

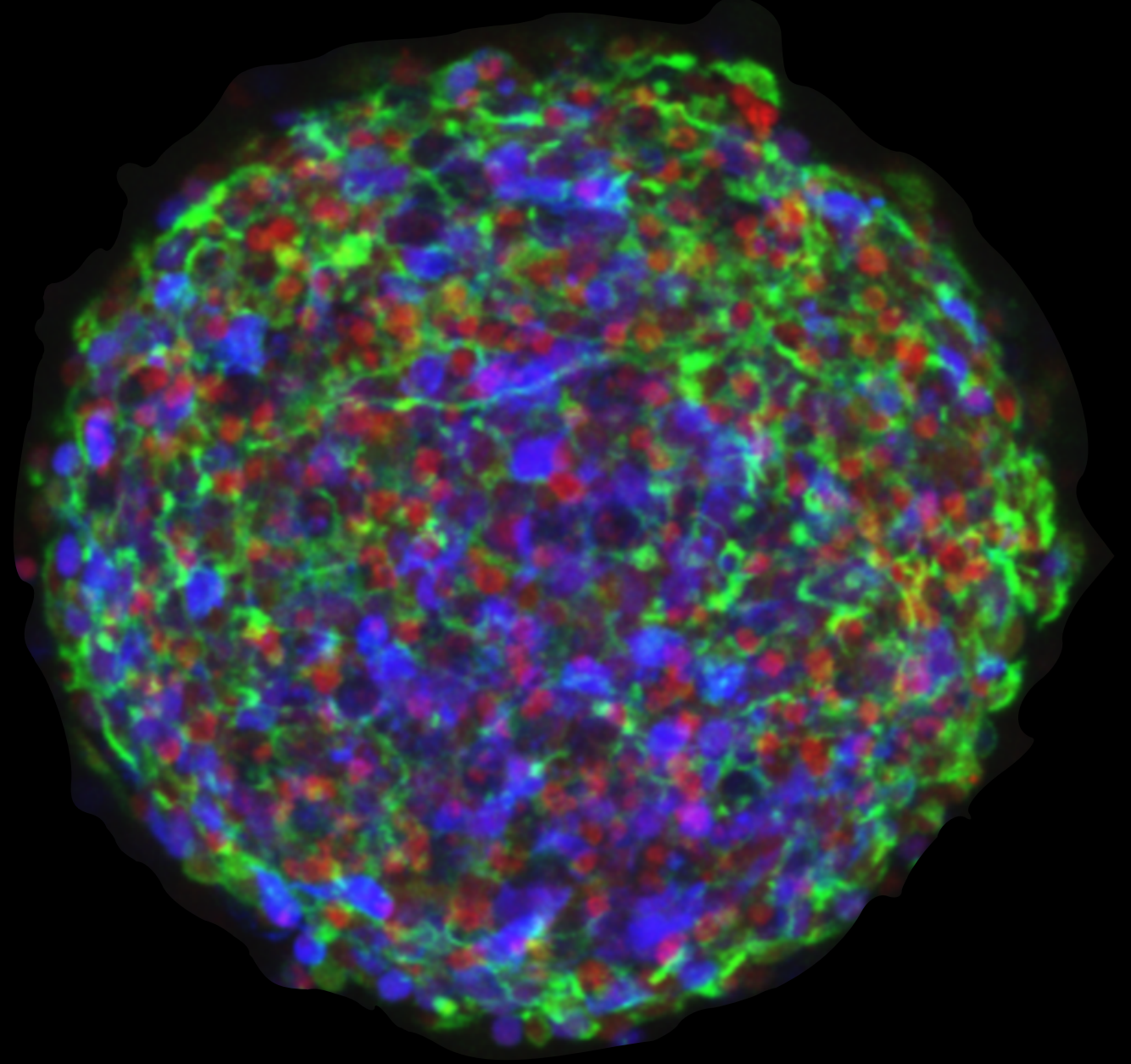
CRISPR-based functional genomics in iPSC models of brain disease

NASEM workshop
October 6, 2021

Martin Kampmann

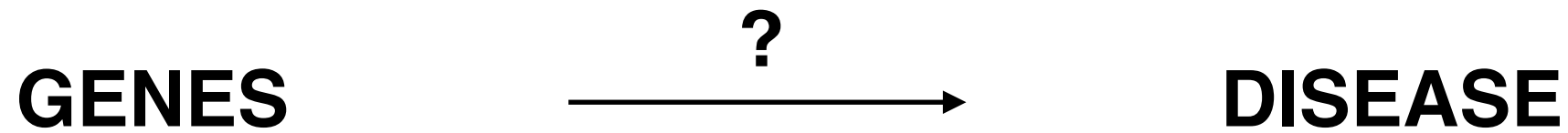
Institute for Neurodegenerative Diseases
Department of Biochemistry & Biophysics, UCSF

Chan Zuckerberg Biohub



UCSF

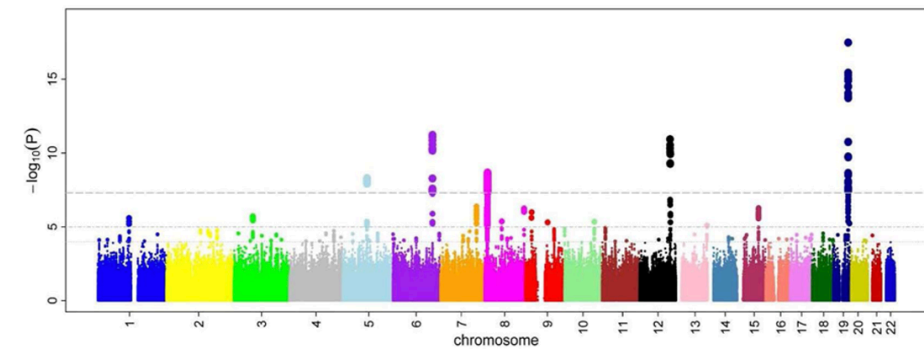




- Variants in the genome
 - Impact of genetic background, ancestry
 - Genetic modifiers
- Differentially expressed genes
 - Selective vulnerability of cell types
 - Disease-relevant cell states
- Significance
 - Stratify patients
 - Understand disease mechanisms
 - Identify new therapeutic targets



Human
genetics

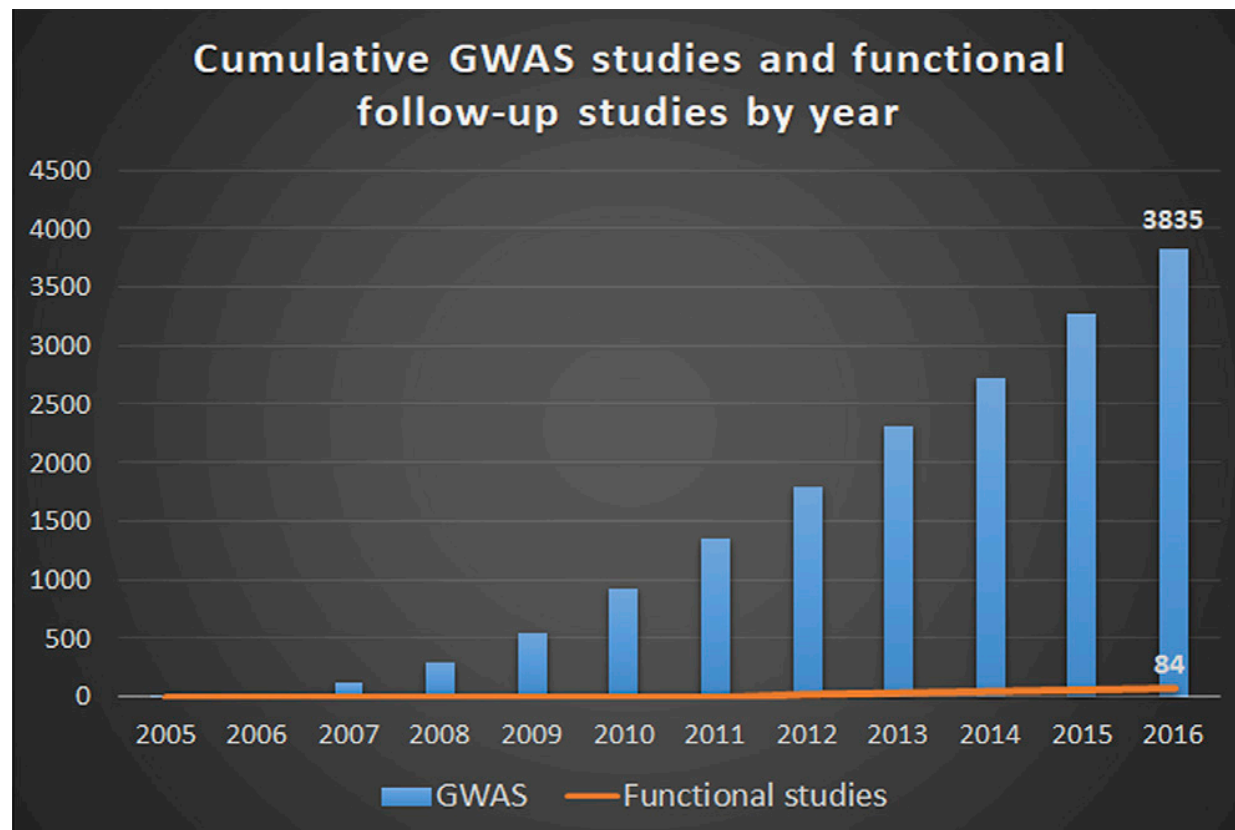


Genetic variants
associated with traits/disease

Functional
Genomics

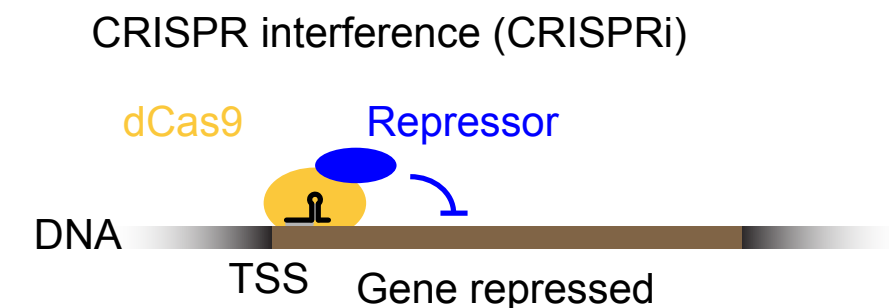
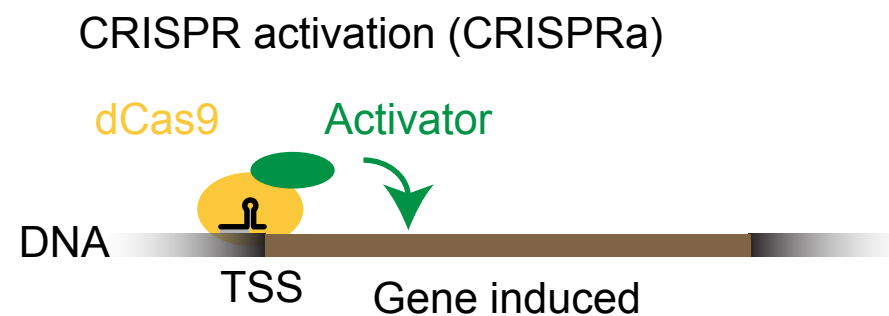
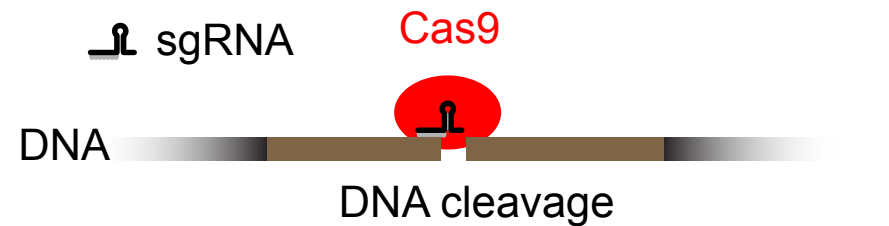
Mechanism?
When?
Where?

Therapeutic
strategy?



Gallagher & Chen-Plotkin (2018) AJHG

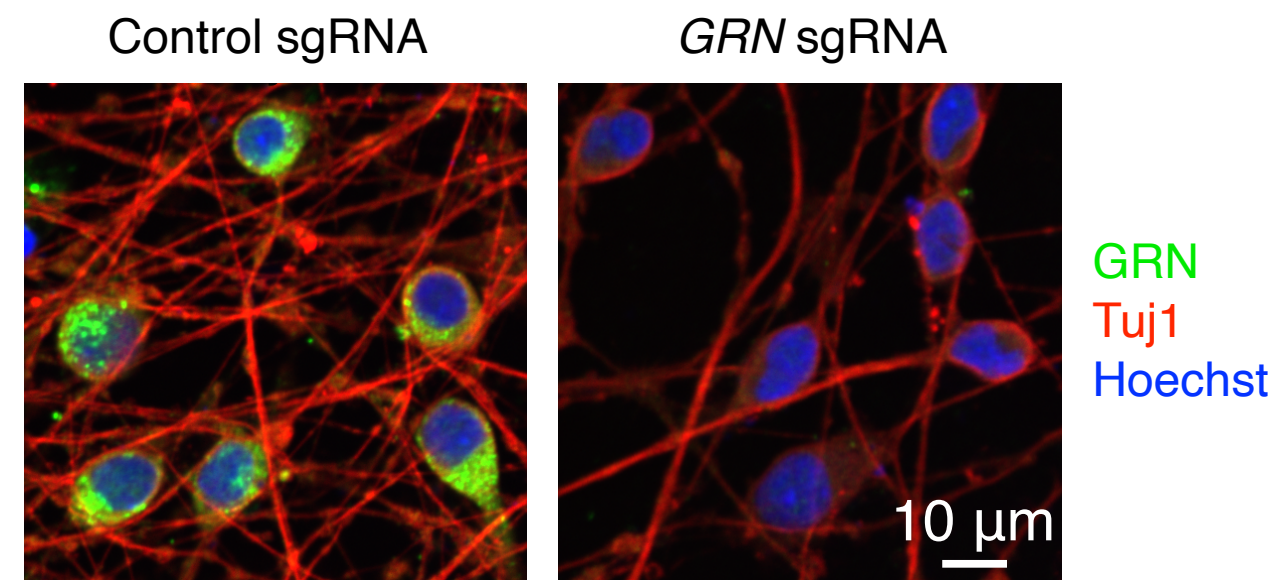
Functional genomics in iPSC-derived models of disease



Genome-wide screening platform

Gilbert ... Kampmann* & Weissman* (2014) *Cell* 159:647

+ iPSC technology



Neurons

Tian *et al.* (2019) *Neuron*

Tian *et al.* (2021) *Nature Neuroscience*

Microglia

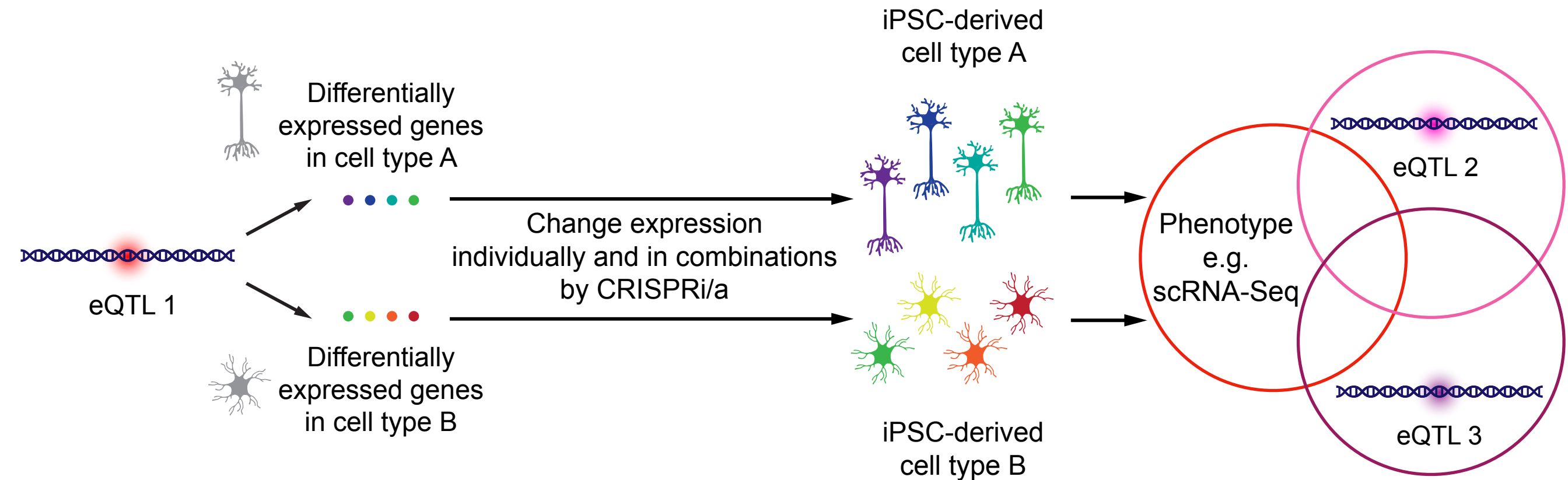
Dräger et al (2021) *bioRxiv* 2021.06.16.448639

Astrocytes

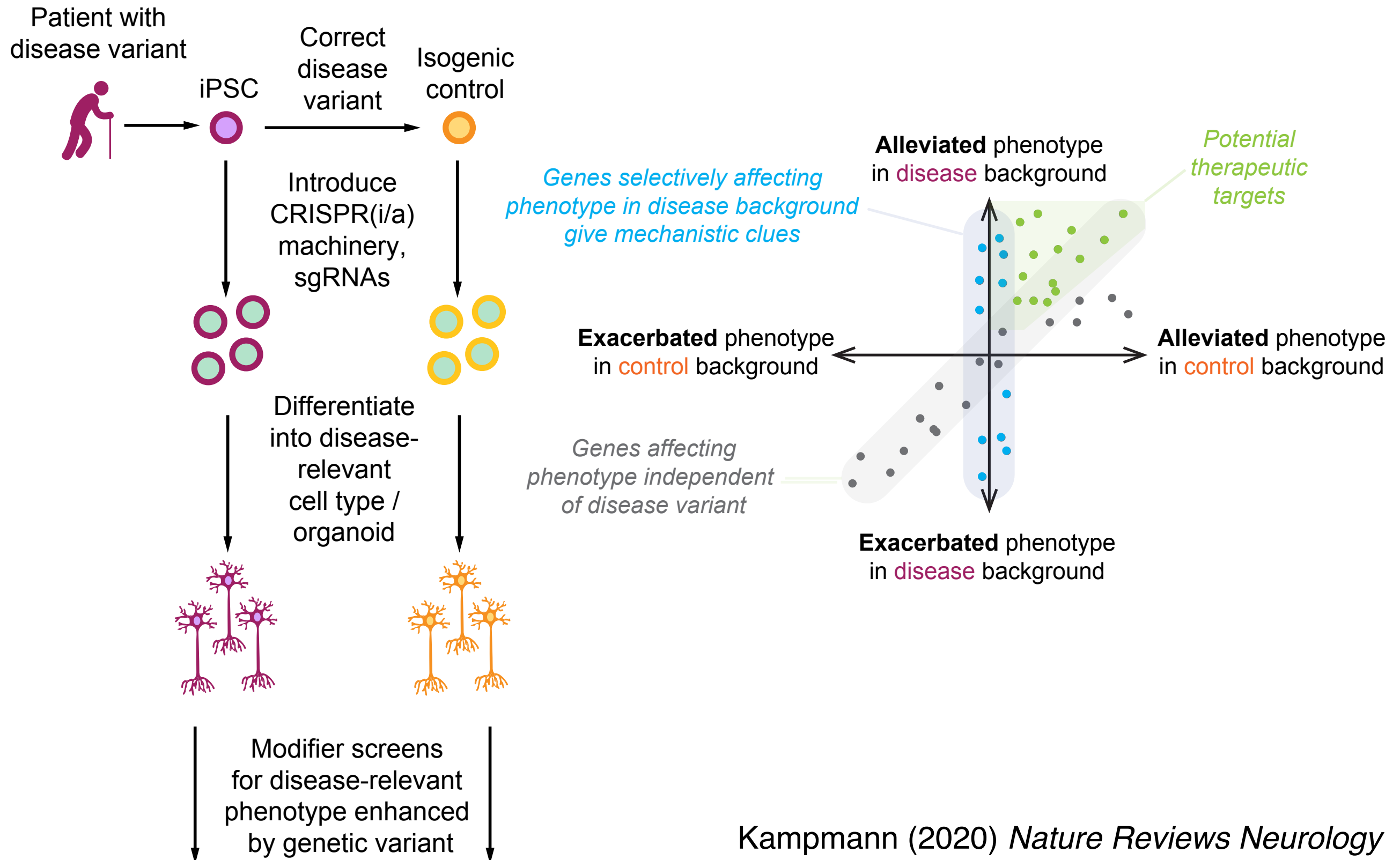
Leng et al (2021) *bioRxiv* 2021.08.23.457400

Rooney*, Leng* et al (2021) *bioRxiv* 2021.09.11.459904

High-throughput modeling of genetic variants / DEGs



Genome-wide modifier screens of disease phenotypes



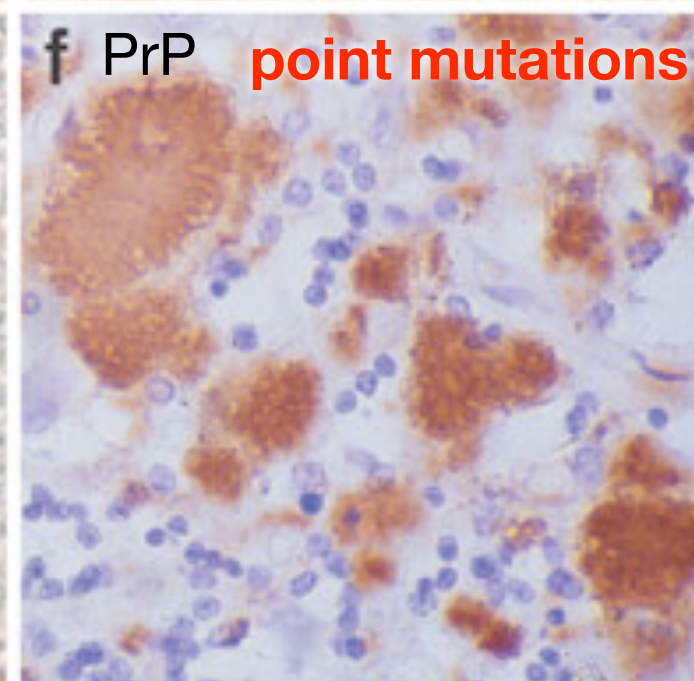
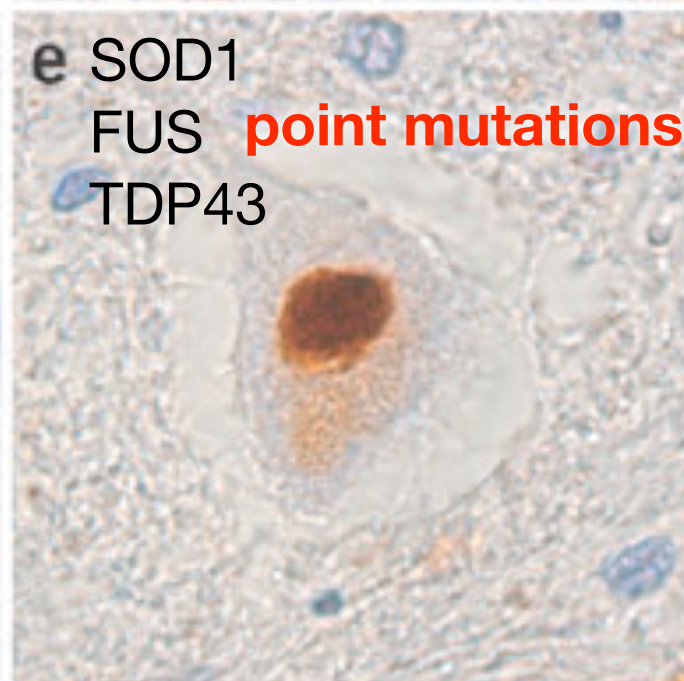
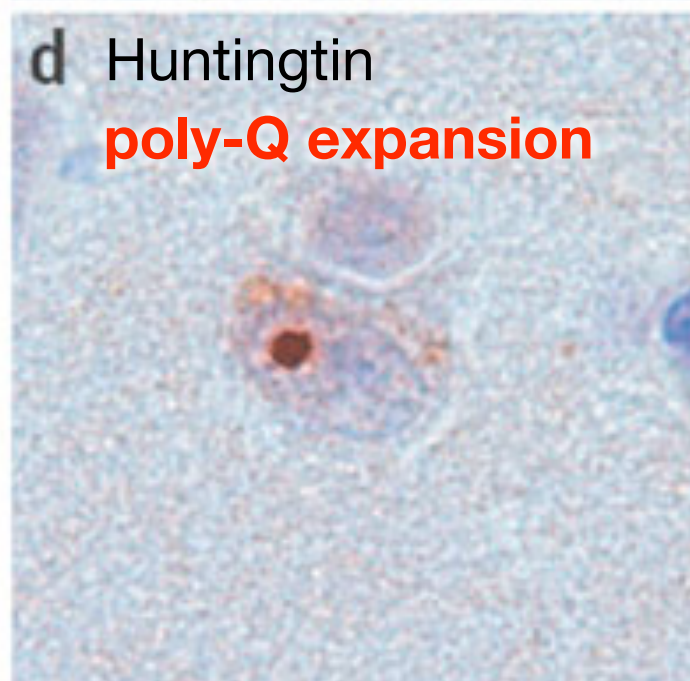
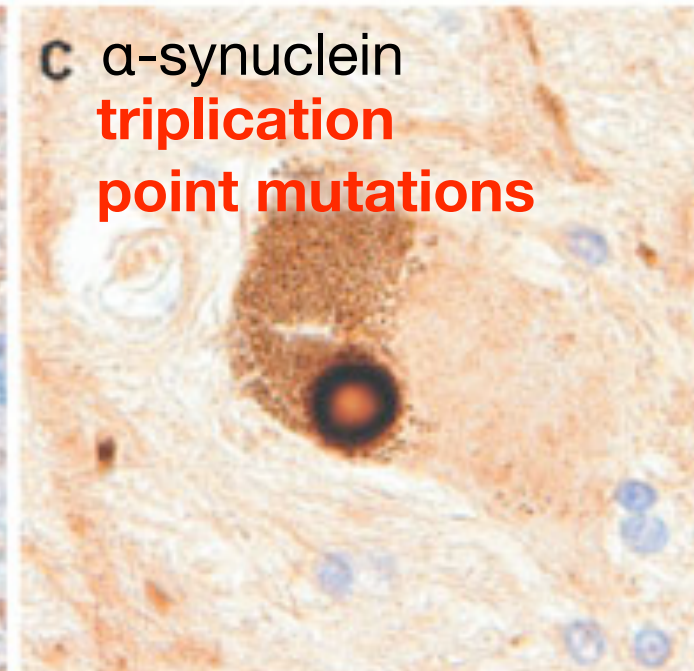
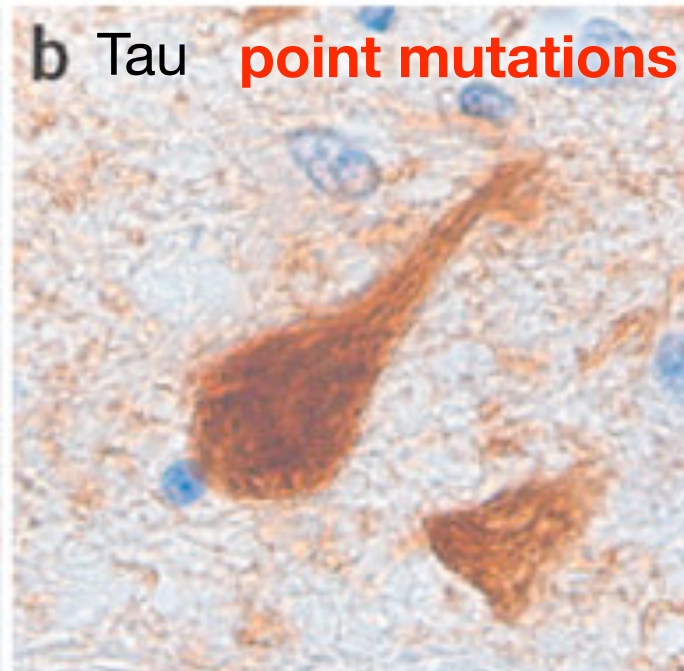
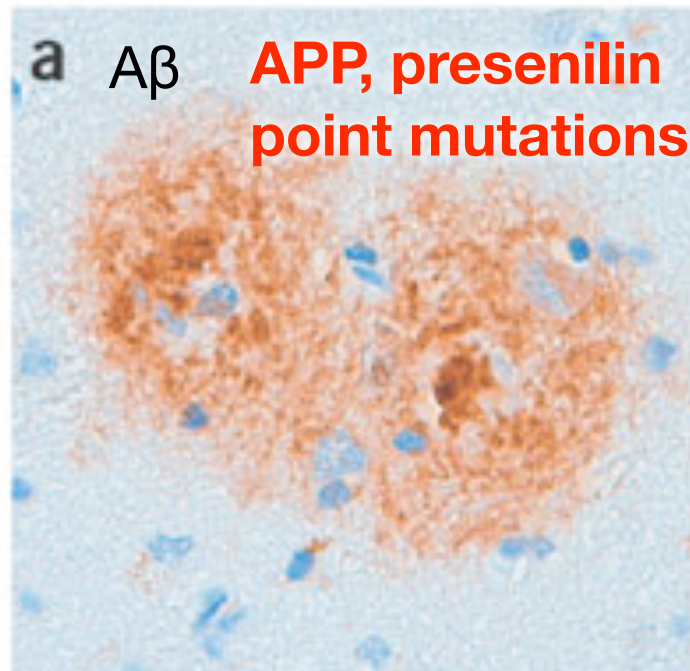


Protein aggregates in neurodegenerative diseases

Alzheimer's Disease

Alzheimer's Disease
Frontotemporal dementia

Parkinson's Disease



Huntington's disease

ALS

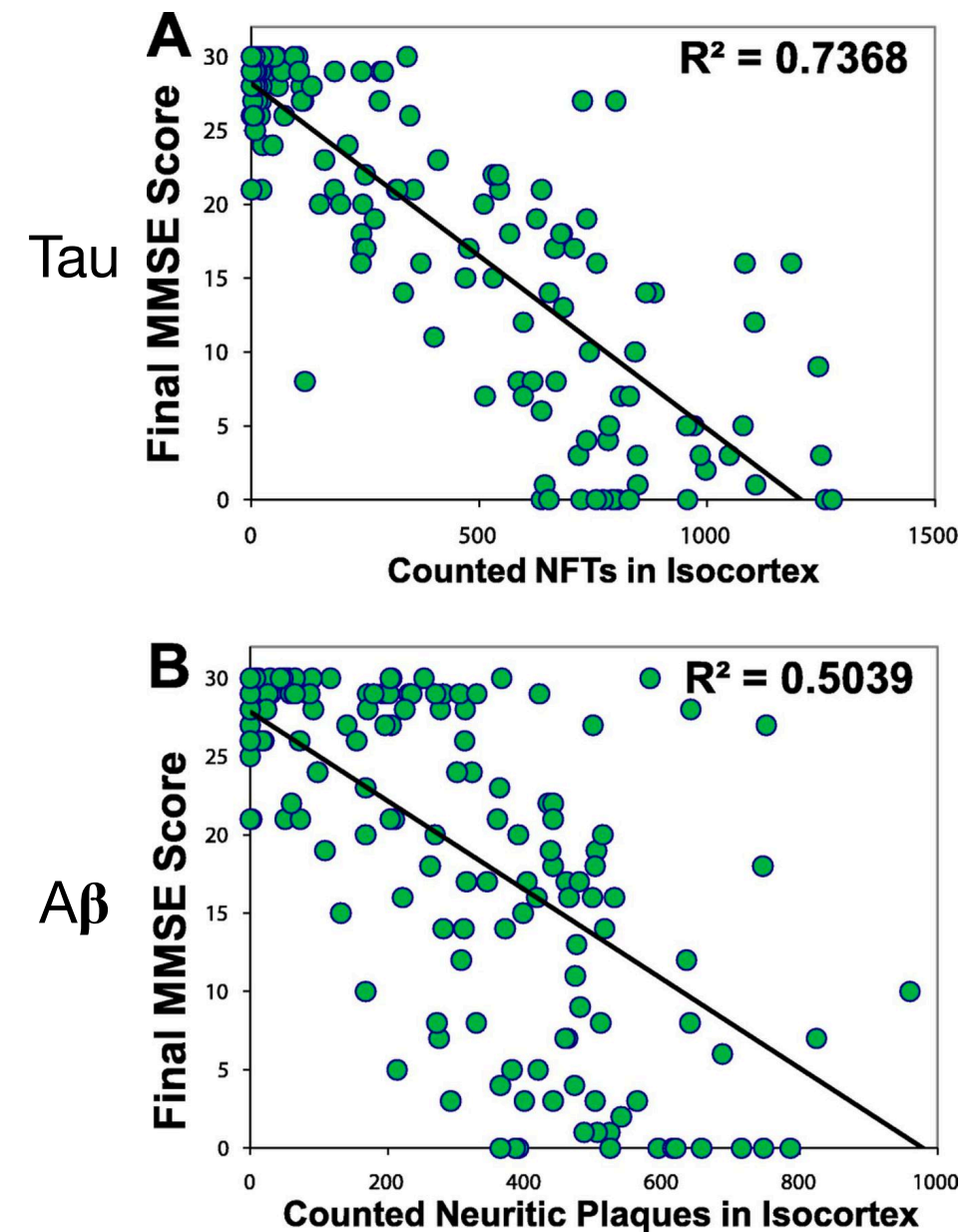
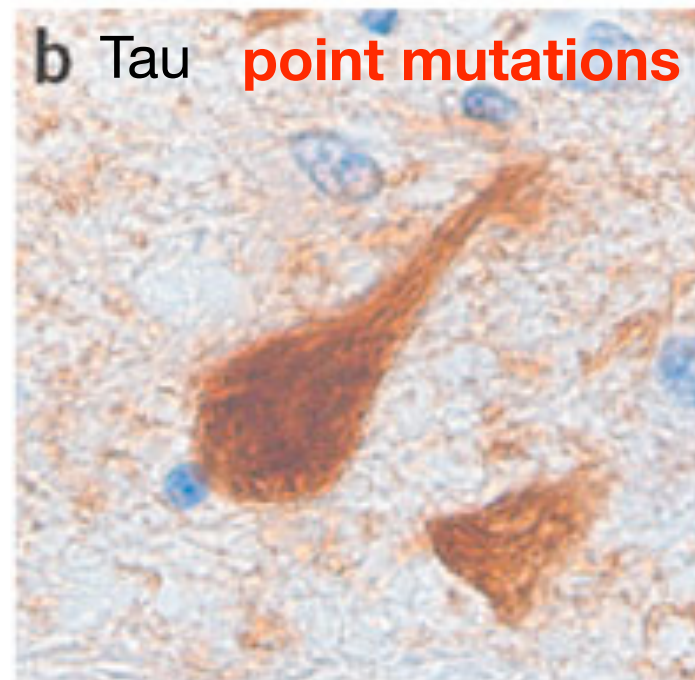
Creutzfeld Jacob Disease

adapted from Forman *et al* (2004)



Protein aggregates in neurodegenerative diseases

Alzheimer's Disease
Frontotemporal dementia

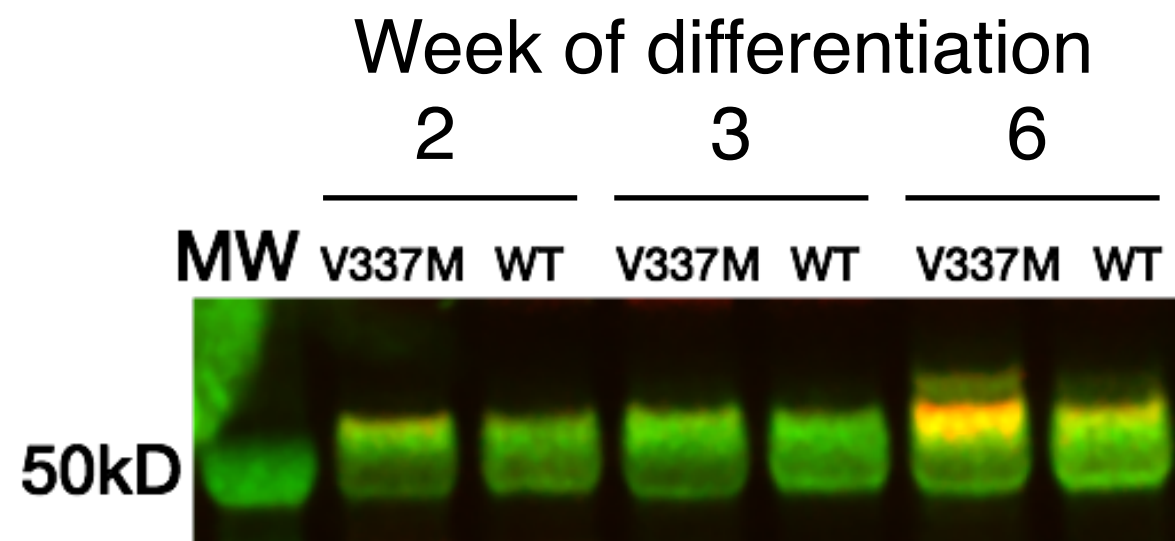


Nelson *et al* (2017) *JNEN*



V337M tau forms oligomers in iPSC-derived neurons

Neurons from isogenic *MAPT* V337M vs. WT iPSCs (Li Gan)

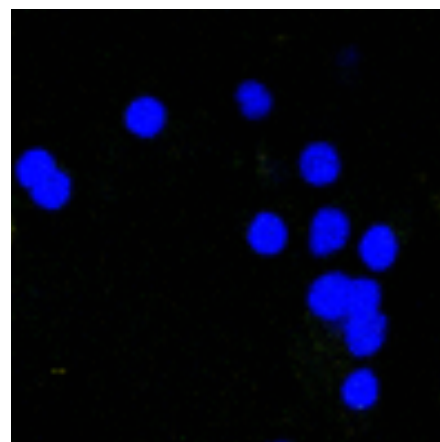


Total tau

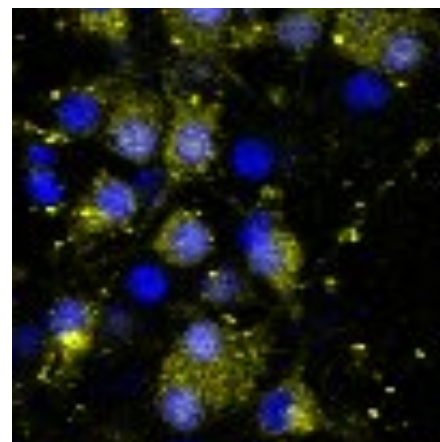
Phospho-tau (AT8)



Avi Samelson



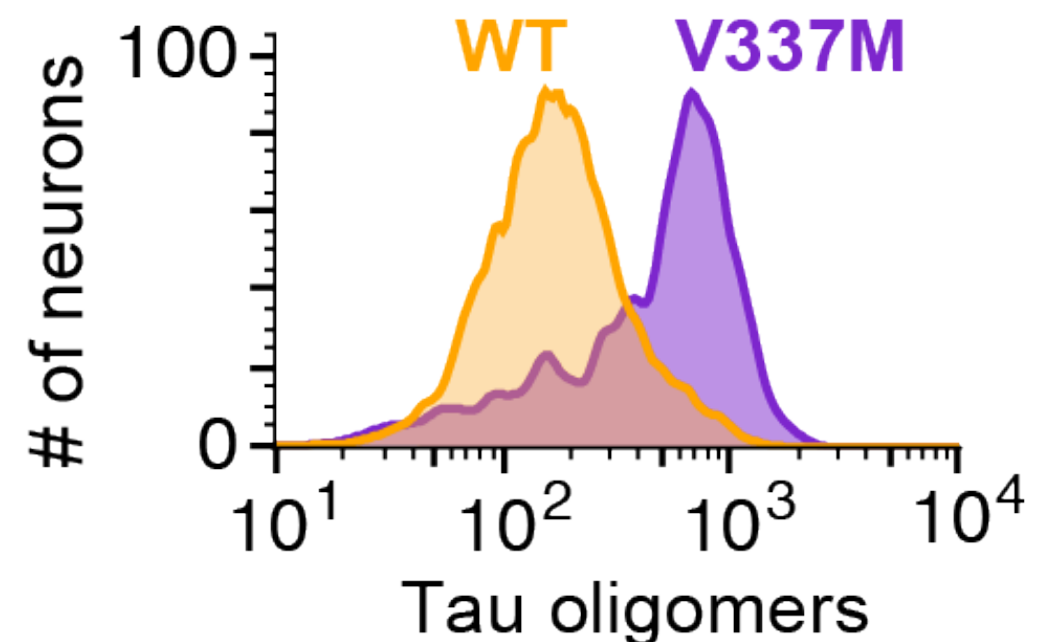
WT



V337M

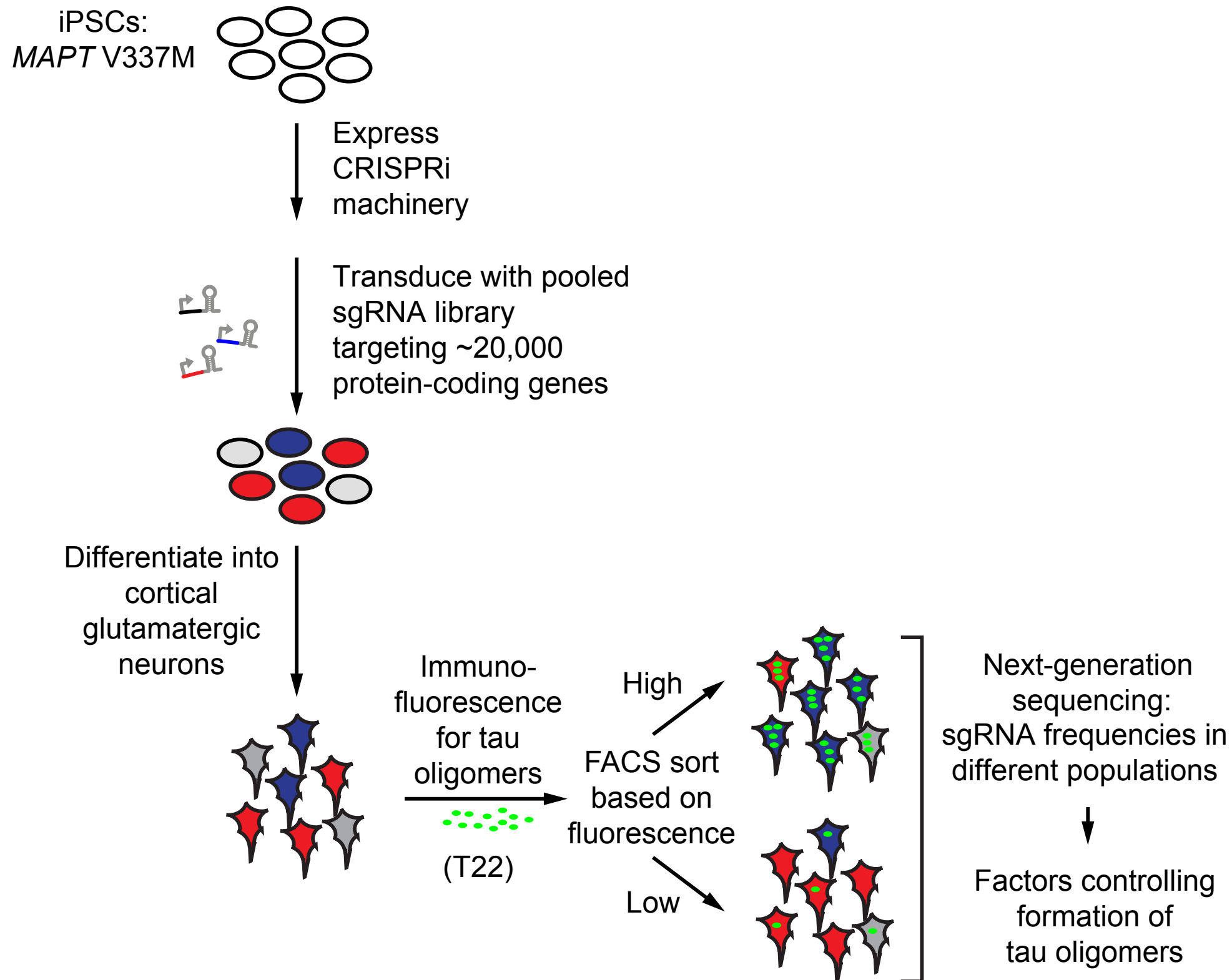
■ Hoechst

■ Tau oligomers (T22)





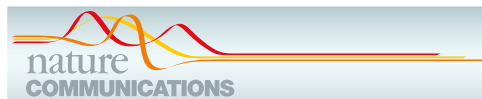
Genome-wide CRISPRi screen for tau aggregation



Avi Samelson



Modifiers of neuronal tau aggregation



ARTICLE

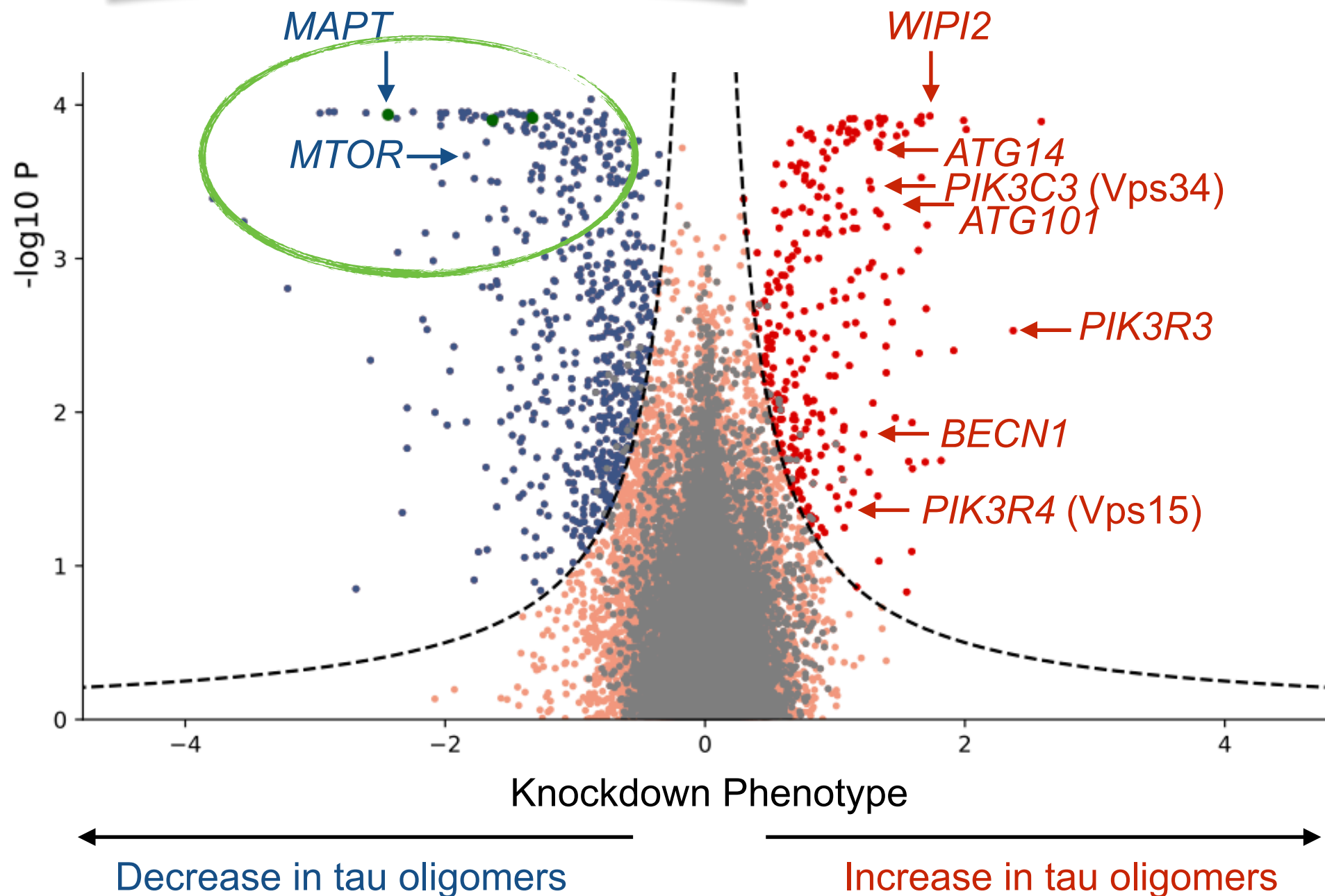
<https://doi.org/10.1038/s41467-020-16984-1>

OPEN

Prolonged tau clearance and stress vulnerability rescue by pharmacological activation of autophagy in tauopathy neurons

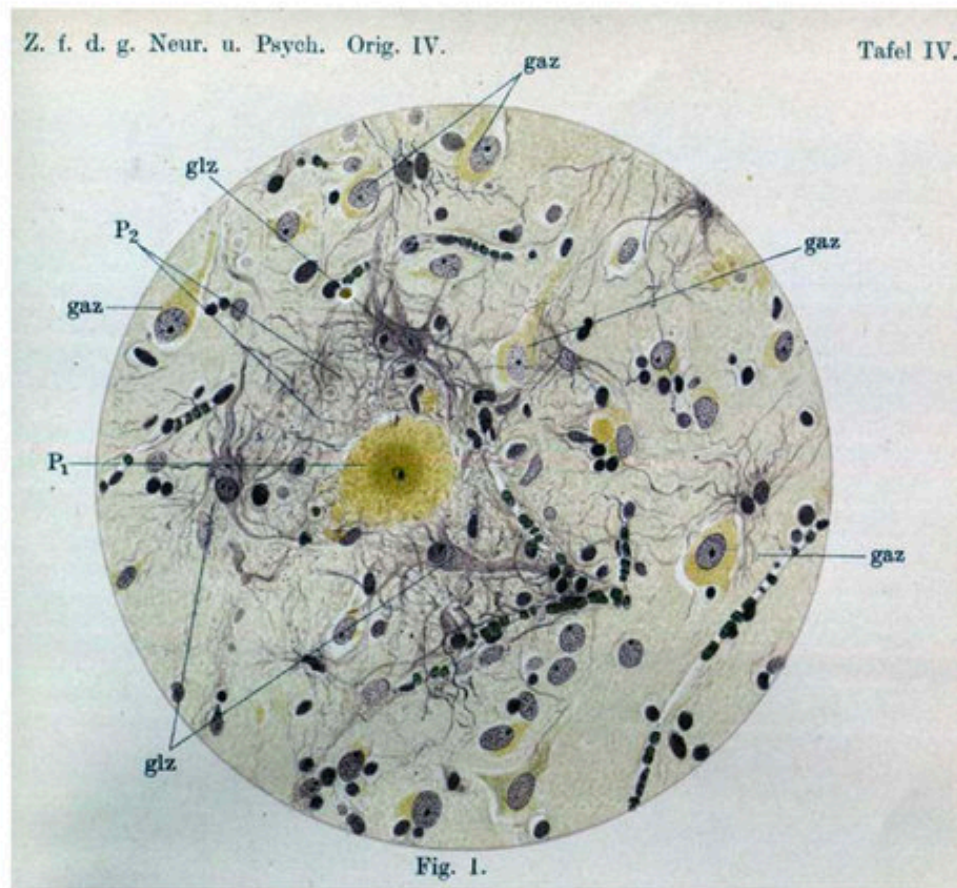
M. Catarina Silva¹, Ghata A. Nandi¹, Sharon Tentarelli², Ian K. Gurrell³, Tanguy Jamier³, Diane Lucente⁴, Bradford C. Dickerson⁵, Dean G. Brown⁶, Nicholas J. Brandon⁷ & Stephen J. Haggarty¹✉

Check for updates

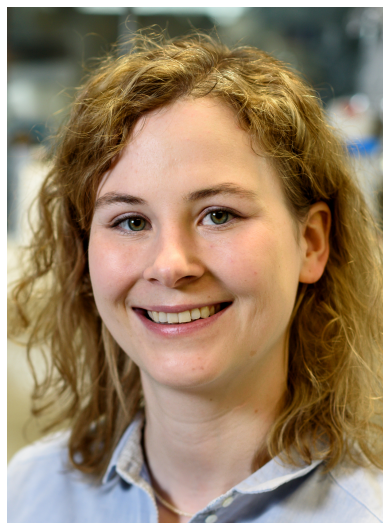


Avi Samelson

How do microglia contribute to neurodegenerative disease?



- Microglia undergo disease-associated changes
- Human genetics supports a causal role for microglia in neurodegenerative diseases
- Which mechanisms control disease states?
- Therapeutic strategies?



Nina Dräger



Syd Sattler

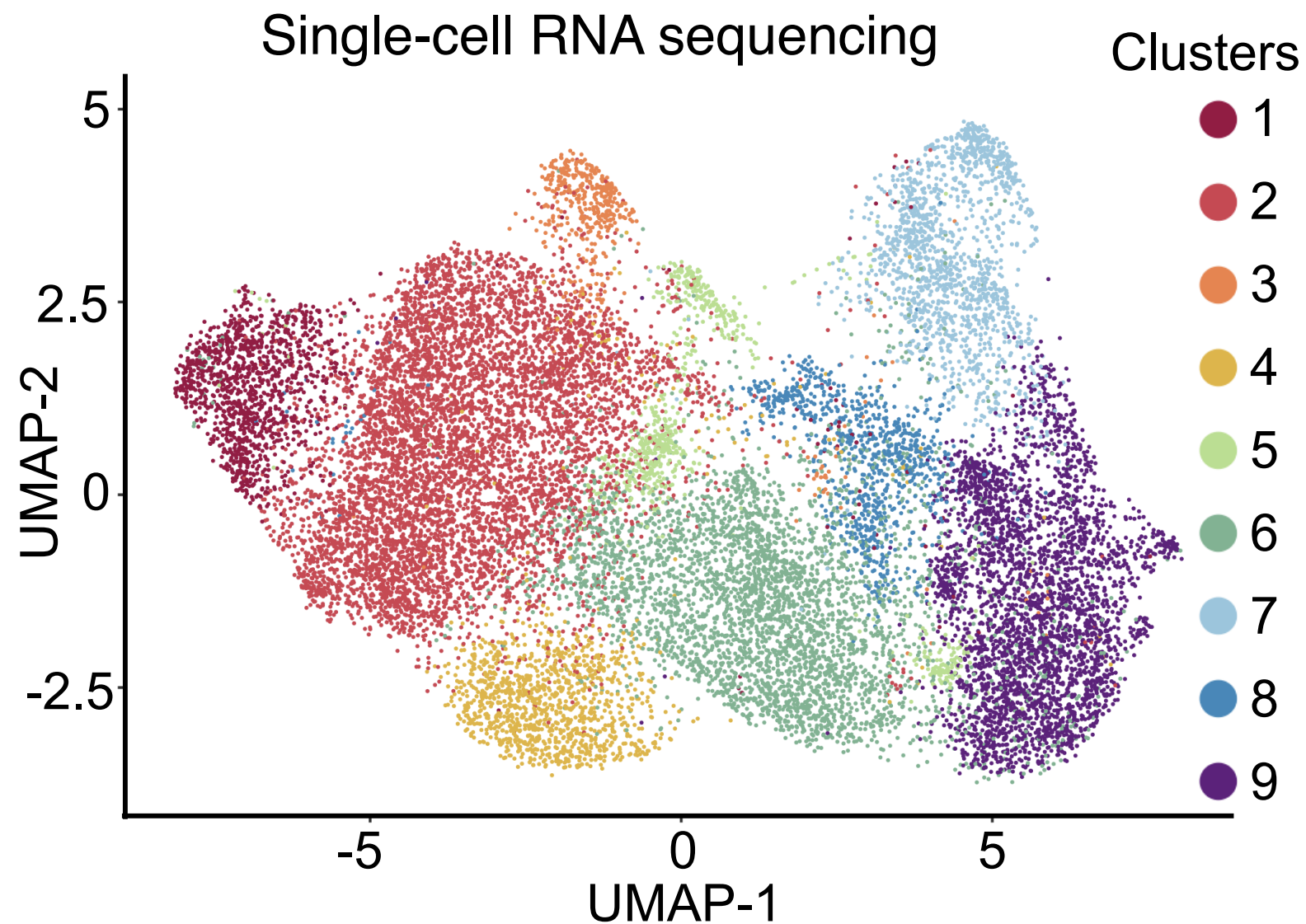
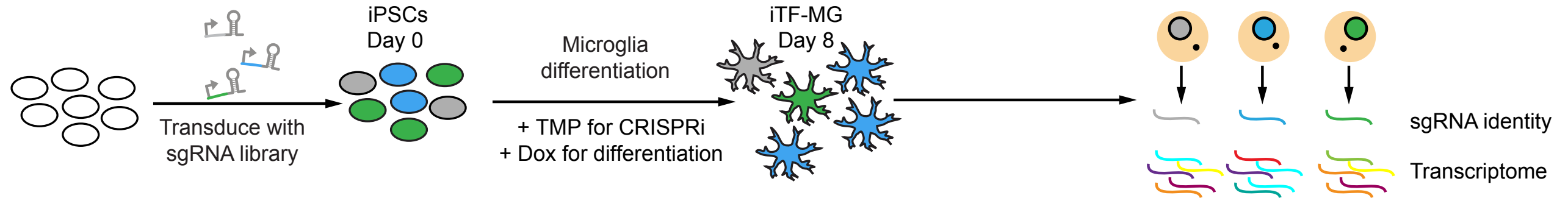


Olivia Teter

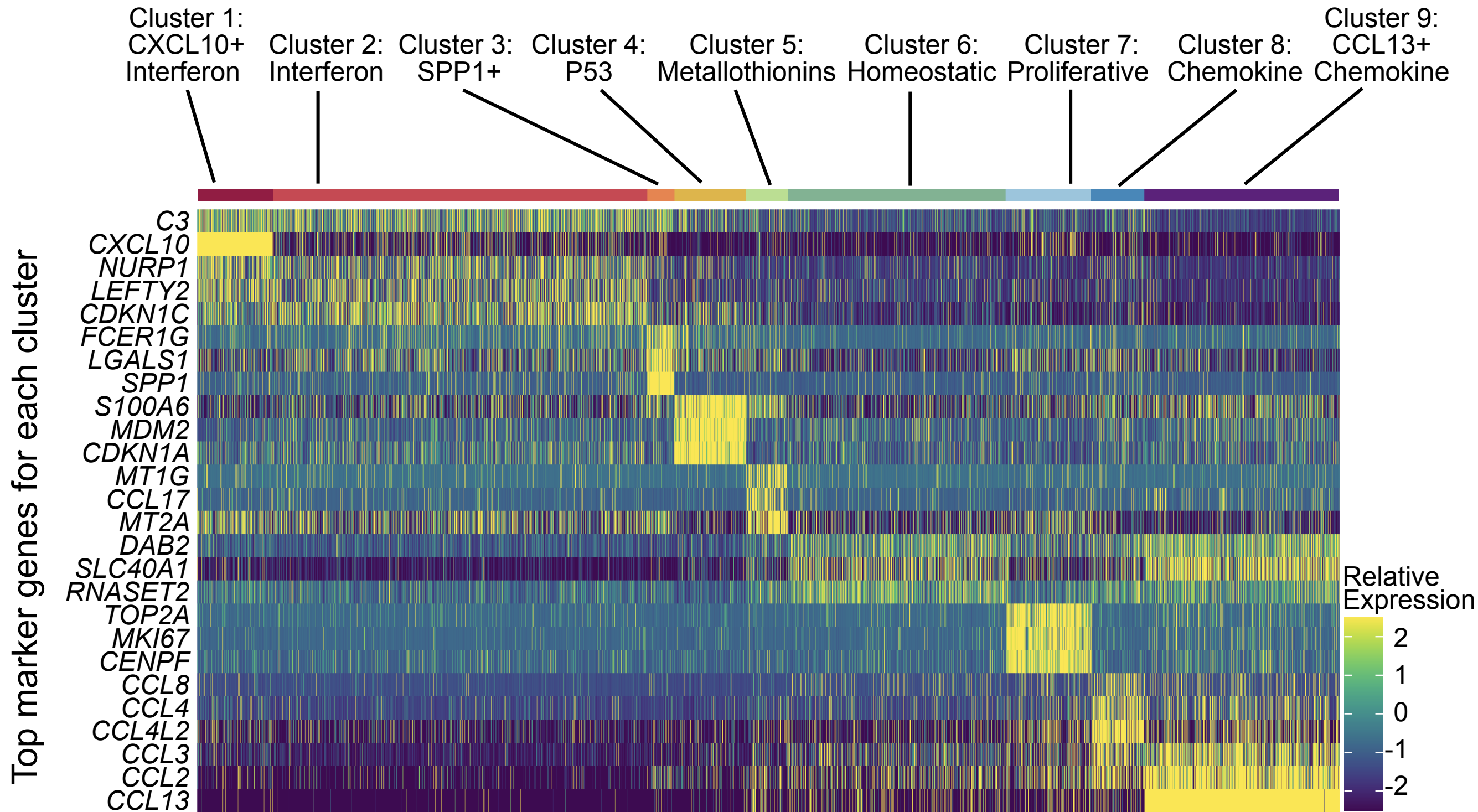
Collaboration
with Li Gan

bioRxiv 2021.06.16.448639

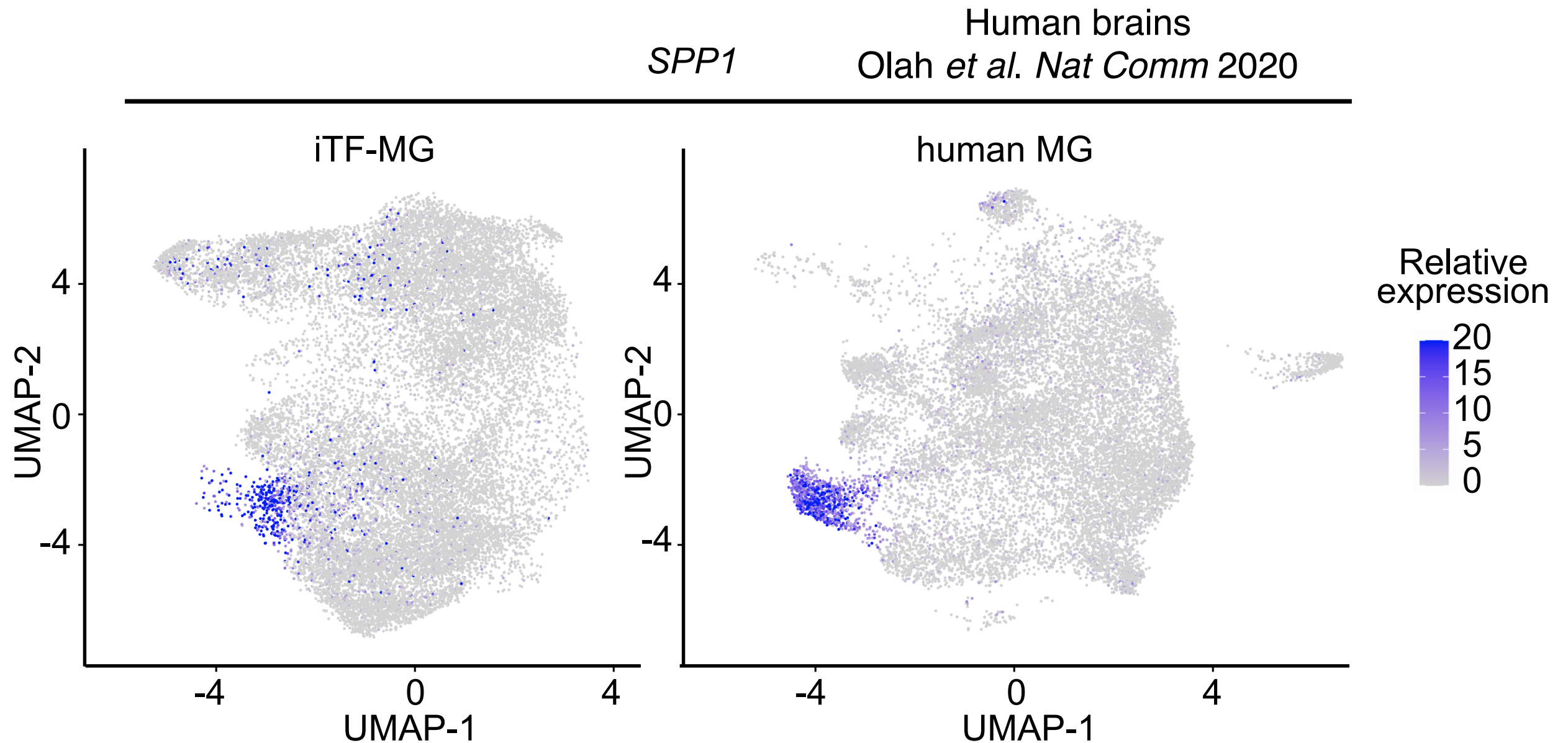
CROP-Seq screen in iPSC-derived microglia



iPSC-derived microglia adopt disease-relevant states

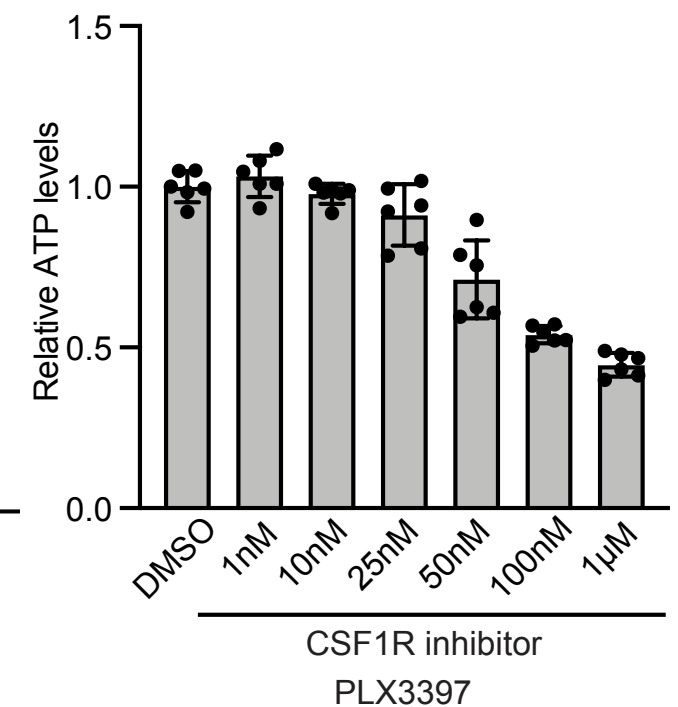
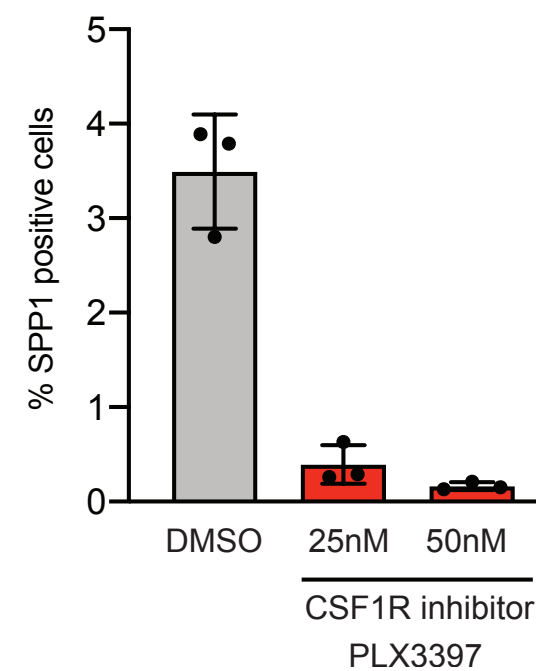
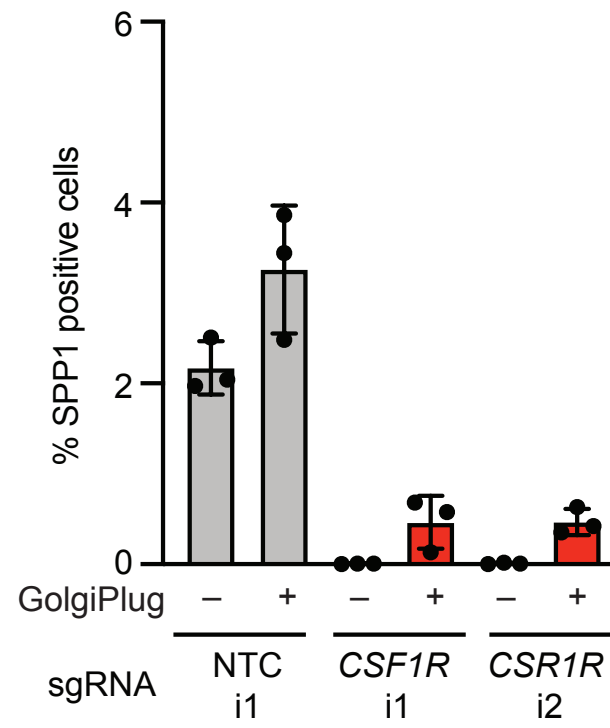
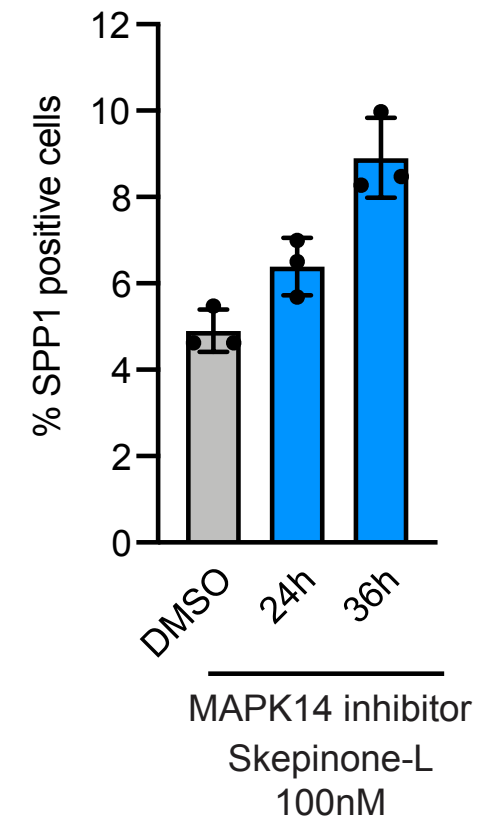
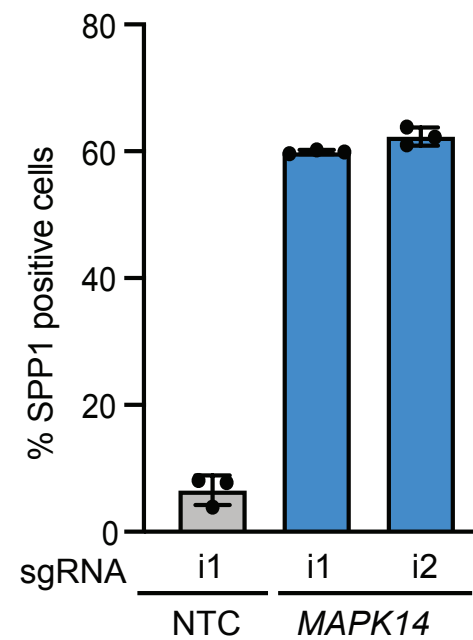
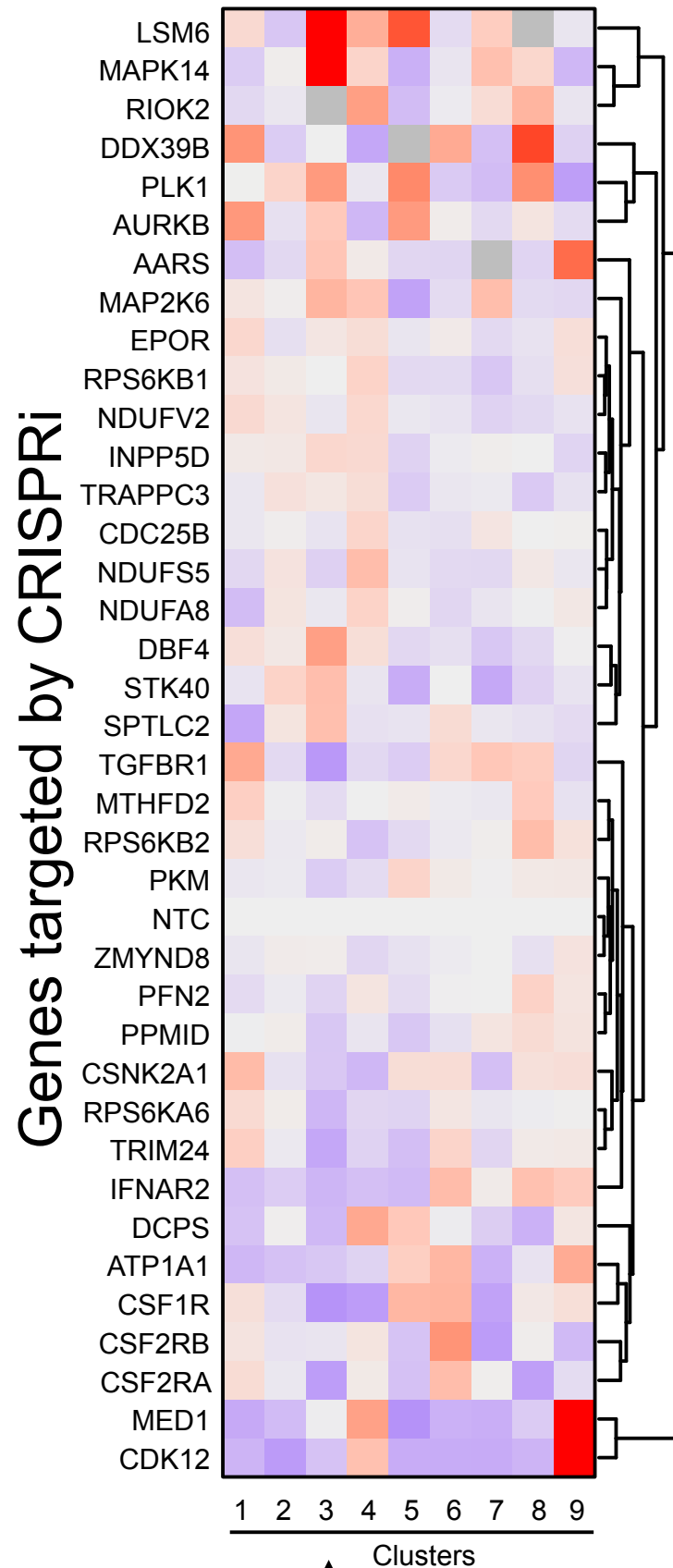


iPSC-derived microglia adopt disease-relevant states



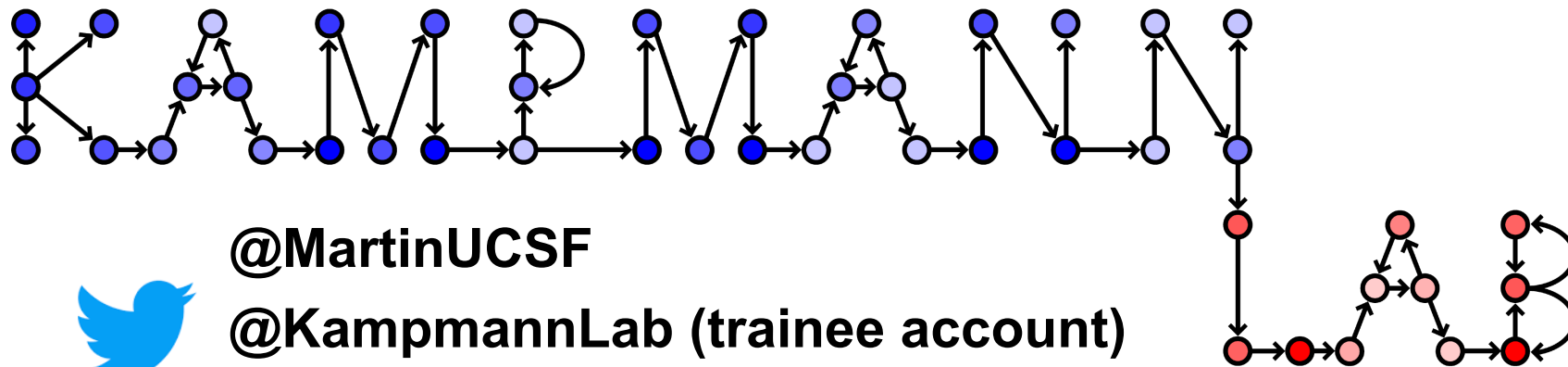
Enrichment of *SPP1*+ cells in
Alzheimer's disease brains over control: $P < 10^{-6}$

Uncovering regulators of microglia states



Future directions / challenges

- Define relevant readouts in cell-based model systems
- Develop CRISPR screens in more physiological systems
 - Specific neuronal subtypes
 - 3D co-culture models
 - Brain organoids
 - In vivo models
- Large-scale characterization of genetic variation on the nucleotide level
 - Base editing / prime editing
 - Deep mutational scanning



@MartinUCSF

@KampmannLab (trainee account)

@CRISPRbrain



Li Gan (Weill Cornell)



CZI
Ben Barres
Early Career
Acceleration
Award



Chan
Zuckerberg
Biohub
Investigator
Award

NIH DIRECTOR'S
NEW INNOVATOR
AWARD



NIH
Director's
New
Innovator
Award



Allen
Distinguished
Investigator
Award



NIH/NIA



Tau
Consortium



NIH/NINDS
Tau Center
without Walls



Alzheimer's
Association