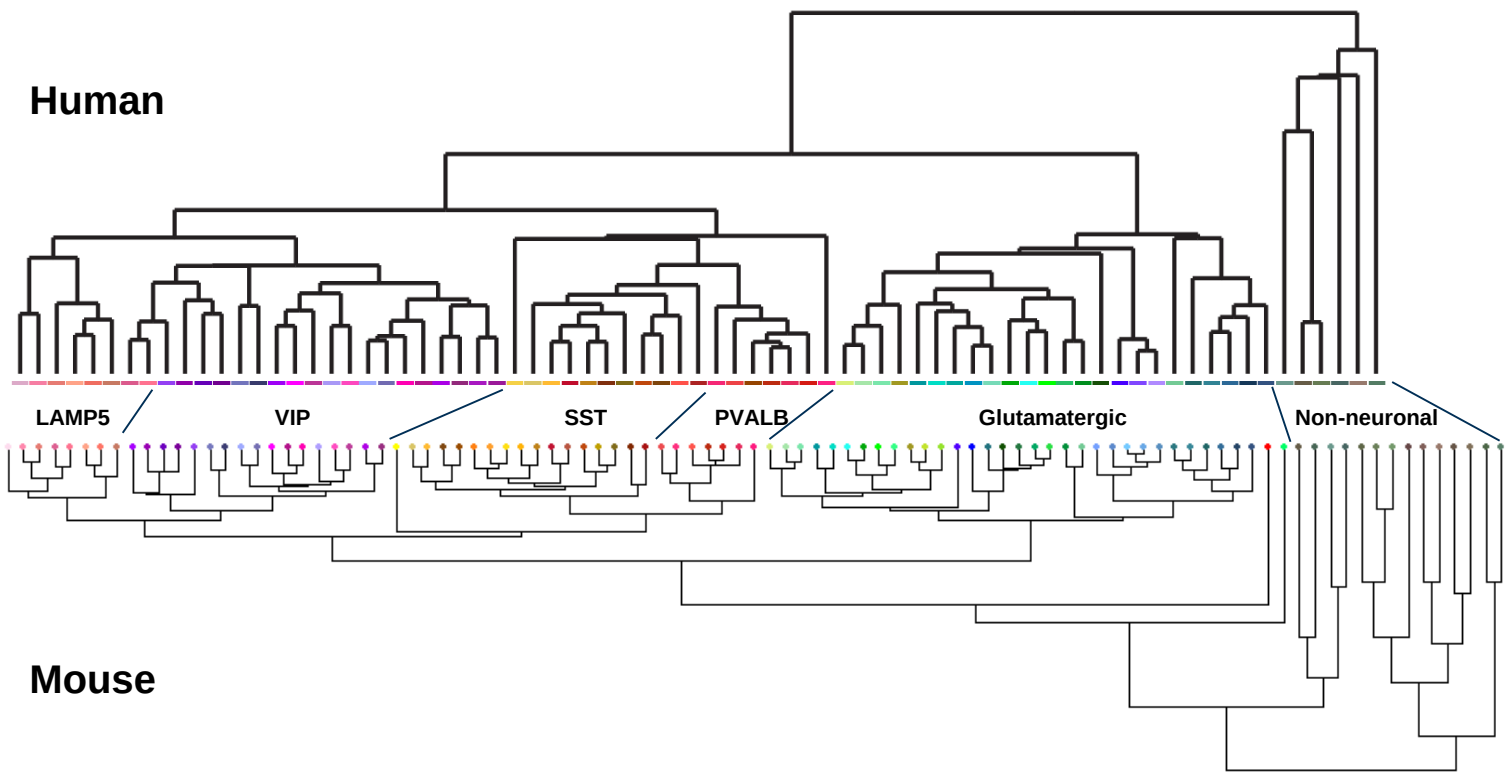
Hodge, Bakken, Miller et al. (BioRxiv)

Check your assumptions: Many excitatory neuron types are not strictly laminar





Broad conservation of human and mouse cortical taxonomies

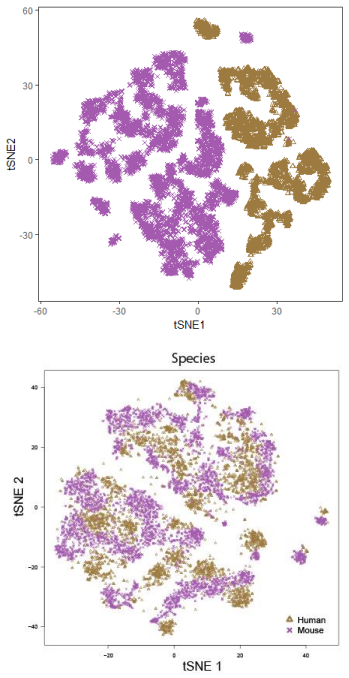


Human and mouse cell types align based on shared co-expression

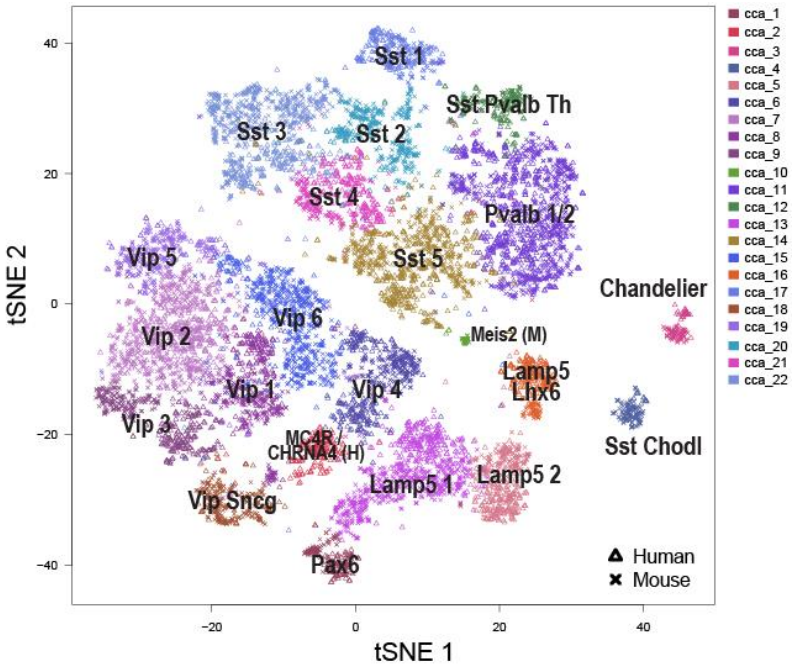
Human and mouse RNA-seq data aligned using canonical correlation analysis (CCA; Satija)

PCA

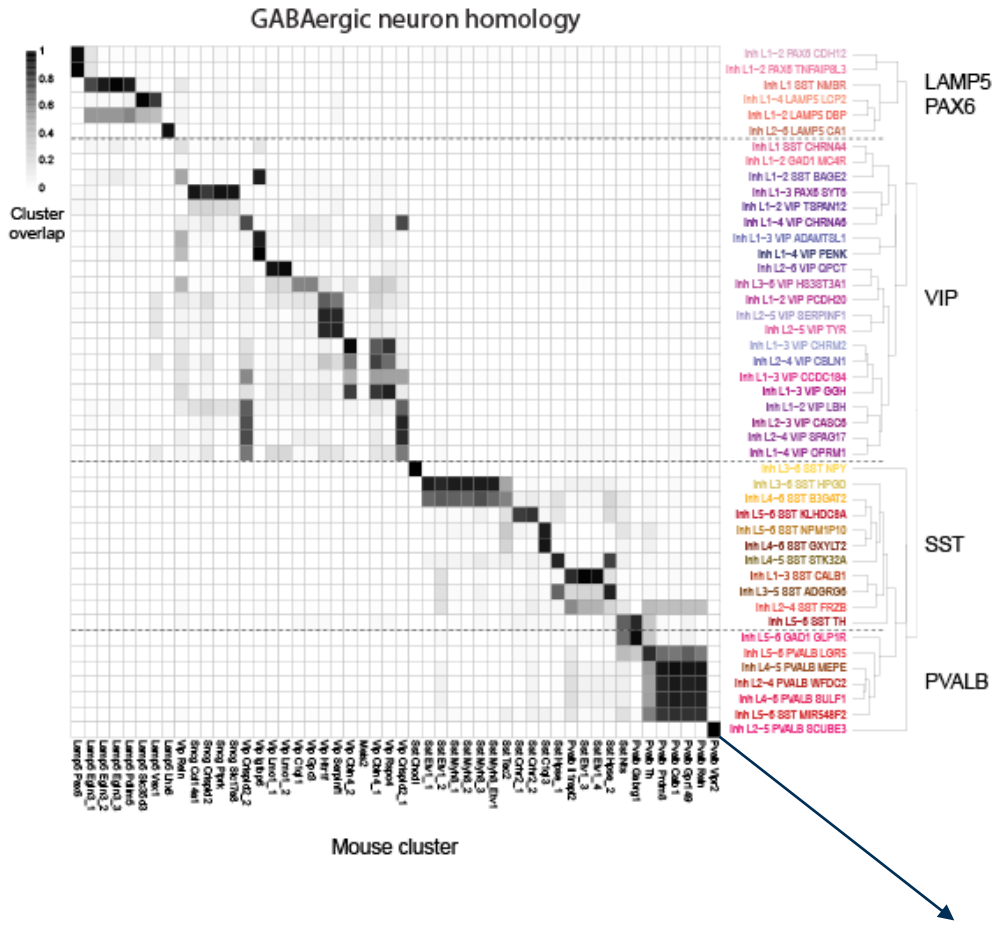
CCA



CCA clusters correspond to GABAergic neuron classes and types



GABAergic neurons align quite well between species



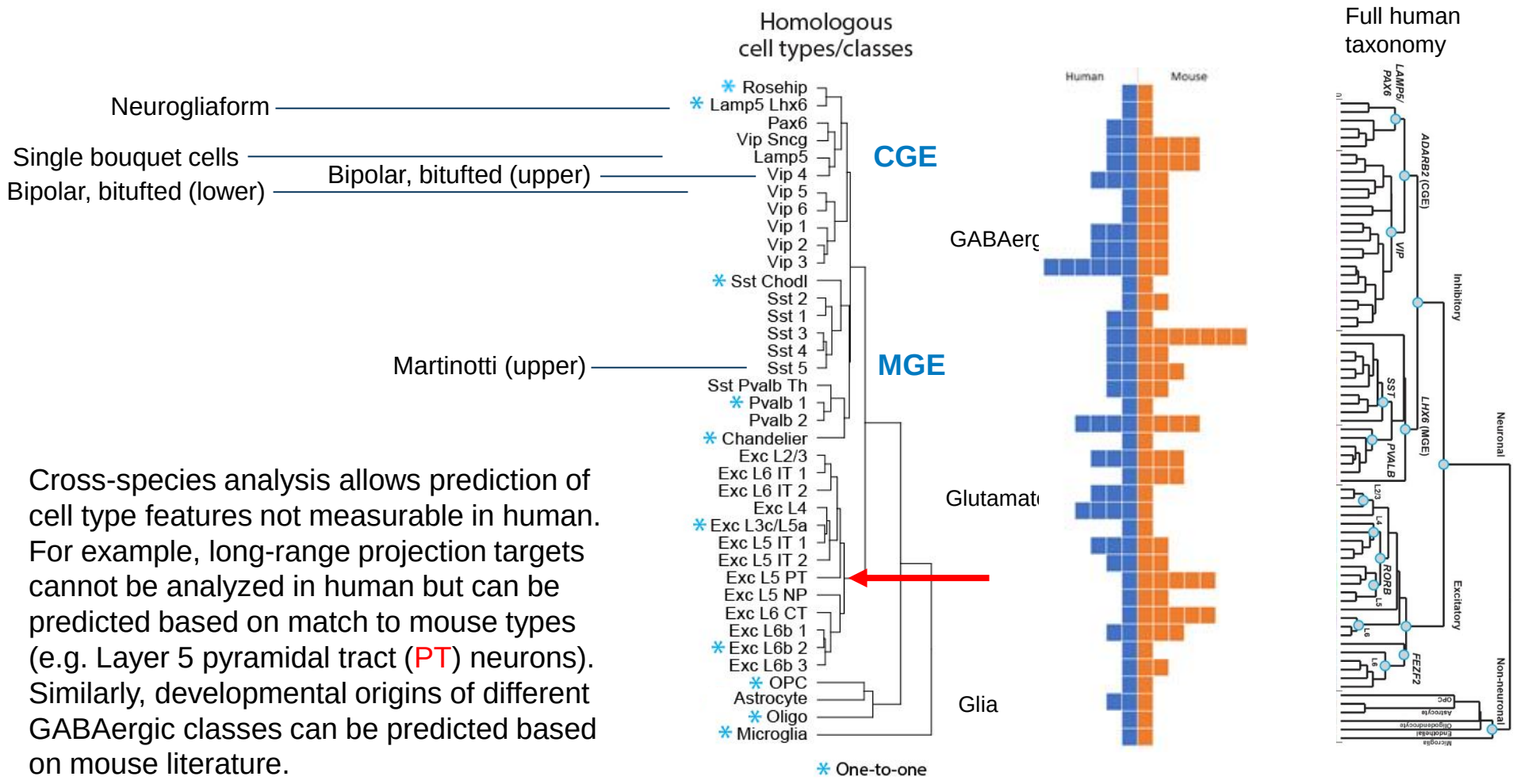
Human GABAergic diversity is likely undersampled due to inability to select for rare populations

Chandelier cell

Consensus or canonical mouse/human V1/MTG taxonomy

38 homologous cell types / classes

* 10 one-to-one homologous types



Cross-species analysis allows prediction of cell type features not measurable in human. For example, long-range projection targets cannot be analyzed in human but can be predicted based on match to mouse types (e.g. Layer 5 pyramidal tract (PT) neurons). Similarly, developmental origins of different GABAergic classes can be predicted based on mouse literature.

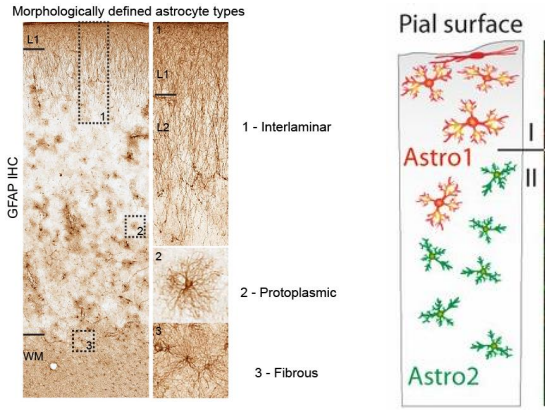
Many cellular differences between mouse and human

Different proportions of cell types

Differential gene regulation in conserved cell types

High phenotypic variation in conserved cell types

Dramatic differences in astrocyte features



Specialized cell types

nature neuroscience
ARTICLES
https://doi.org/10.1038/s41593-018-0205-2

Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type

Eszter Boldog[1,8], Trygve E. Bakken[2,8], Rebecca D. Hodge[2,8], Mark Novotny[3], Brian D. Aevermann[3], Judith Baka[1], Sándor Bordé[1], Jennie L. Close[2], Francisco Diez-Fuertes[3], Song-Lin Ding[2], Nóra Faragó[1], Ágnes K. Kocsis[1], Balázs Kovács[1], Zoe Maltzer[2], Jamison M. McCorrison[3], Jeremy A. Miller[2], Gábor Molnár[1], Gáspár Oláh[1], Attila Ozsvár[1], Márton Rózsa[1], Soraya I. Shehata[2], Kimberly A. Smith[2], Susan M. Sunkin[2], Danny N. Tran[3], Pratap Venepally[3], Abby Wall[2], László G. Puskás[4], Pál Barzó[5], Frank J. Steemers[6], Nicholas J. Schork[3], Richard H. Scheuermann[3,7], Roger S. Lasken[3], Ed S. Lein[2*] and Gábor Tamás[1*]

Evolutionary scaling of the human brain compared to mouse

The isotopic fractionator method

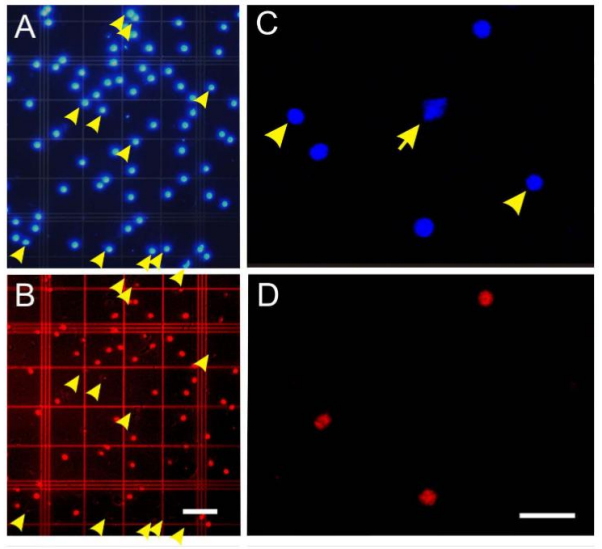
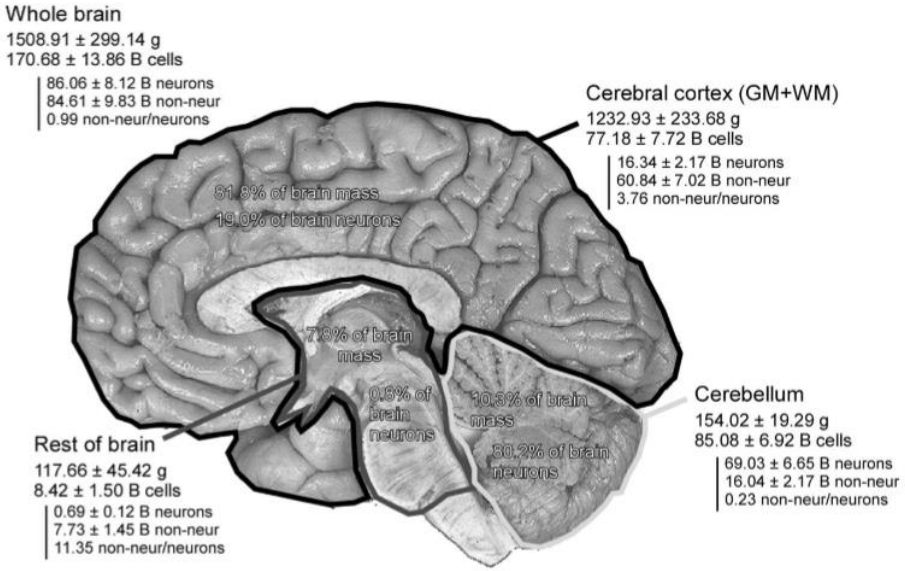


Figure 1.
Aspect of the nuclei in the hemocytometer. A,B: Typical low-magnification fluorescent micrographs of the same field of cerebellar cell nuclei in suspension stained with DAPI (A) and for NeuN immunoreactivity (B). The arrowheads indicate nuclei that are NeuN negative and therefore identified as nonneuronal nuclei. All other nuclei are NeuN positive and therefore identified as neuronal. Note that nuclei are intact and well scattered. C,D: High-magnification confocal image of NeuN-negative (arrowheads; arrow, nonneuronal nucleus undergoing cell division) and NeuN-labeled cerebellar cell nuclei. The clear, debris-free preparation of free cell nuclei makes the anti-NeuN immunoreactivity easy to distinguish from the virtually nonnexistent background. Scale bars = 40 μm in B (applies to A,B); 20 μm in D (applies to C,D).



Azevedo…Herculano-Houzel (2009)

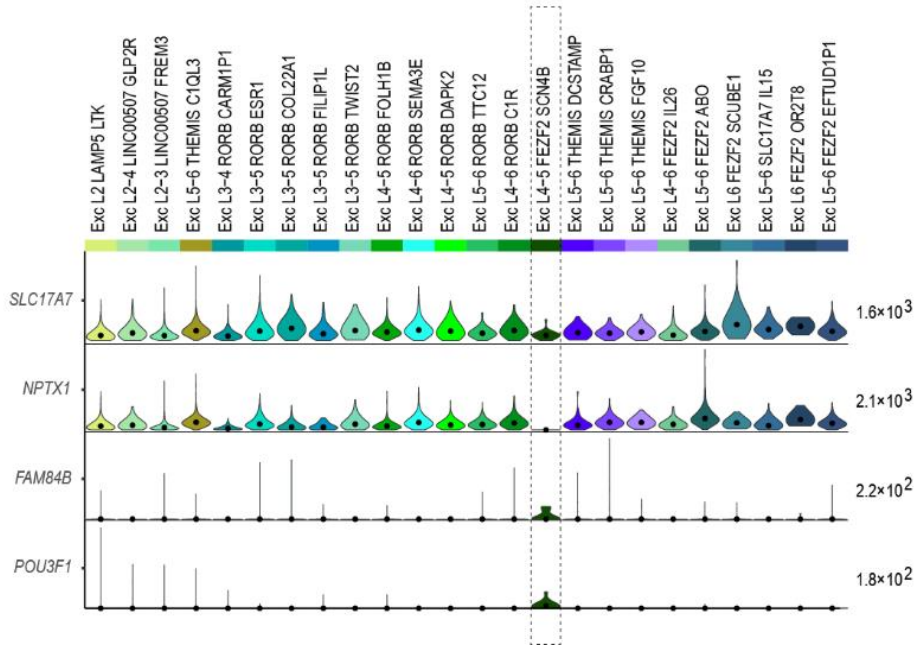
Neocortical cell number is expanded 20-30-fold compared to subcortical targets

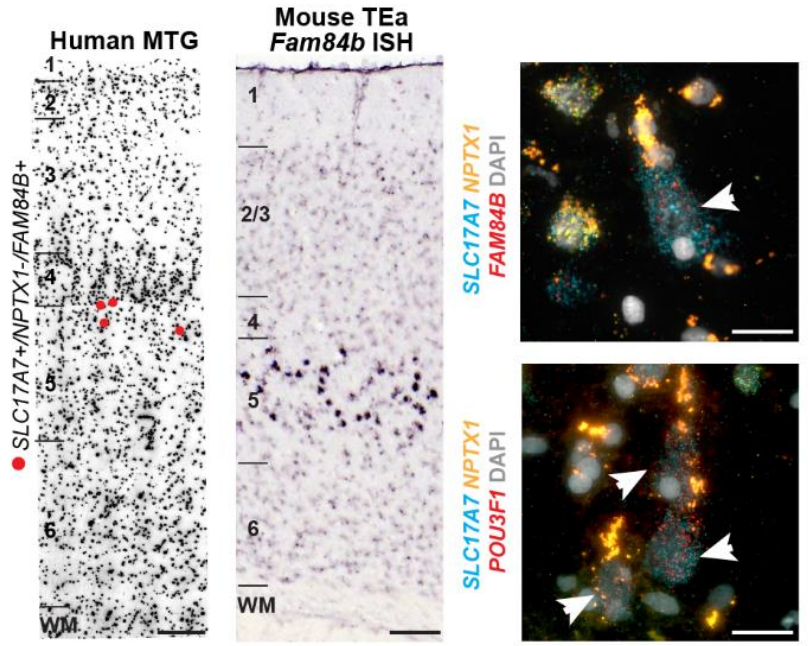
Number of neurons

	Human	Mouse	Human fold-expansion
Cortex	16,340,000,000	13,690,000	1194
Sub-cortex	690,000,000	11,960,000	58
Spinal cord	196,100,000	4,400,000	45
Corticospinal	2,200,000	65,000	34

Human	Mouse
Azevedo et al. 2009	Herculano-Houzel et al. 2006
Azevedo et al. 2009	Herculano-Houzel et al. 2006
Bahney and Bartheld 2018	Bjugn 1993
Lassek and Rasmussen 1940	Lassek and Rasmussen 1940

Layer 5 Pyramidal Tract (PT) neurons are >20x less abundant in human

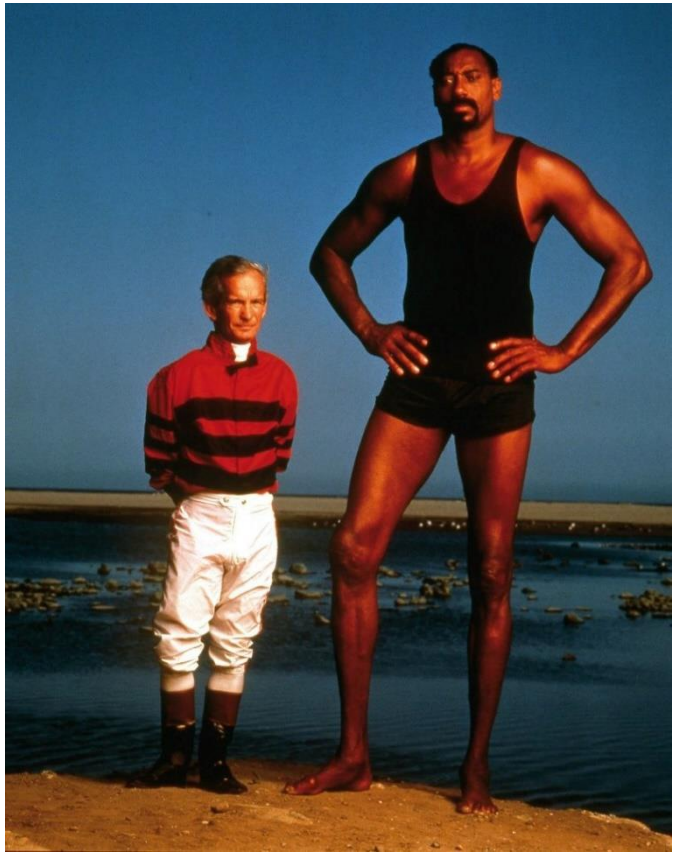




Subcortically projecting neuron numbers scale with the size of projection targets, not cortex

For layer 5 PT neurons, the solution to a mismatch between source and target seems to have been to sparsify the population across the whole cortex

Gene expression fold-differences: What should we consider significant?

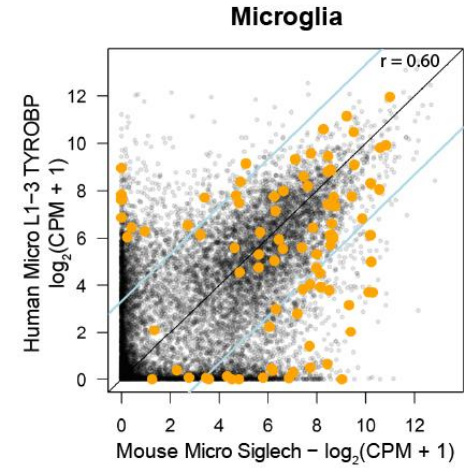


1.4x difference
(Credit to Rob Williams)

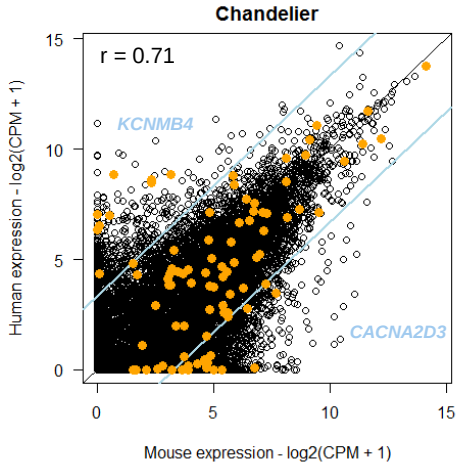
4.9x difference
(Credit to Guinness Book)

We chose 10-fold to be a major difference

Species-specific expression within homologous cell types



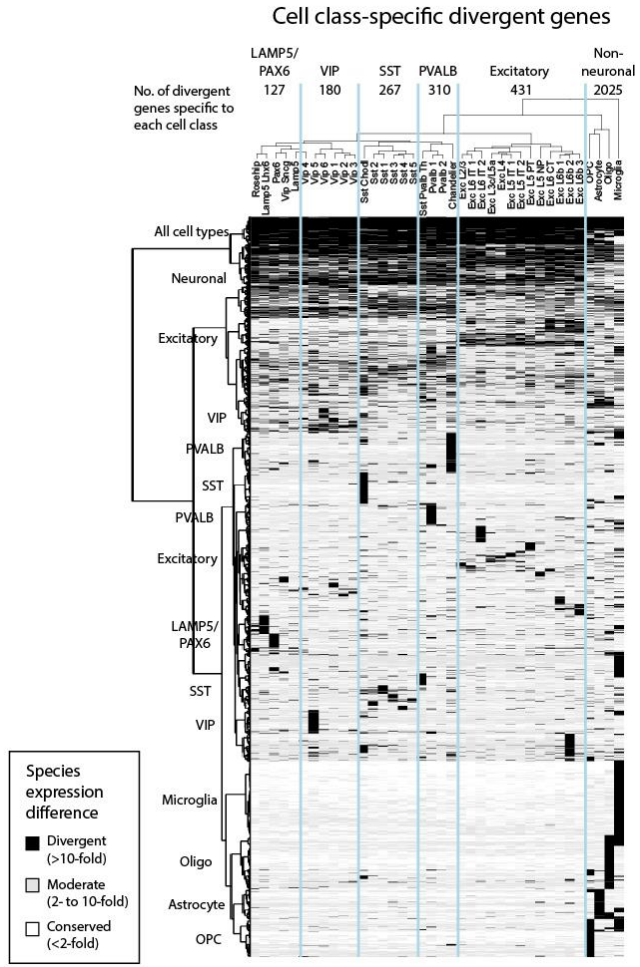
20% of genes have >10-fold expression difference including cell-type specific markers



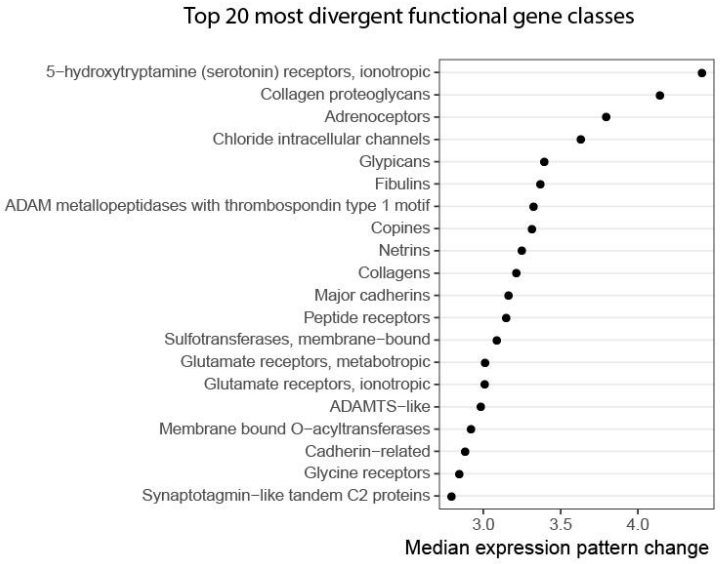
12% of genes have >10-fold expression difference including cell-type specific markers

57% of all genes expressed showed highly divergent expression in at least one homologous cell class/type

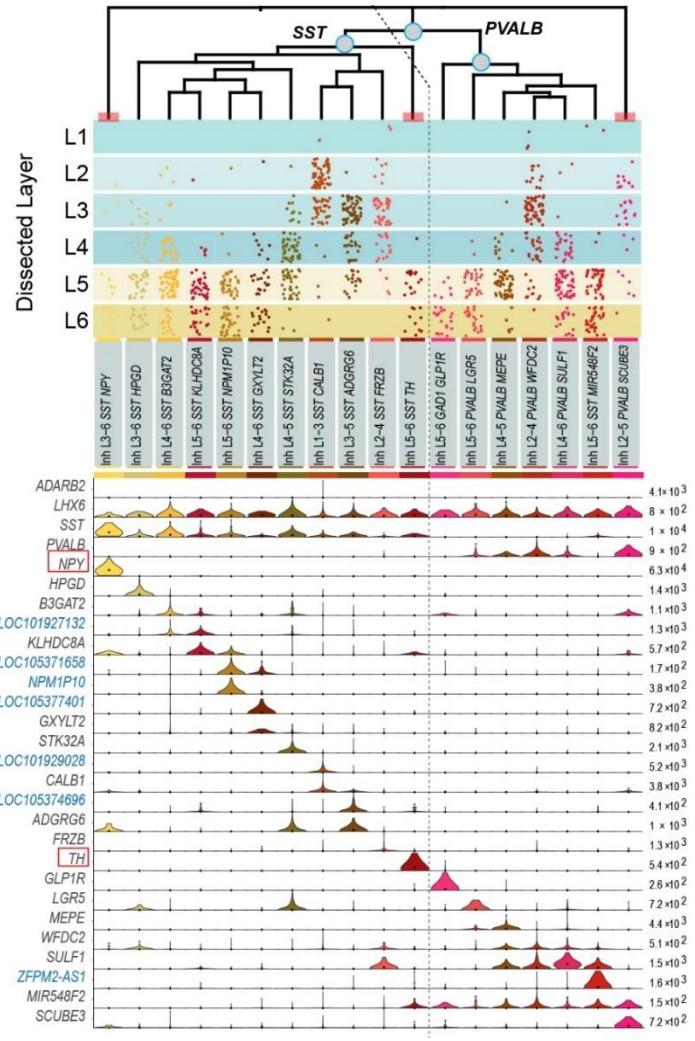
Non-neuronal cells show more highly divergent expression

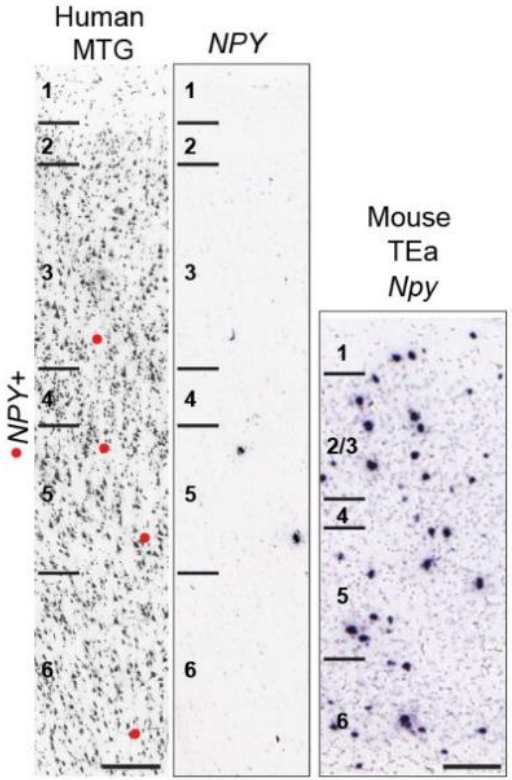


Divergent genes are functionally relevant

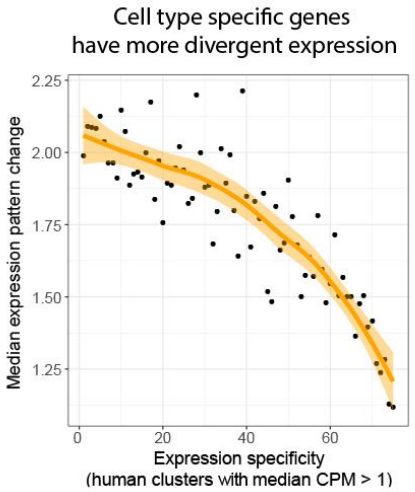


“Marker genes” are more divergent

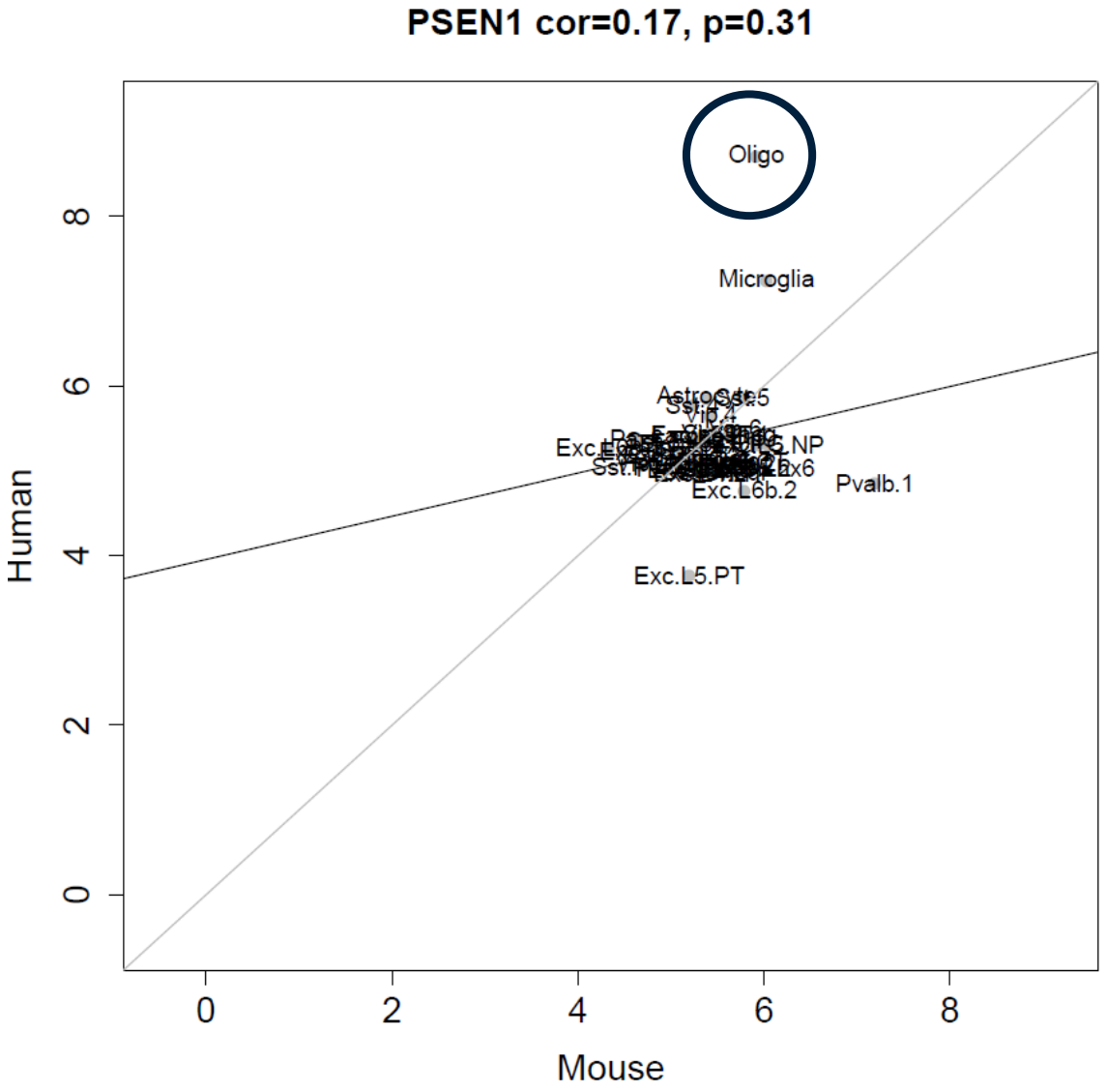


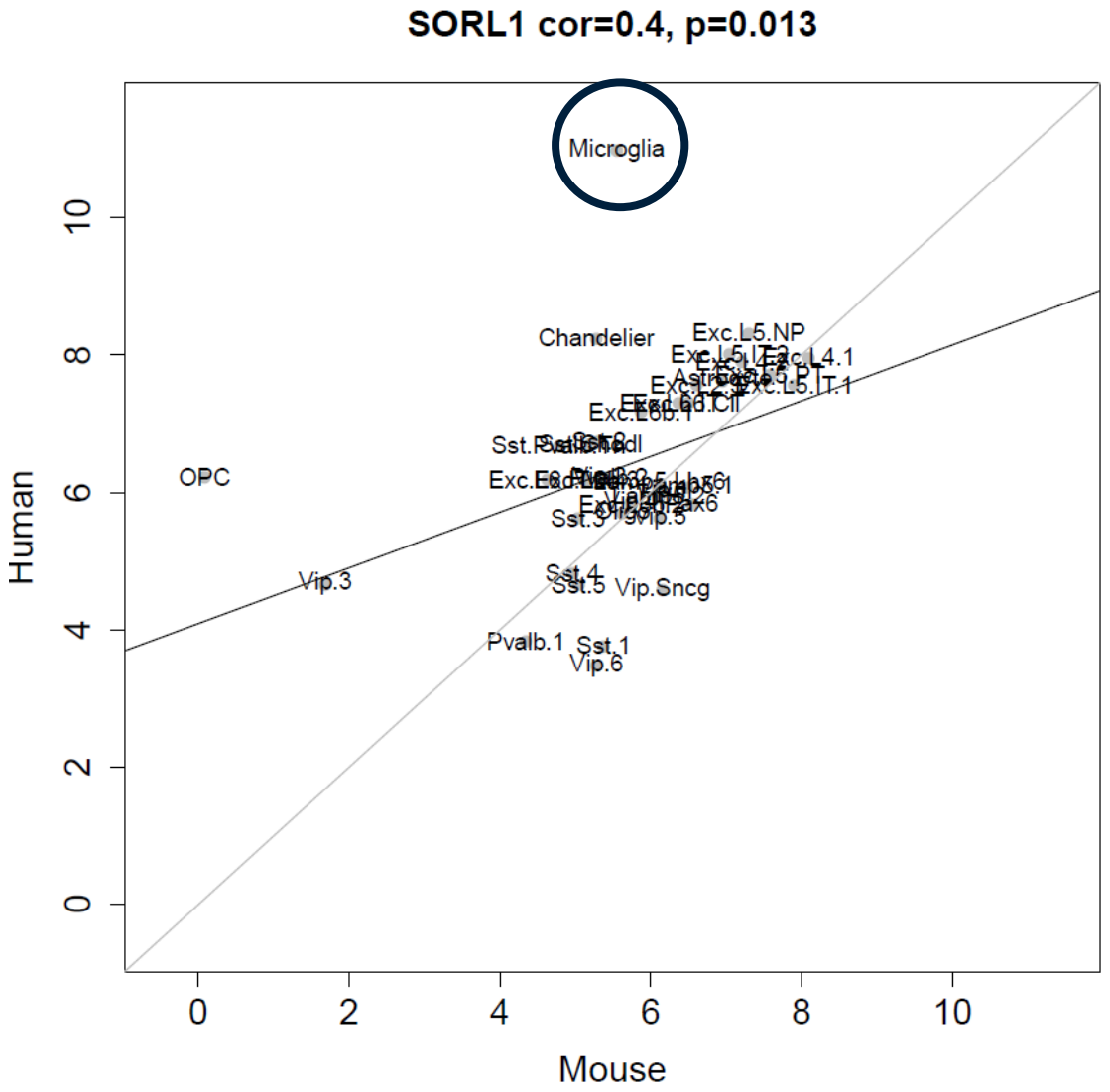


Best marker for putative long-range projecting GABAergic neurons in human, broad expression in mouse GABAergic cells



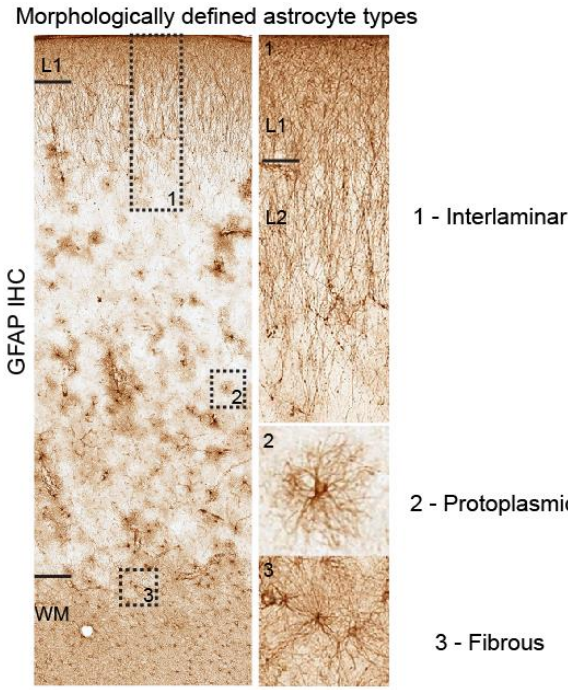
Species differences for AD-related genes

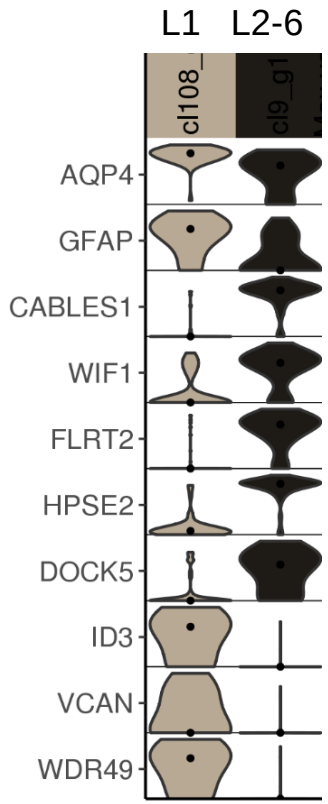




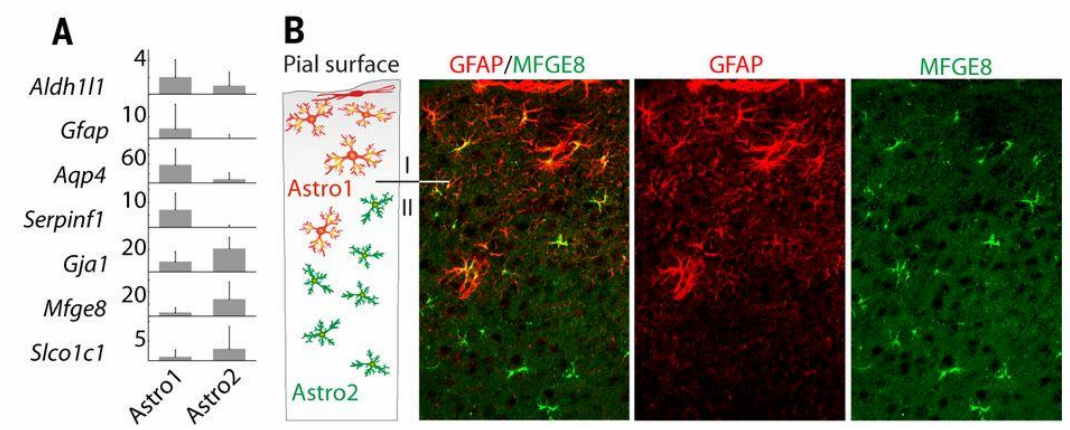
Conserved, and specialized

Human





Mouse



Zeisel et al. Science 2015

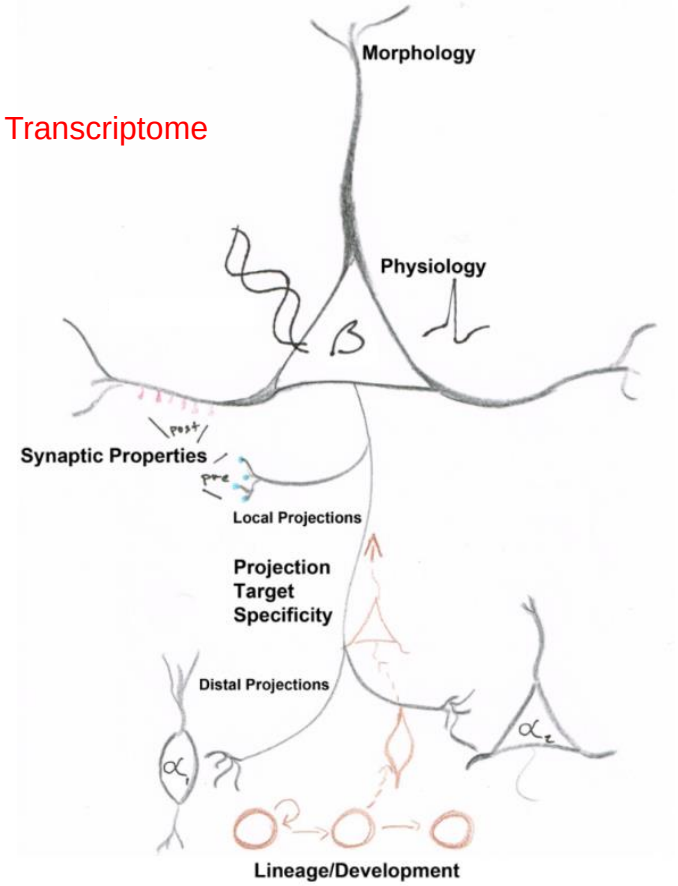
Core transcriptomic conservation, but species-specific feature specialization:

10x size increase

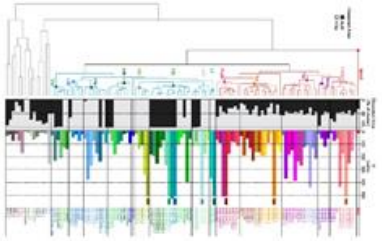
1mm long processes in human

Major differences in gene expression and cell type markers

Annotating the atlas: Phenotyping of transcriptomic cell types

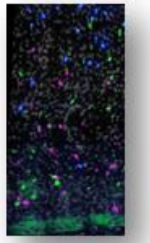


Unbiased transcriptome-based cell type classification in different brain regions



Single cell transcriptomics

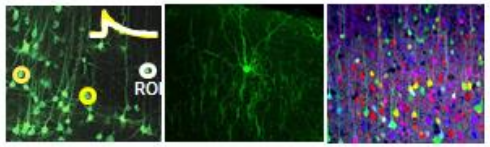
Spatial mapping in tissue sections (“census”)



Spatial transcriptomics

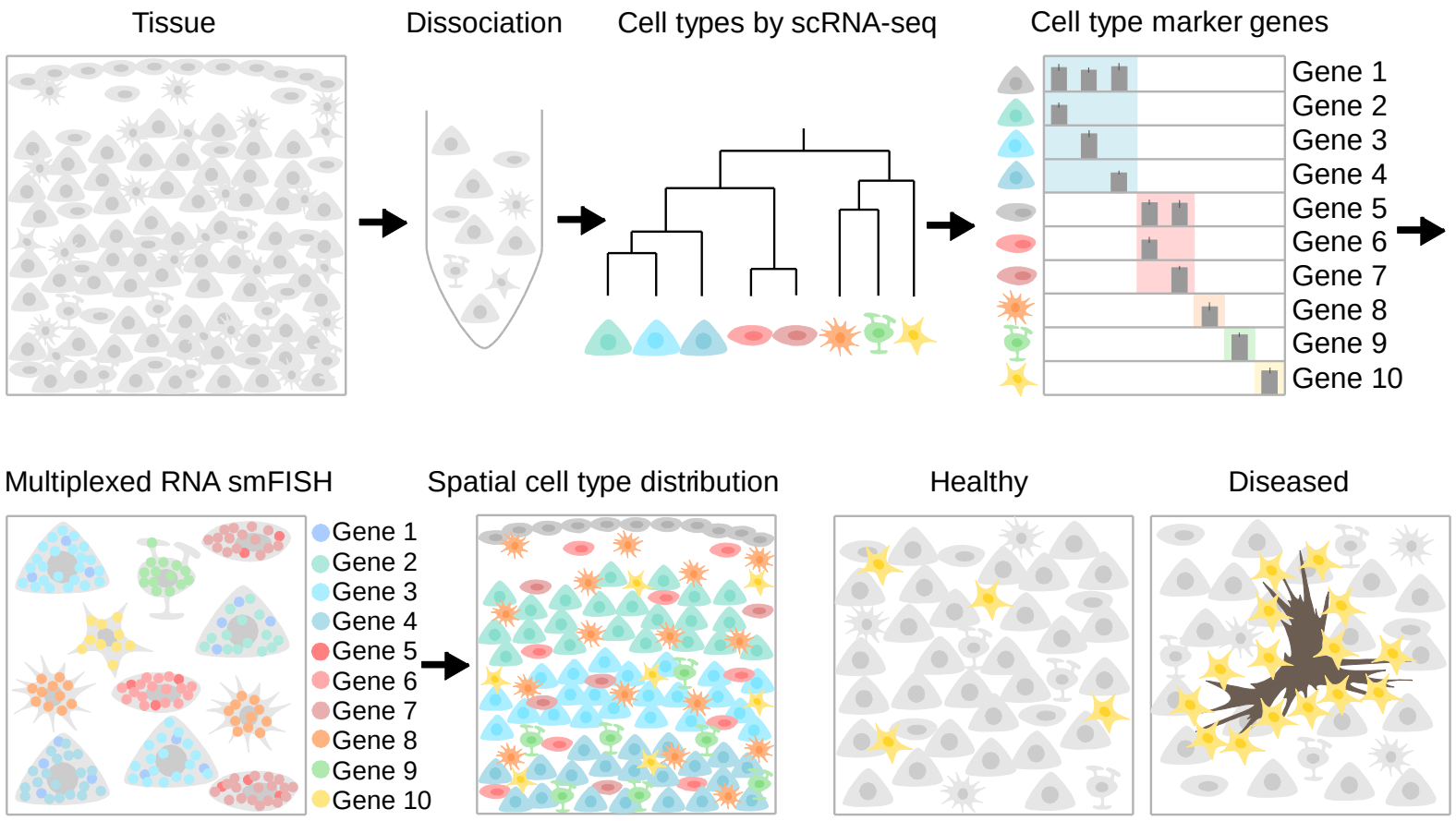
Analyze features of transcriptomic types

Multimodal analysis
Post-hoc spatial transcriptomics
Specific genetic tools



Patch-seq
smFISH
Cre lines,
viruses

In situ spatial transcriptomics methods to identify transcriptomic cell types in tissue sections

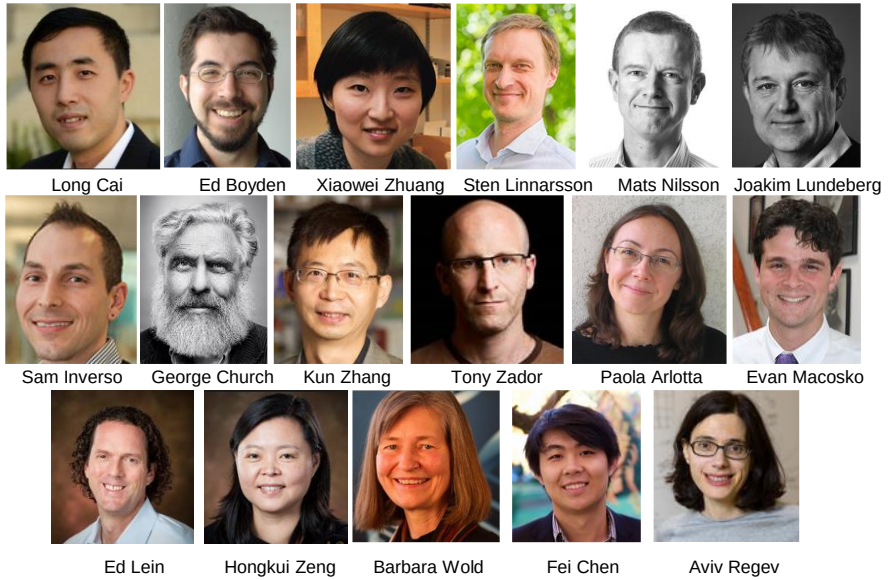


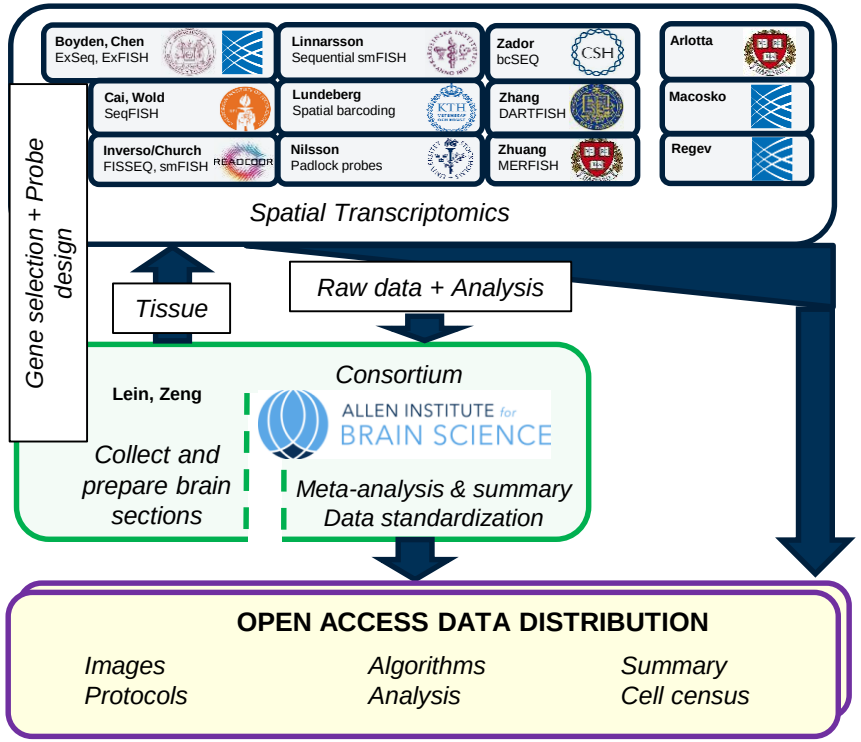
Census

Lein, Borm, Linnarsson (2017) Science

Consortium approach for accelerating development and comparing strengths of different spatial transcriptomics methods

The SpaceTx Team



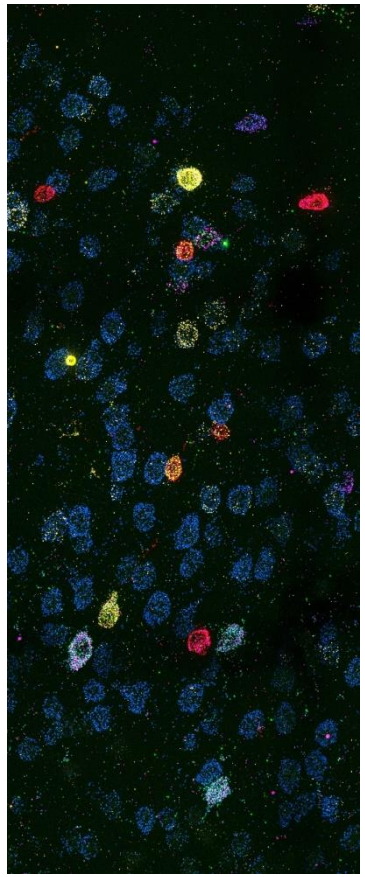


Additional collaborators have joined on computational and visualization challenges
Peter Kharchenko (Harvard)
Richard Scheuermann, Brian Aevermann (J. Craig Venter Institute)
Ken Harris (University College London)
Boudewijn Lelieveldt (Delft, The Netherlands)

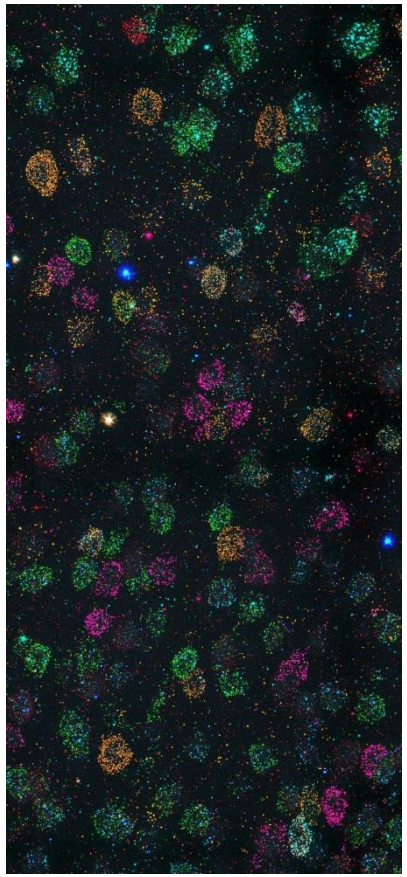
HUMAN CELL ATLAS
CHAN ZUCKERBERG INITIATIVE
HCA Pilot Project

smFISH analysis in cortical tissues

Hairpin chain reaction (HCR)-based FISH in mouse tissues

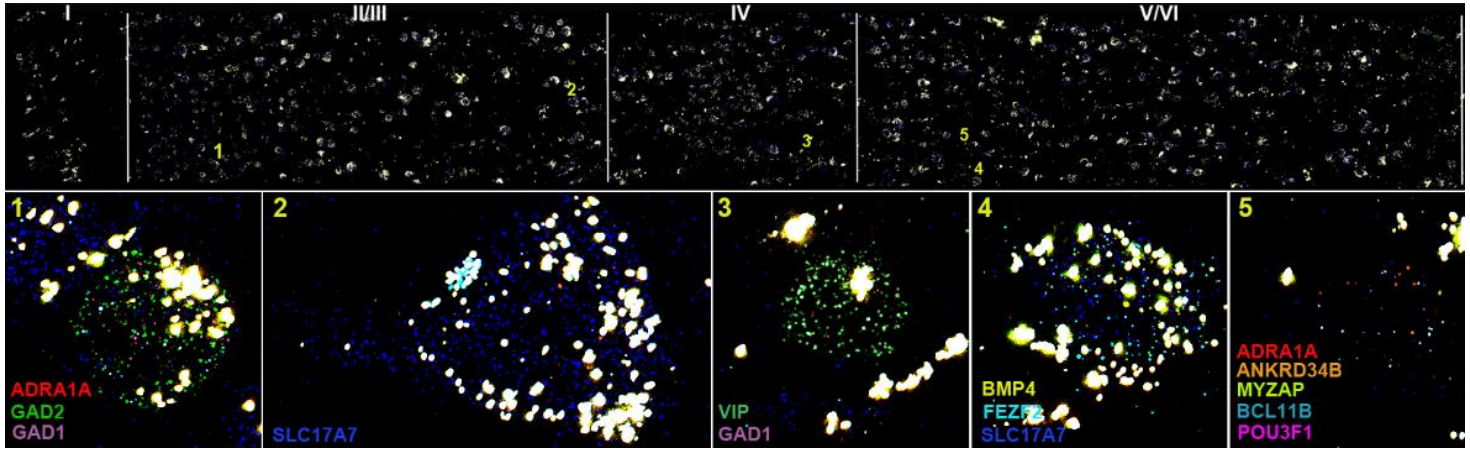


Inhibitory neurons



Excitatory neurons

smFISH in human cortical tissues

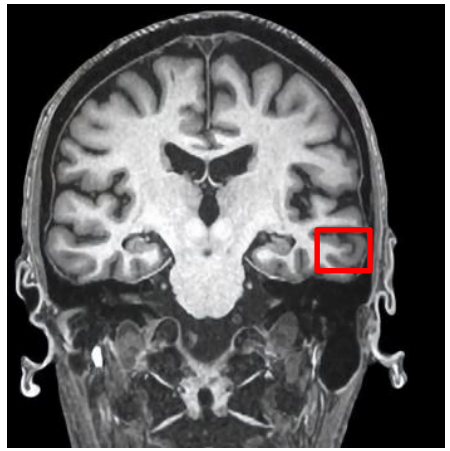


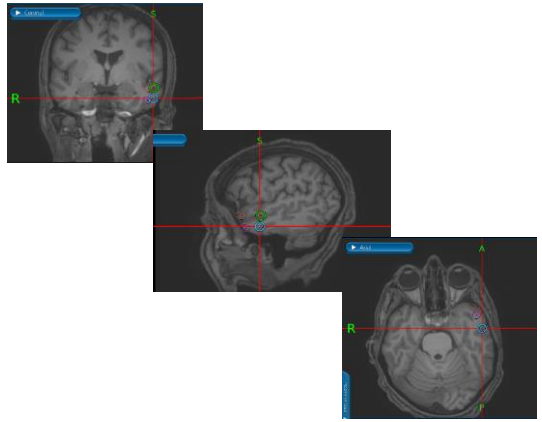
Note autofluorescent lipofuscin granules

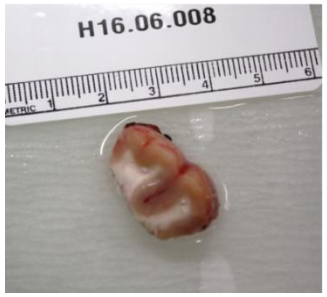
Multiplexing moving into dozens to hundreds of genes, combinable with protein labeling

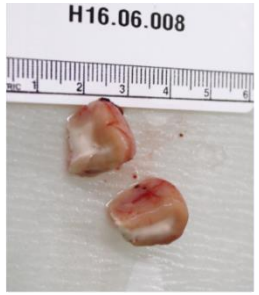
Boaz Levi, Jennie Close

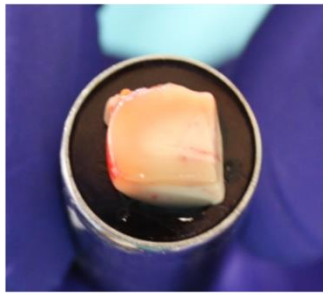
Human slice physiology using neurosurgically resected tissues

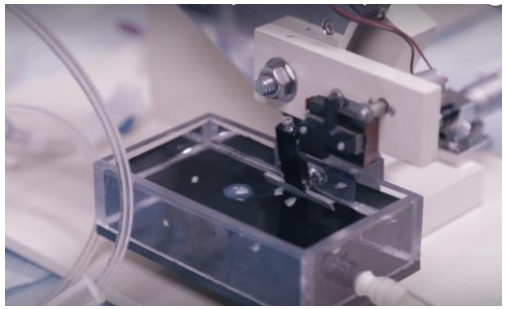


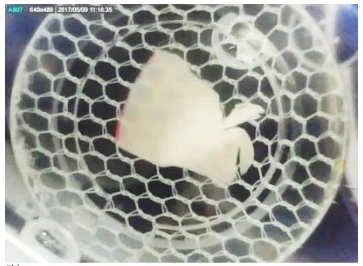








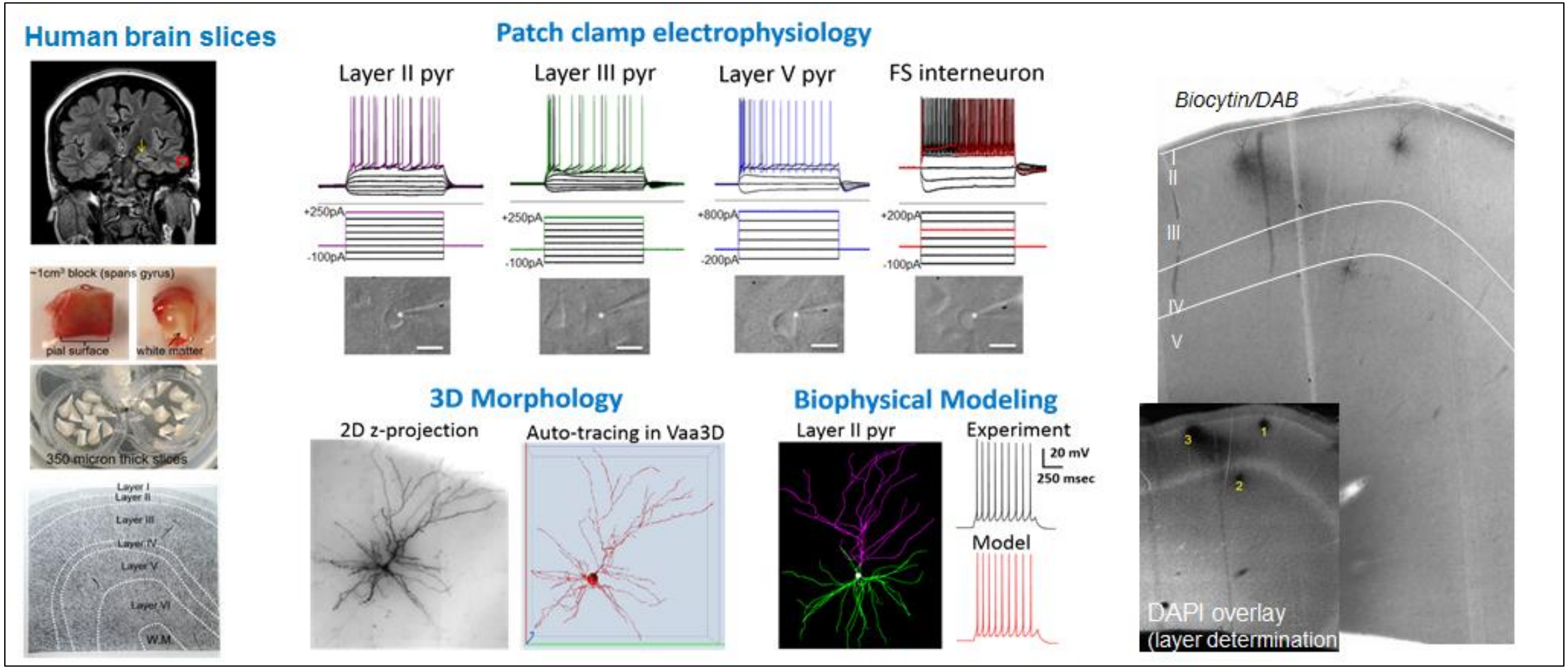




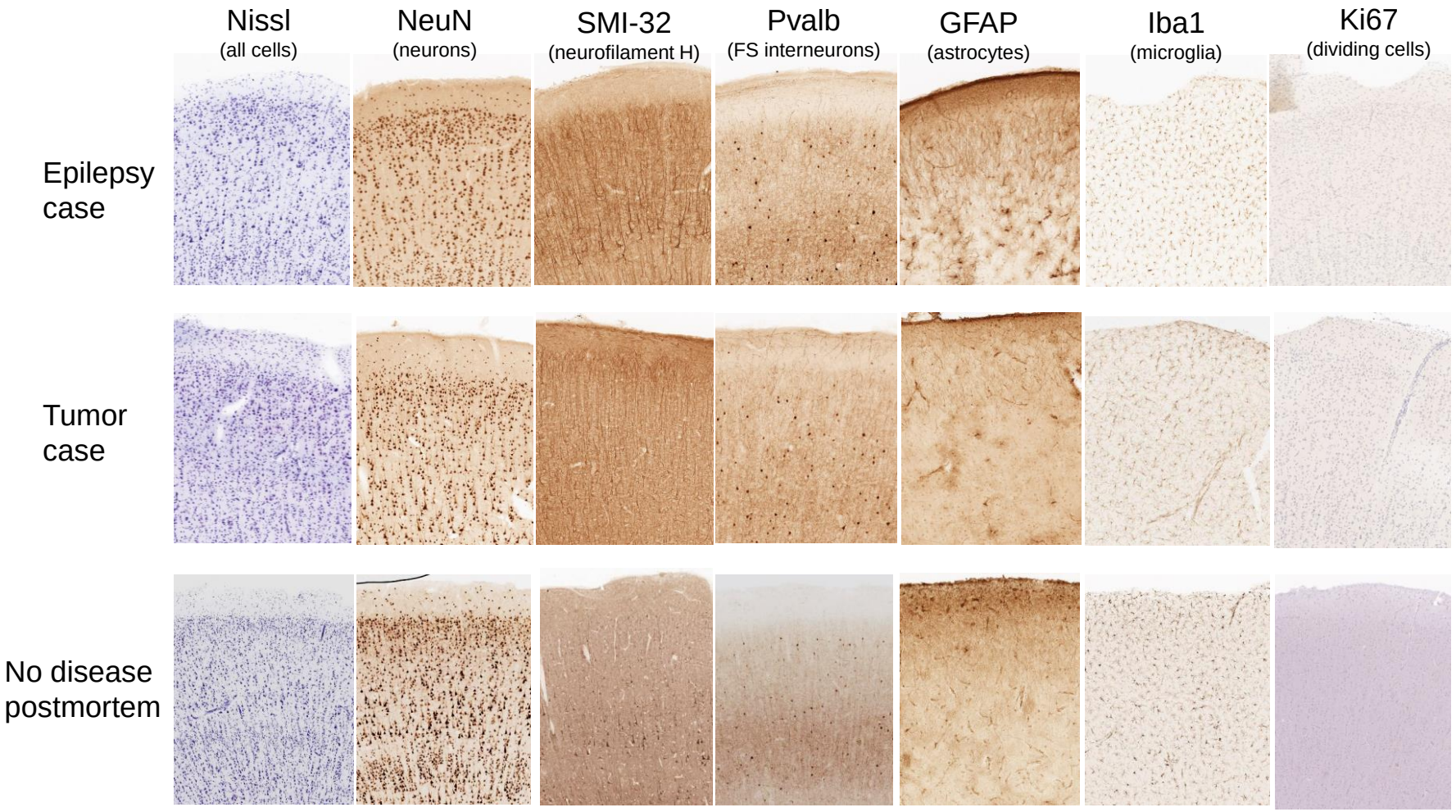
Neurosurgically resected brain tissues are a precious and woefully underutilized resource

JonathanTing, Jim Berg

Allen Institute human slice physiology

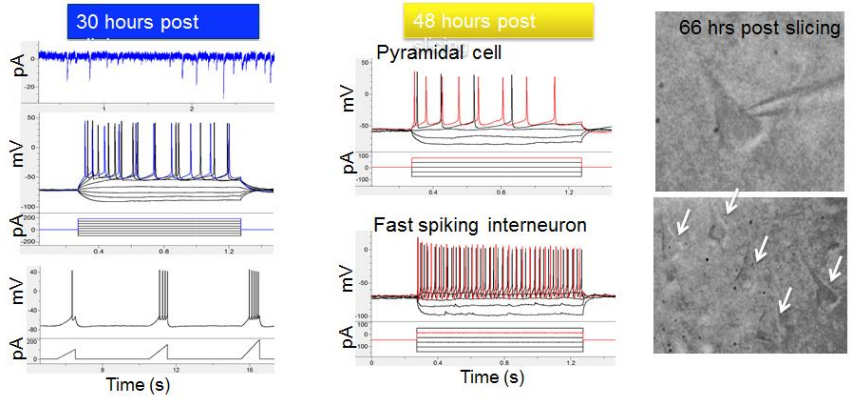


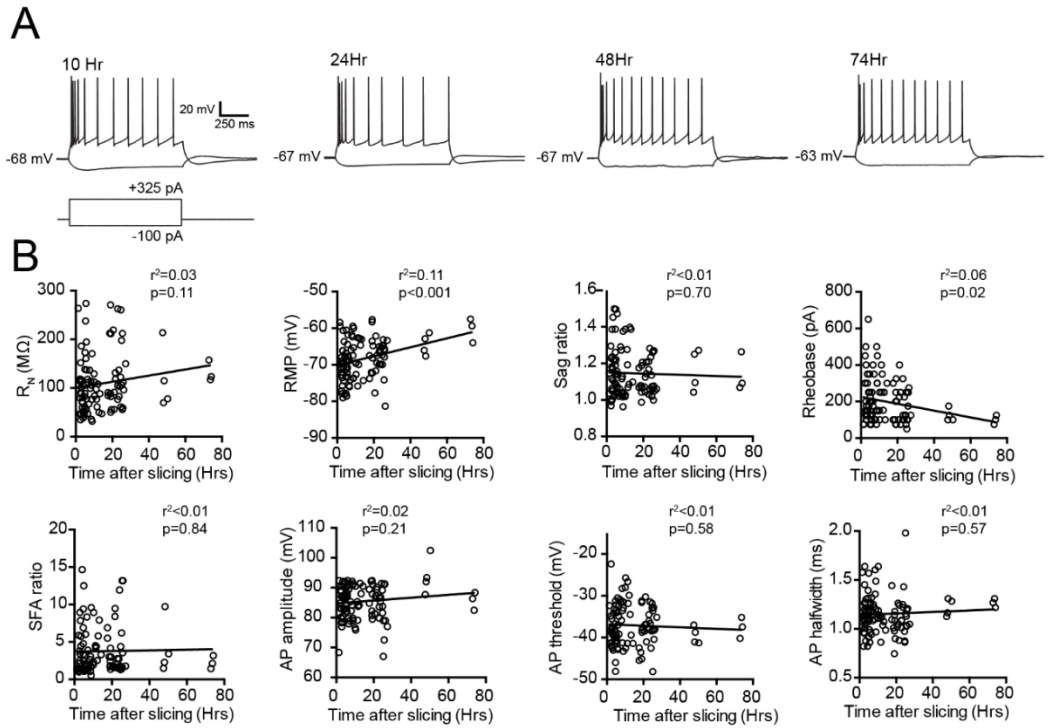
Histological characterization of cases for qualitative and quantitative assessment of cytoarchitecture and pathology



Human *ex vivo* brain slices are robust and exhibit remarkable viability

Time zero: slices are prepared

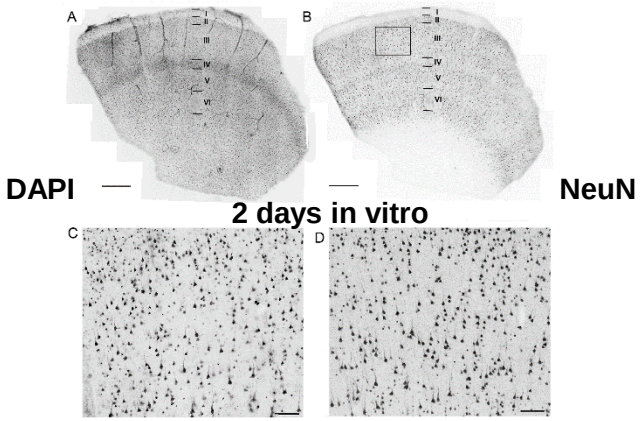




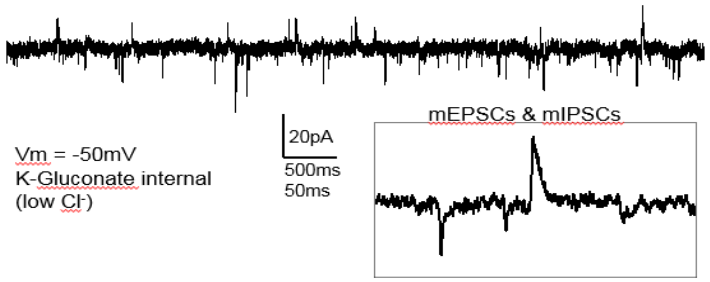
Jonathan Ting et al. (BioRxiv)

Human slices are robust enough to establish an adult human brain slice culture platform

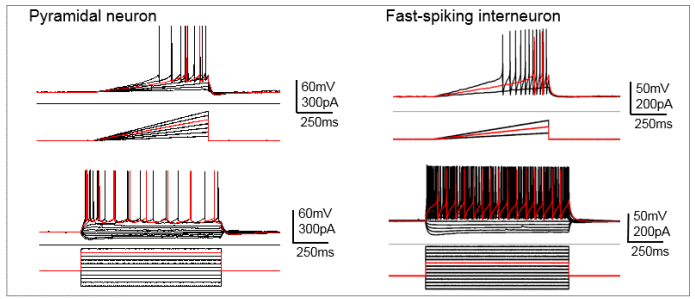
Laminar architecture preserved *in vitro*



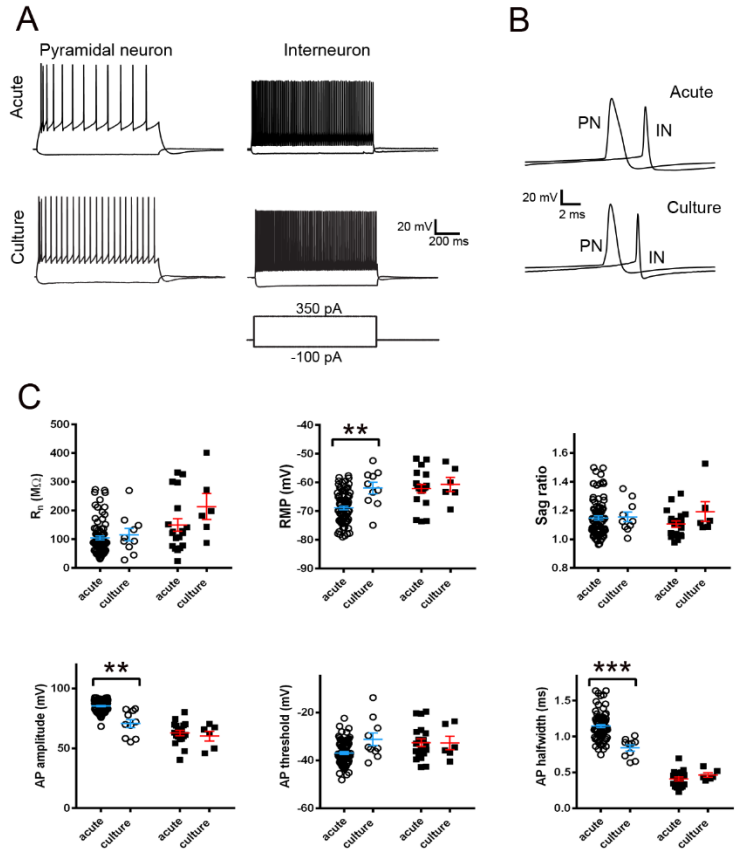
Patch clamp recordings at 3 days in vitro (DIV):



**Functional excitatory and inhibitory synapses well preserved*

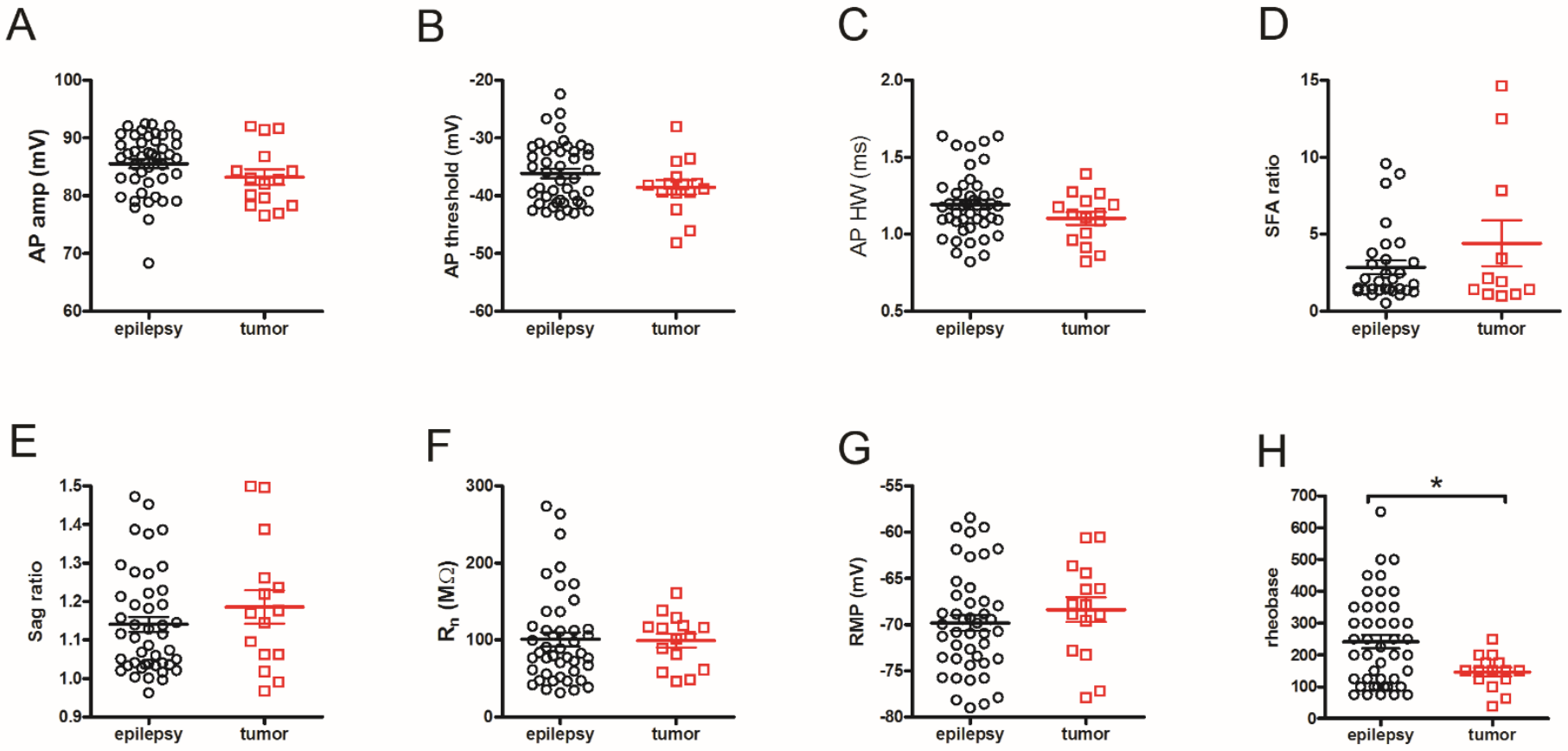


Preservation of physiological properties over time in culture



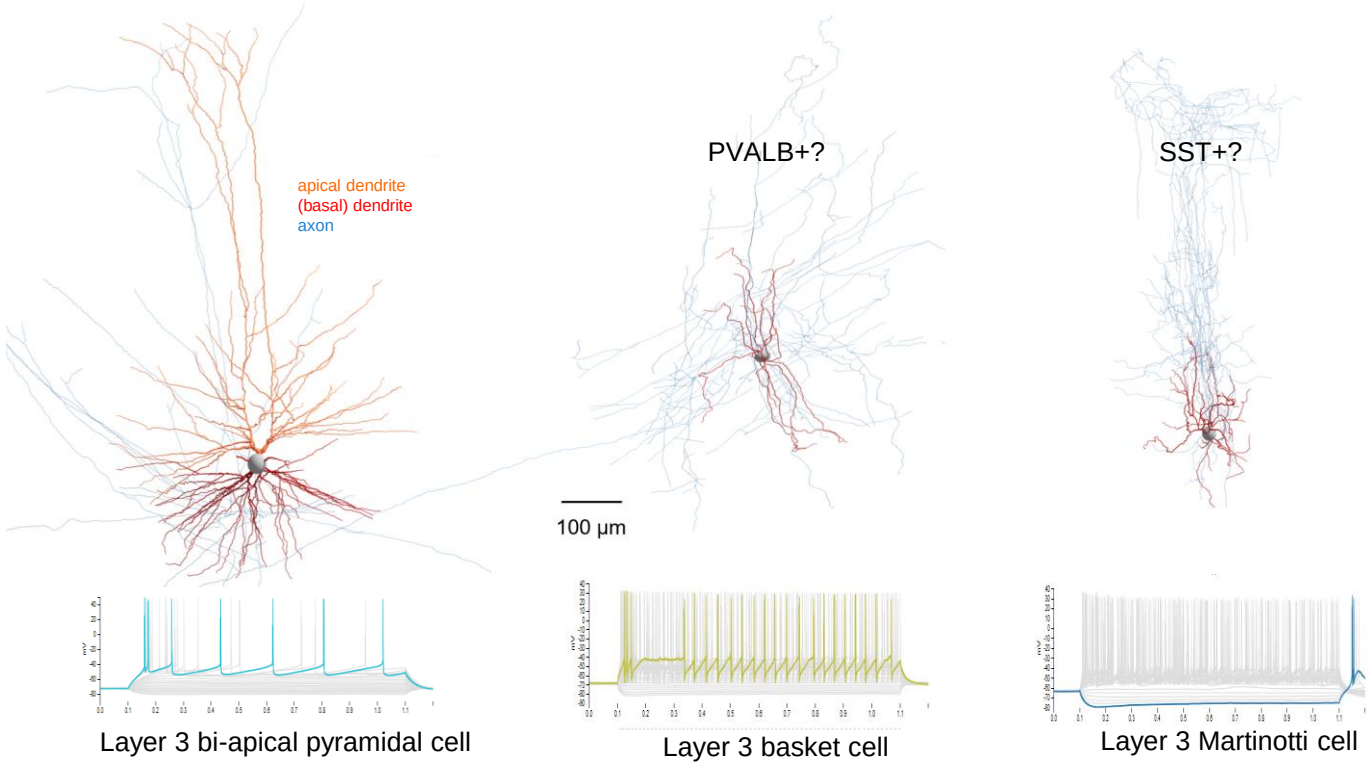
Jonathan Ting

Tumor and epilepsy surgery-derived tissues yield similar results



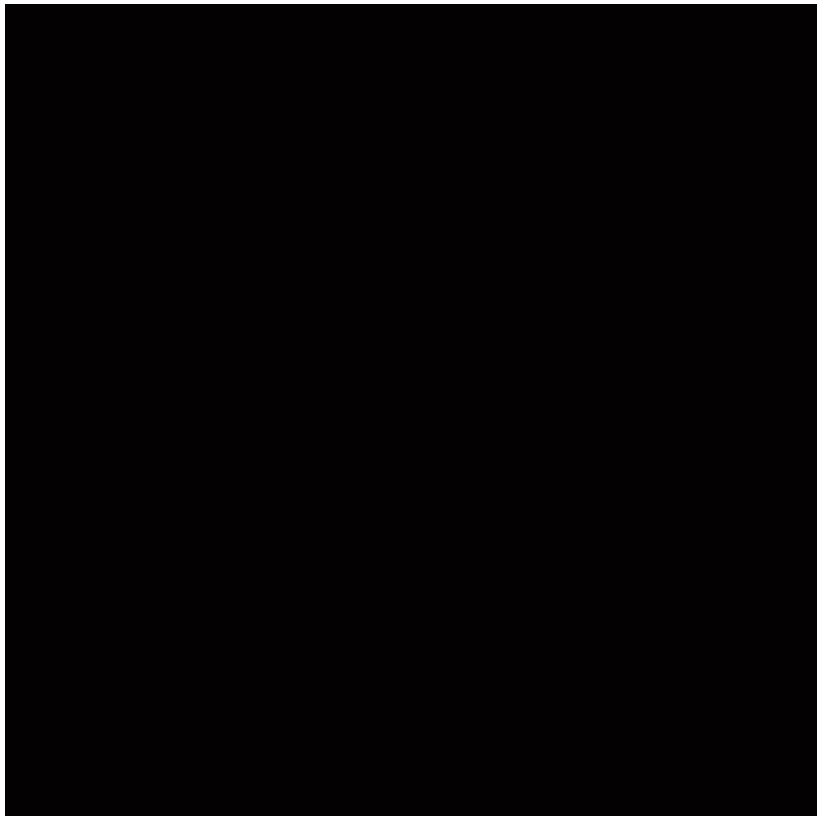
0-12 hours post slicing recordings, layer 2/3 pyramidal neurons
N-14 tumor cases, n=44 epilepsy cases.

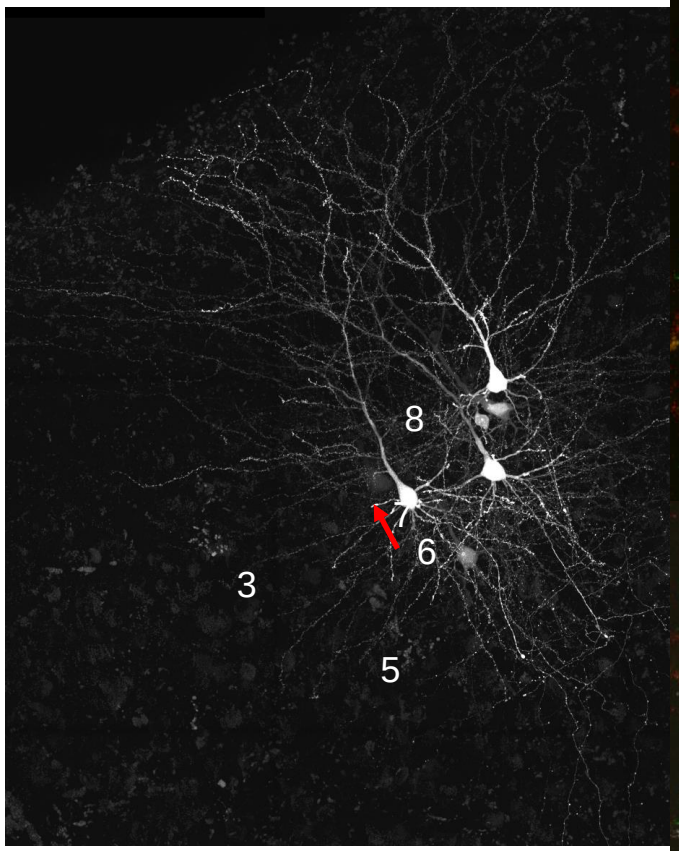
What is the relationship between transcriptome, anatomy and physiology?

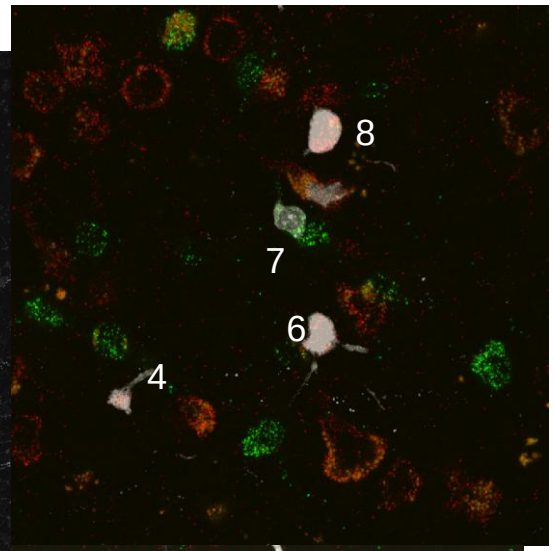


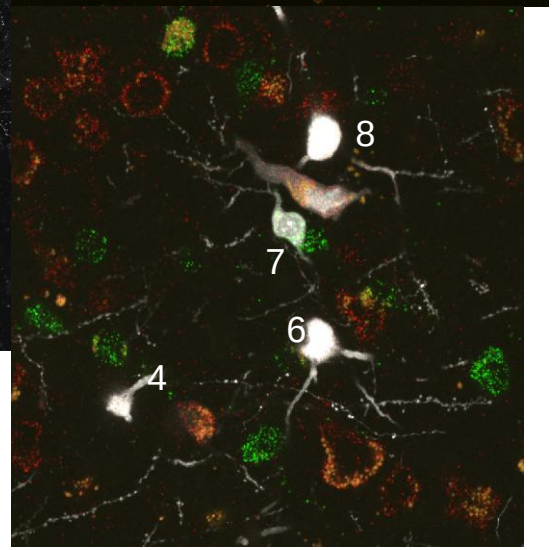
Pinning a transcriptional identity on functionally characterized neurons

Cleared thick section smFISH





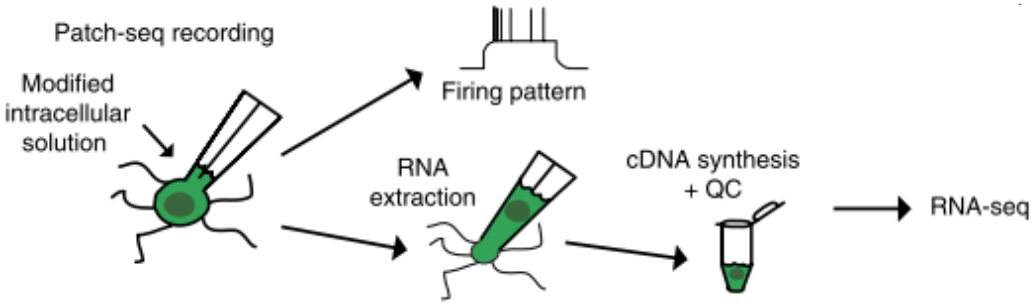




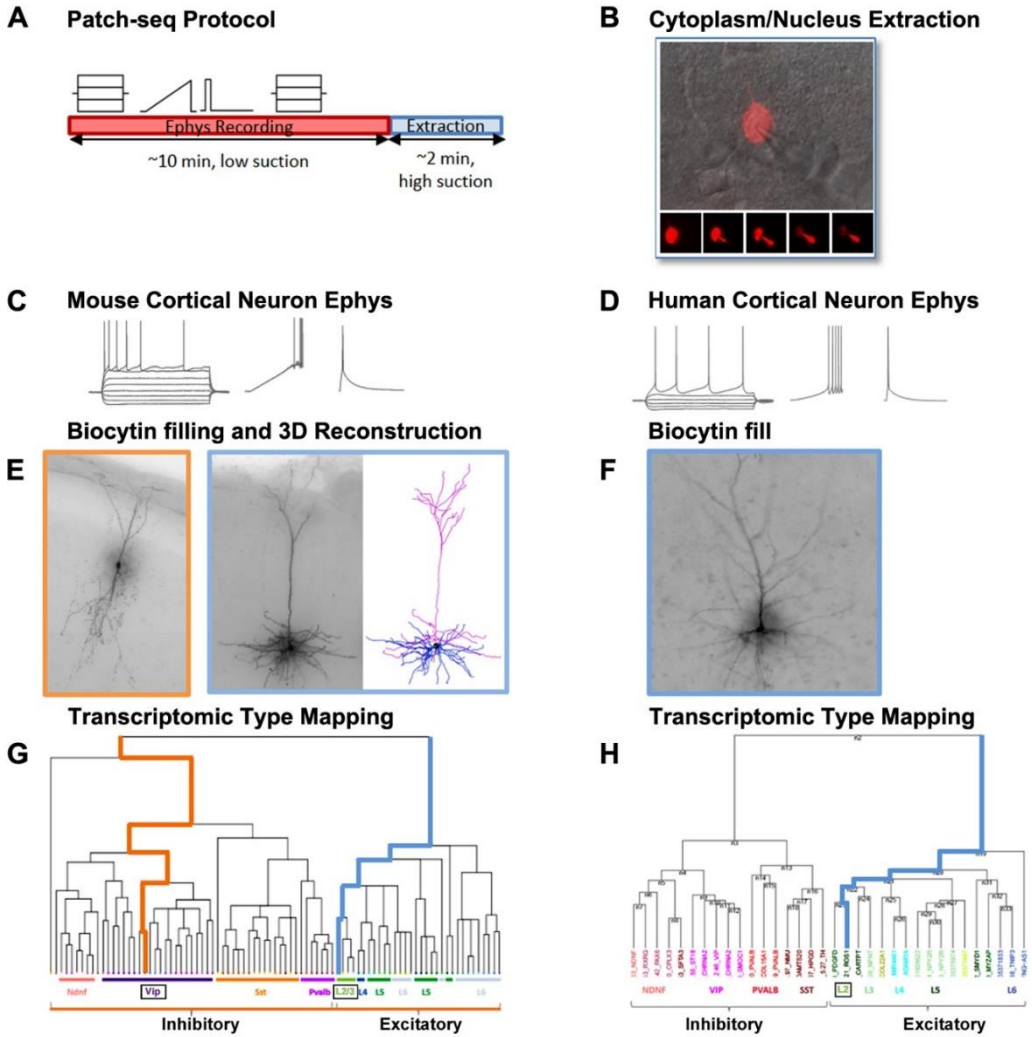
C004: GAD1-B3-A647
C003: SLC17A7-B1-A546
C002: Streptavidin-A488
C001: DAPI

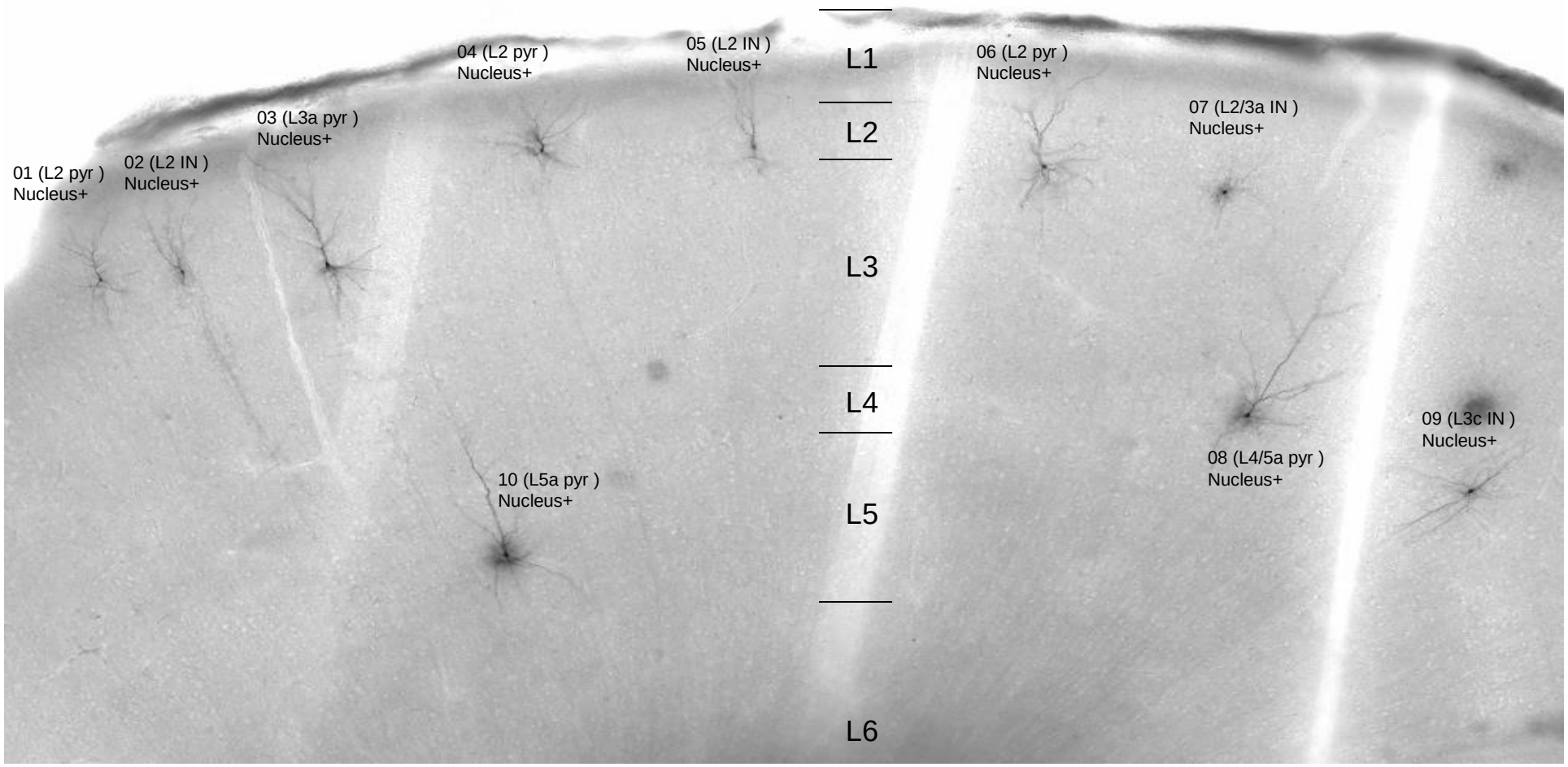
Meanhwan Kim,
Jonathan Ting,
Boaz Levi

Solving the correspondence problem: 3-modality Patch-seq

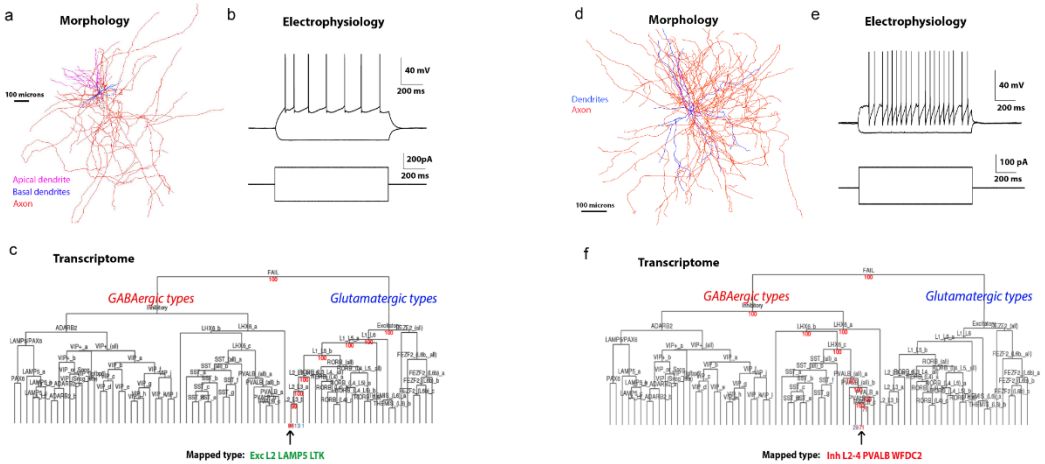


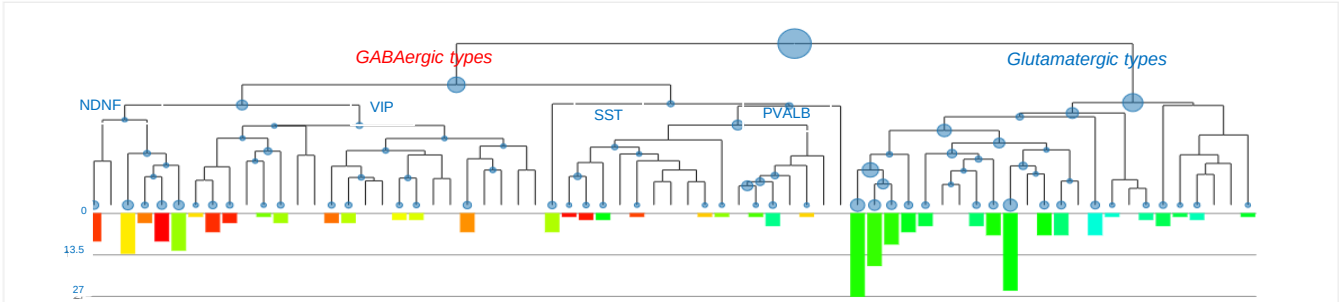
Cadwell et al. 2015 *Nat Biotech*



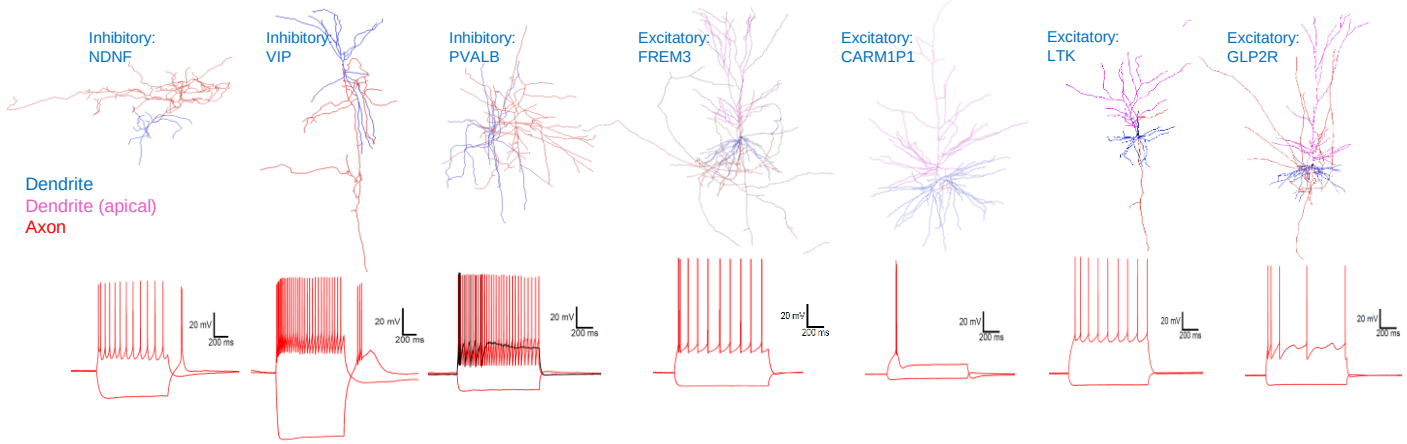

01 (L2 pyr)
Nucleus+
02 (L2 IN)
Nucleus+
03 (L3a pyr)
Nucleus+
04 (L2 pyr)
Nucleus+
05 (L2 IN)
Nucleus+
06 (L2 pyr)
Nucleus+
07 (L2/3a IN)
Nucleus+
08 (L4/5a pyr)
Nucleus+
09 (L3c IN)
Nucleus+
10 (L5a pyr)
Nucleus+
L1
L2
L3
L4
L5
L6

Functional annotation of the transcriptomic classification in human

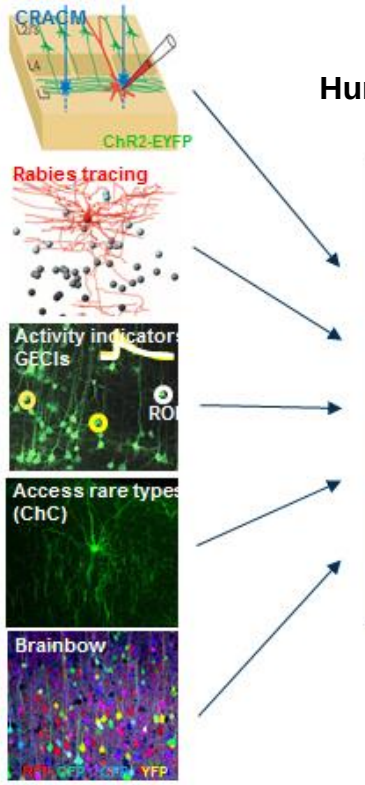




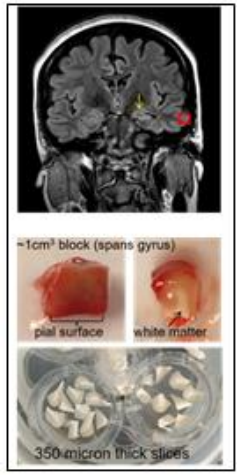
Triple modality exemplars (not to scale):



Bringing the power of molecular genetics to the study of human cortex

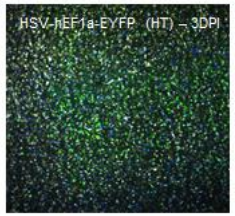


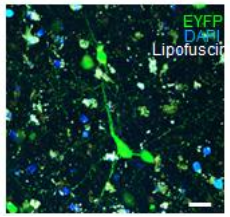
Human neurosurgical specimens

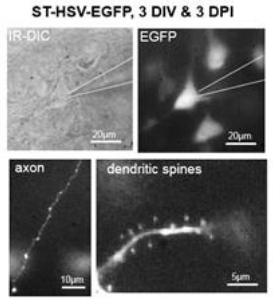


HSV-mediated neuronal labeling

High density is achievable, titratable



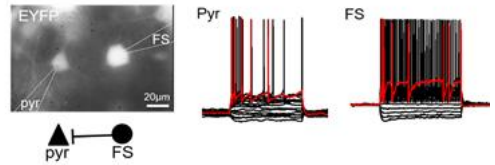


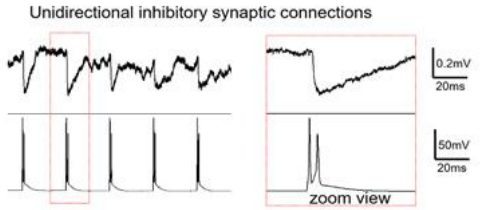


Morphological features are maintained in culture, including dendritic spines, axons, and layer organization

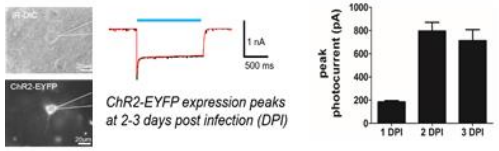
Targeting fluorescently labeled cells

Patch clamp recording, multipatch recording



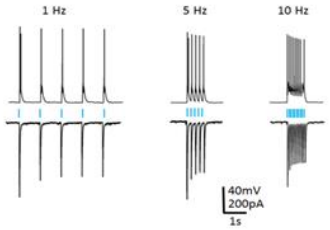


Optical control of neuron firing with Channelrhodopsin-2

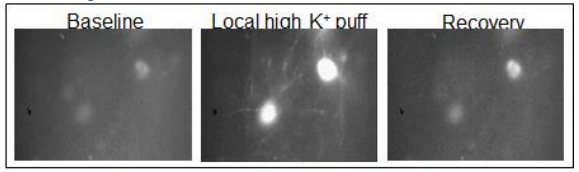


ChR2-EYFP expression peaks at 2-3 days post infection (DPI)

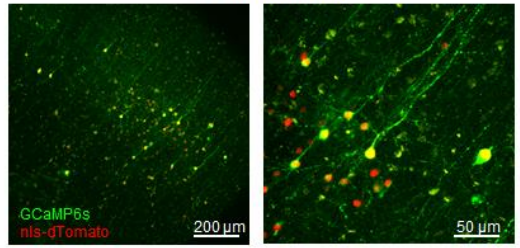
Precise patterned blue light-evoked responses (whole-cell patch):



GCaMP6s for optical monitoring of neuronal activity



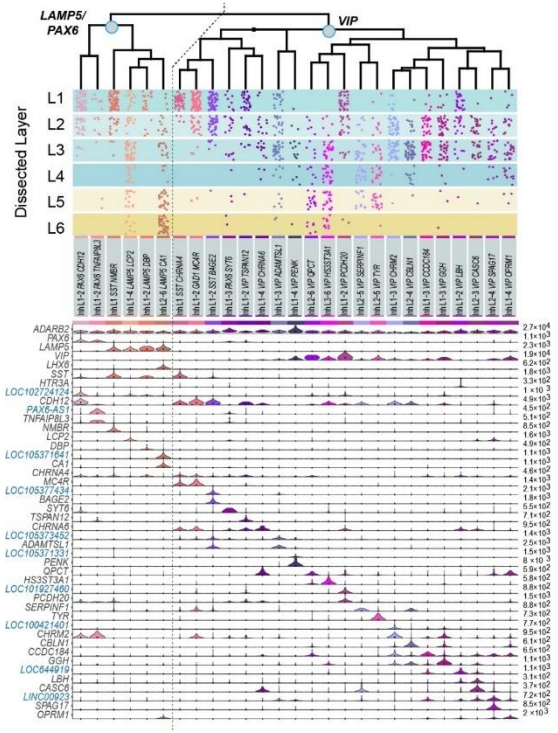
HSV-hEF1a-GCaMP6s-P2A-nls-dTomato
3 days in vitro, 3 days post infection
Native fluorescence



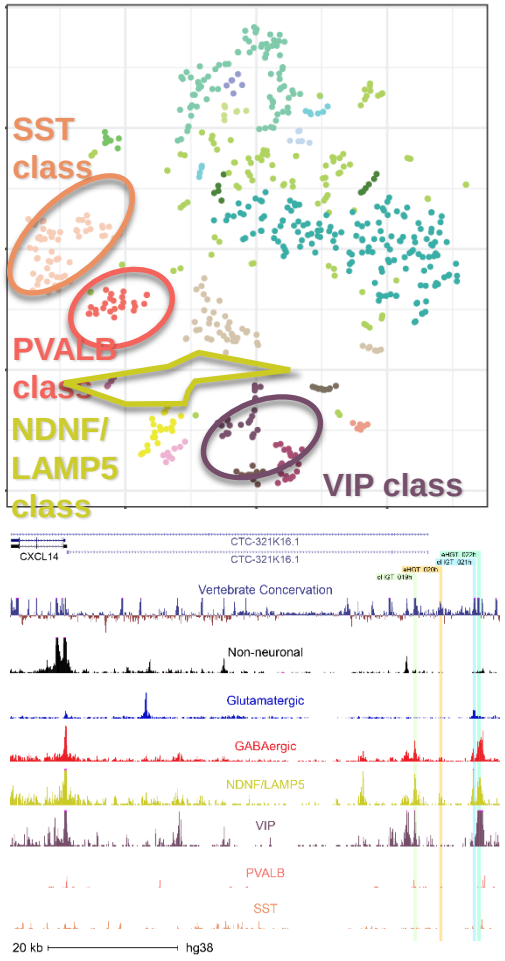
Strategy for generating cell type-specific enhancers

Single cell –omics data allows rationale design of viral tools to target cell types

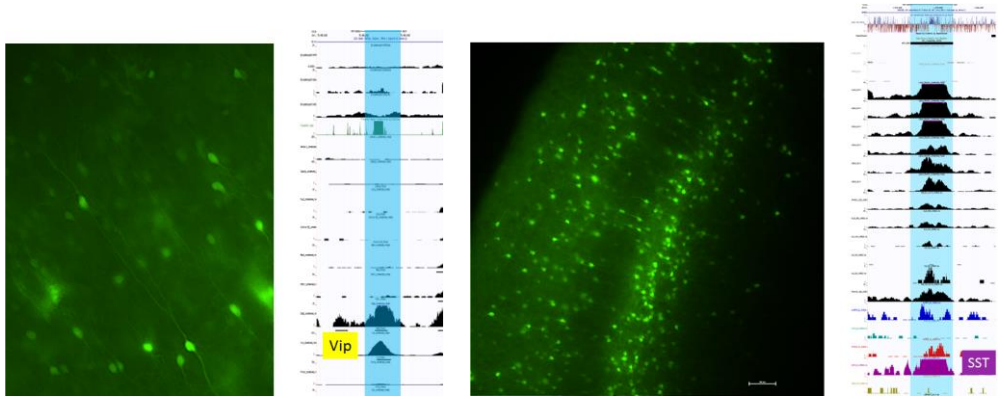
Transcriptomic classification, marker identification



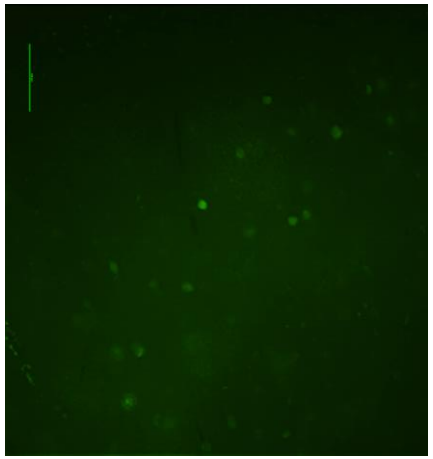
Putative enhancer identification based on single cell ATAC-seq



Enhancer screening in viral context in mouse, monkey and human



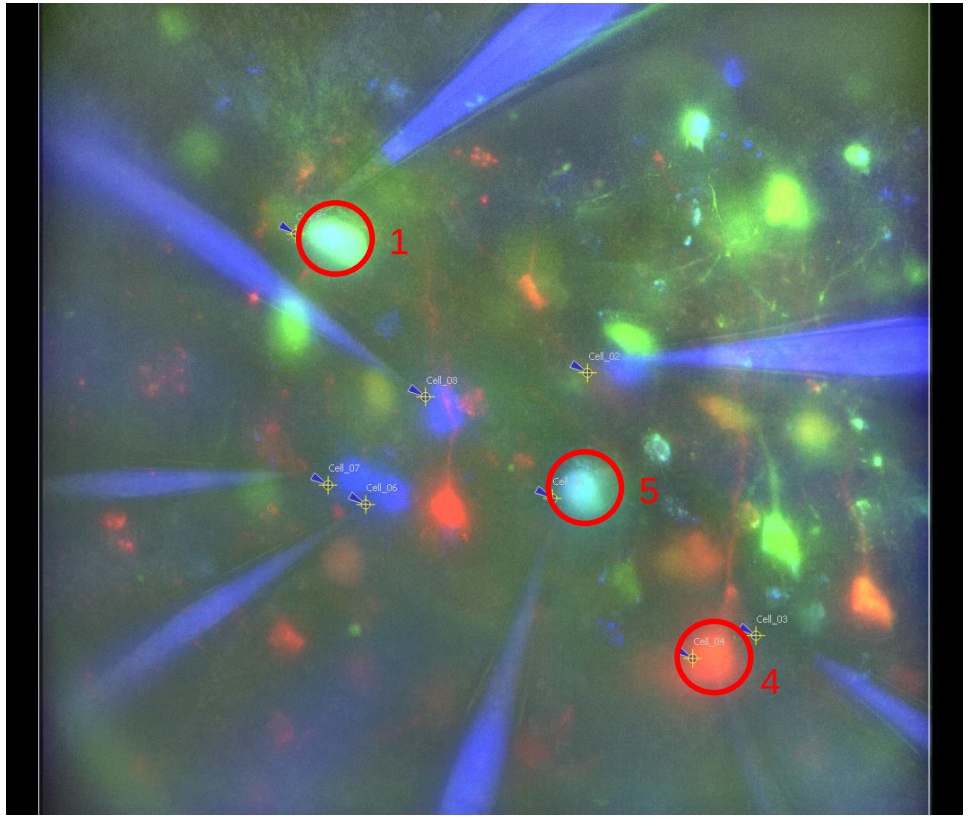
Rapid viral transduction and specificity in acute human cortical slices



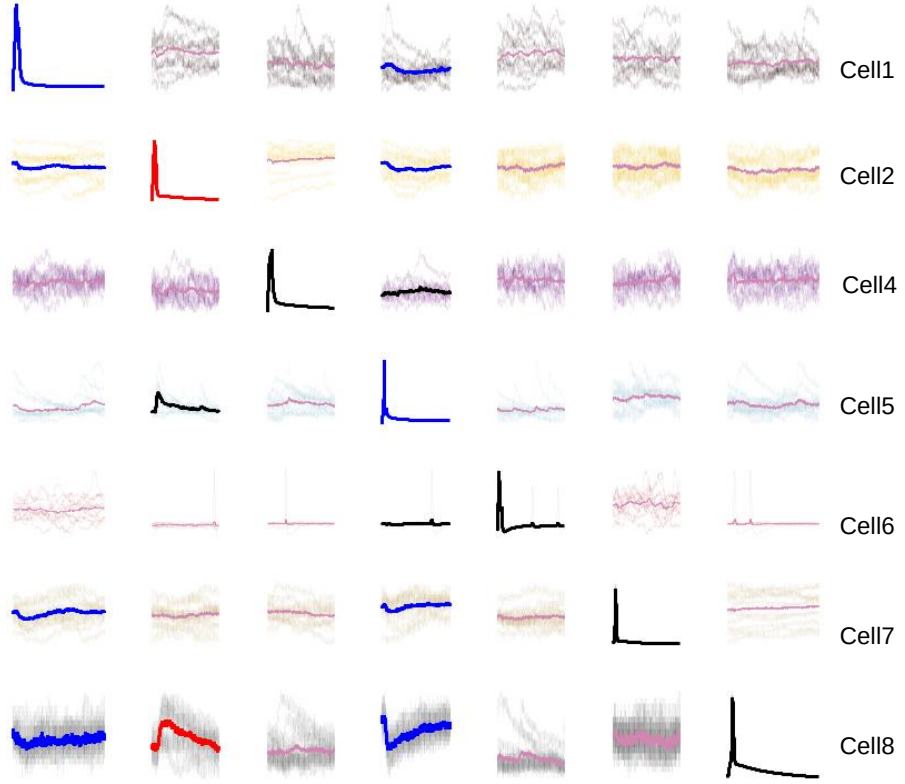
An emerging genetic toolbox for studying human brain…and gene therapy

human slice culture
AAV infection
2.5 DIV/ 2.5 DPI
panGABA-YFP
hSyn1-tdTomato
Cascade blue in pipette

site_000
Cell1, YFP
Cell2, unlabeled
Cell3, unlabeled
Cell4, tdTomato
Cell5, YFP
Cell6, unlabeled
Cell7, unlabeled
Cell8, unlabeled

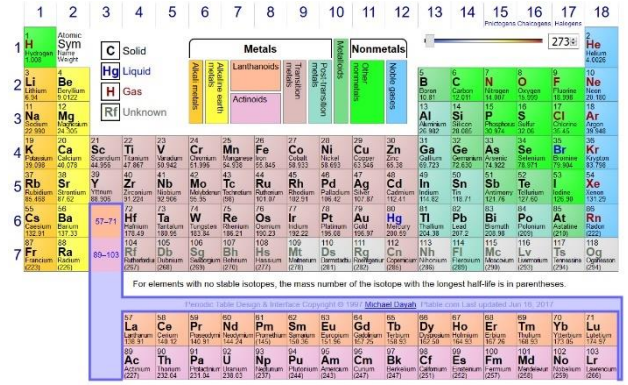


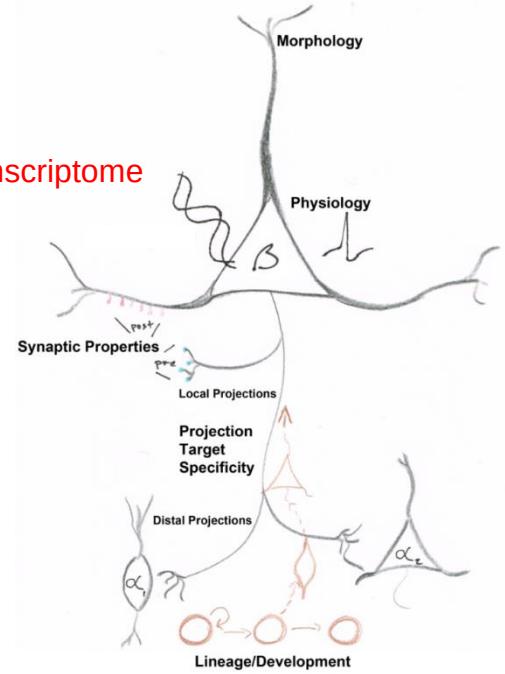
Synaptic connectivity analysis



Meanhwan Kim, Jonathan Ting, Boaz Levi

A cellular lens on disease





Transcriptome

Do neurological, neuropsychiatric, or neurodegenerative diseases involve pathology of specific cell types?

The molecular tools are available now to probe this question by building on the baseline “periodic table”:

- **Are some cell types selectively vulnerable or resistant?**
- **What molecular pathways are perturbed in which cell types?**
- **Where is the best cellular and molecular target for intervention?**

- **Need to foster interaction between pathologists and researchers to improve tissue collection procedures and access to tissues for experimental work, and to provide feedback to improve quantitative neuropathology.**
- **Need to standardize tissue collection, banking and characterization.**
- **Need investment in development and application of these tools specifically to study neurodegenerative diseases.**
- **Need to push hard on developing a better understanding of disease in many ways and push the boundaries on what we think is possible.**

Quantitative phenotypes -> Diagnosis -> Intervention

Team science, big science, open science

Cell Types Program and Project Leads


Hongkui Zeng


Ed Lein


Christof Koch


Allan Jones

Mouse Transcriptomics


Bosiljka Tasic


Zizhen Yao

Human Transcriptomics


Rebecca Hodge


Trygve Bakken

Mouse and Human IVSCC


Gabe Murphy


Staci Sorensen


Jonathan Ting


Jim Berg

Mouse Full Morphology


Staci Sorensen


Julie Harris


Hanchuan Peng

EM Connectomics


Nuno da Costa


Clay Reid

Shotgun Connectomics


Stephen Smith


Forrest Collman

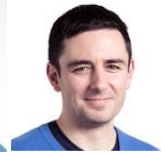
Mesoscale Connectomics


Julie Harris


Stefan Mihalas

Synaptic Physiology


Tim Jarsky


Gabe Murphy

Cell Type Taxonomy


Nathan Gouwens


Jeremy Miller

Multiplex FISH


Bosiljka Tasic


Jennie Close

Mouse Cell Counting


Julie Harris


Nick Cain

Mouse Genetic Tools


Tanya Daigle


Bosiljka Tasic

Human Genetic Tools


Boaz Levi


Jonathan Ting


Ali Cetin

THANK YOU

We wish to thank the Allen Institute founder, Paul G. Allen, for his vision, encouragement, and support.

NIMH National Institute of Mental Health

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THANK YOU

We wish to thank the Allen Institute founder, Paul G. Allen, for his vision, encouragement and support.

We honor his legacy today, and every day into the long future of the Allen Institute, by carrying out our mission of tackling the hard problems in bioscience and making a significant difference in our respective fields.

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