The DESSH Foundation

DESSH Symposium
Gabel Lab Research Update

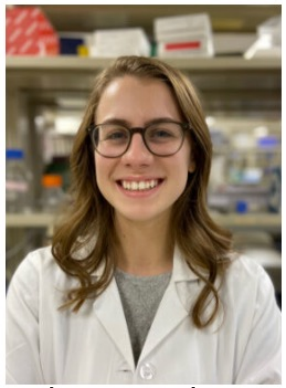
Harrison Gabel, PhD

Alyssa Erickson

9-30-23

Gabel lab at Washington University in St. Louis

- Lab established in 2015 to study gene regulation in brain development and function
- Studying the basic molecular functions of multiple genes in the brain
- Applying what we learn to understanding neurodevelopmental disorders



Alyssa Erickson
Carrying out DESSH research

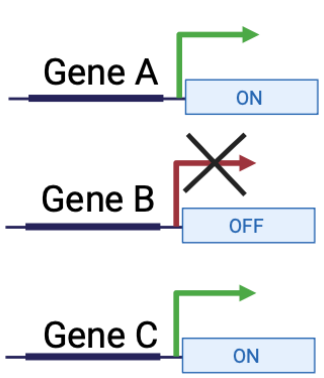
TBRS community

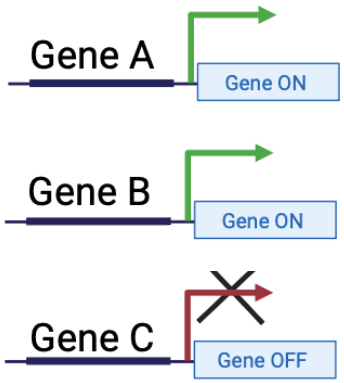
rett syndrome research trust

Neurons in the brain require precise gene regulation to carry out their functions

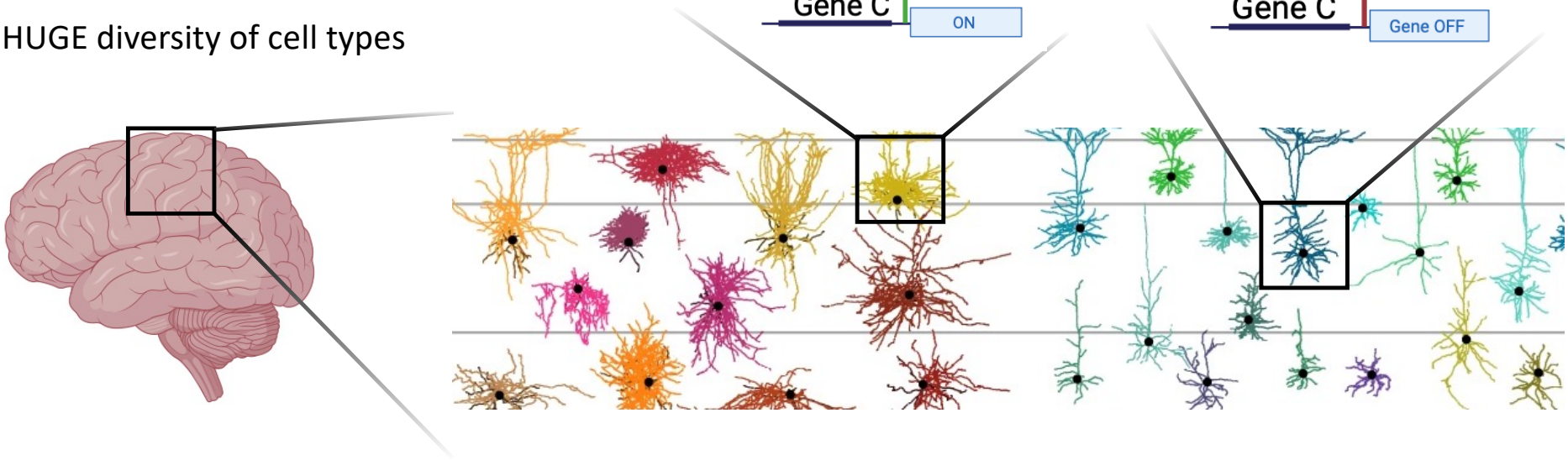
Functions are controlled by gene expression

DNA (Genes) → RNA → Proteins → Cellular functions





HUGE diversity of cell types



Neurons in the brain require precise gene regulation to carry out their functions

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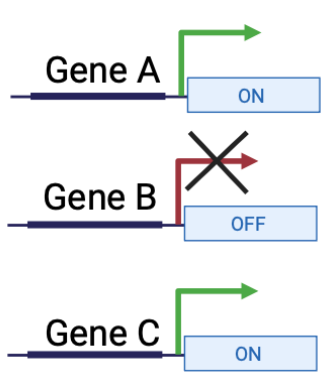
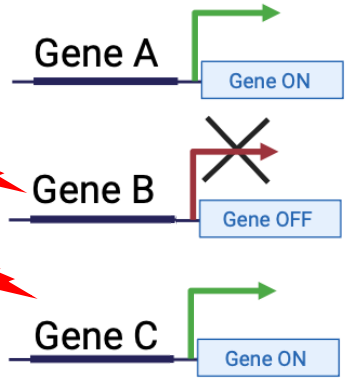
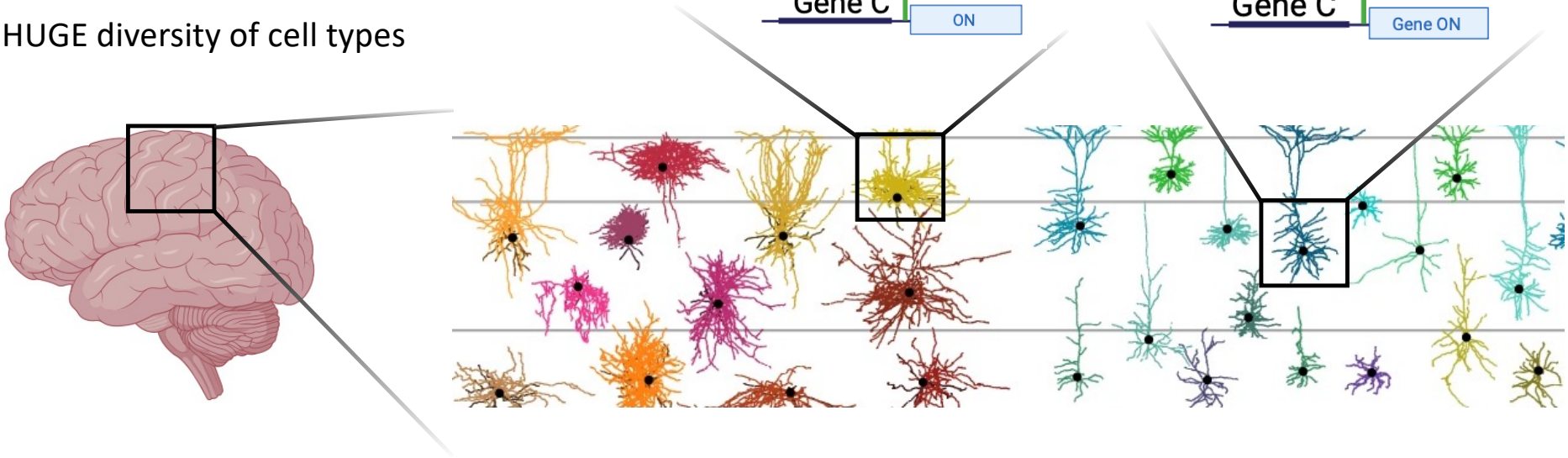


Genetic Disorders



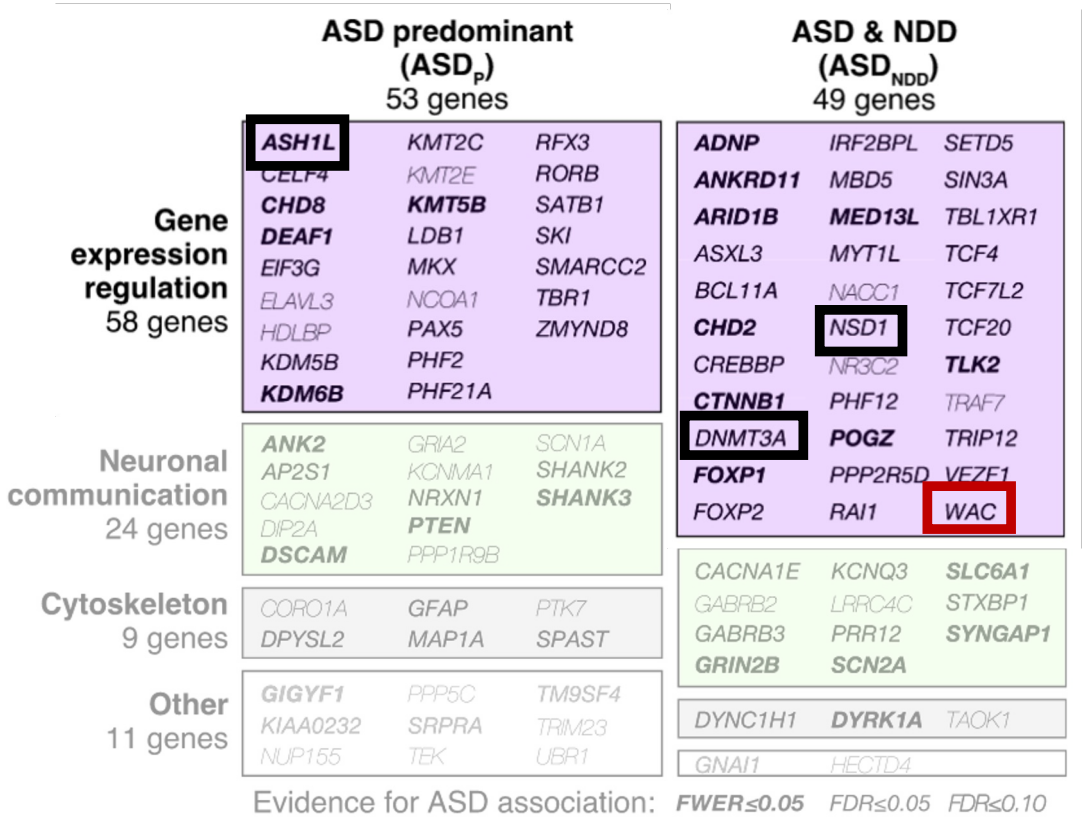
Altered Functions

HUGE diversity of cell types

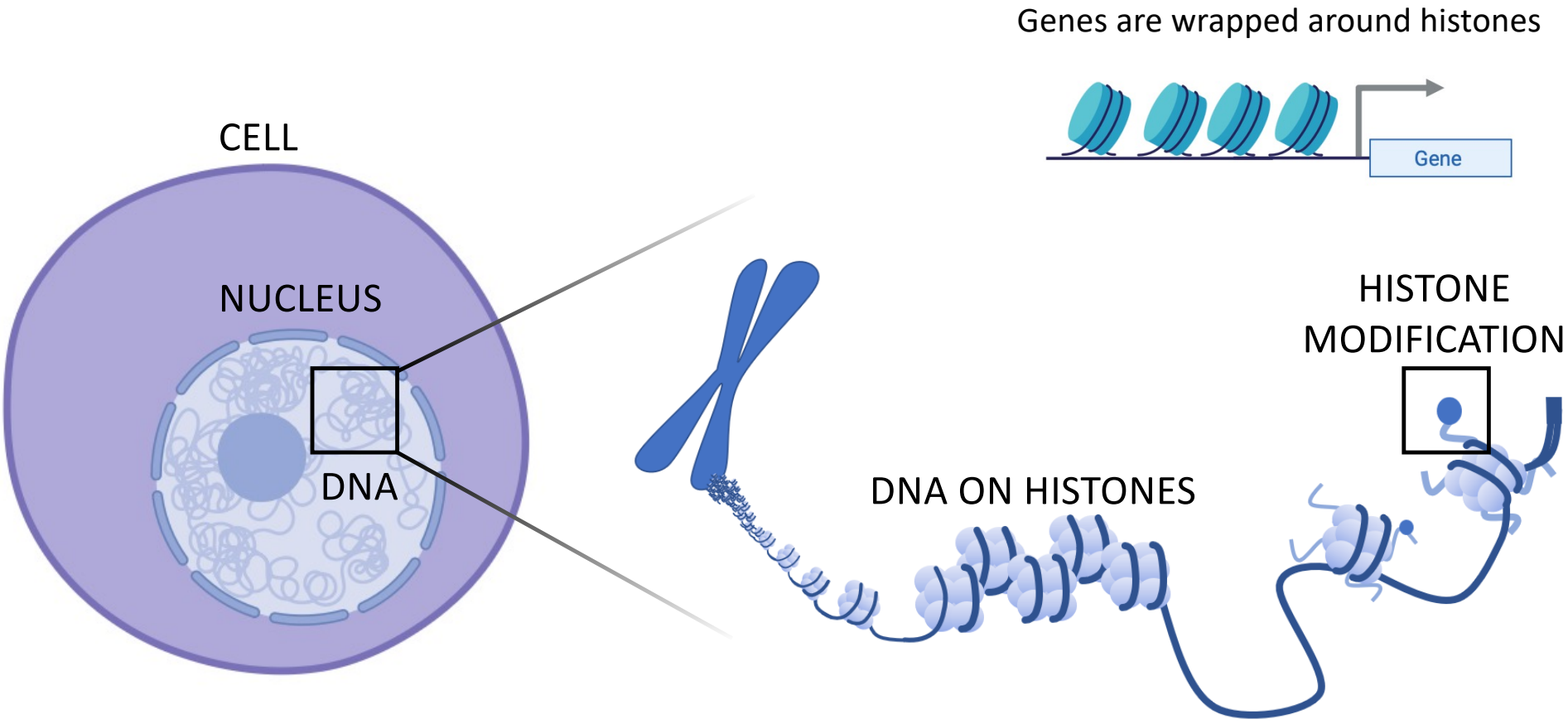


Neurons in the brain require precise gene regulation to carry out their functions

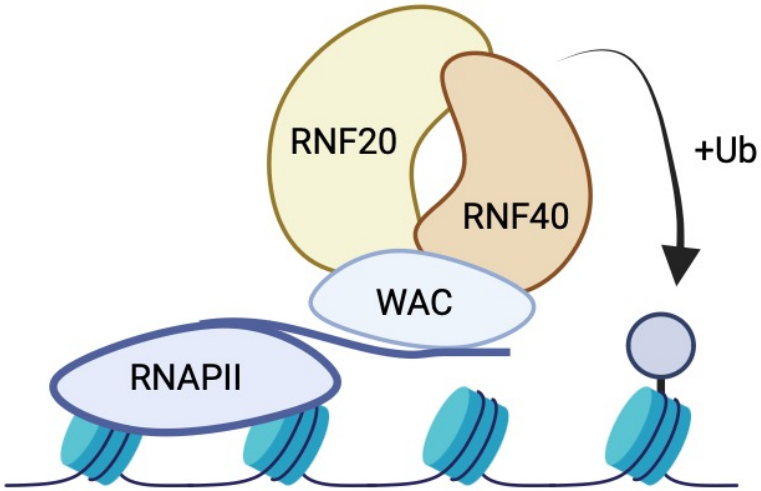
Neurodevelopmental disorders commonly arise from to disruption of **genes that regulate other genes**



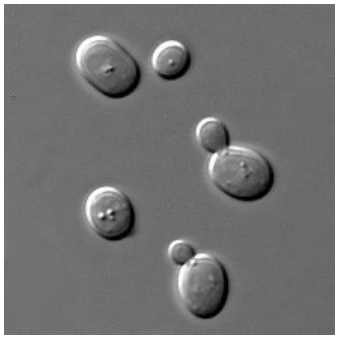
Histone modifications help regulate genes



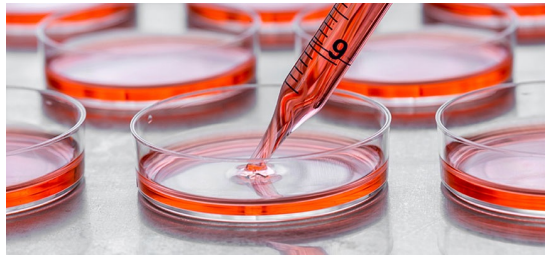
WAC facilitates the histone modification H2B monoubiquitin (H2Bub)

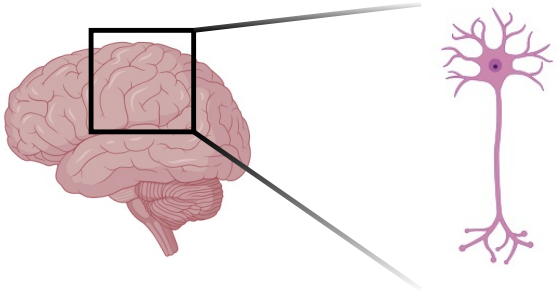


Yeast



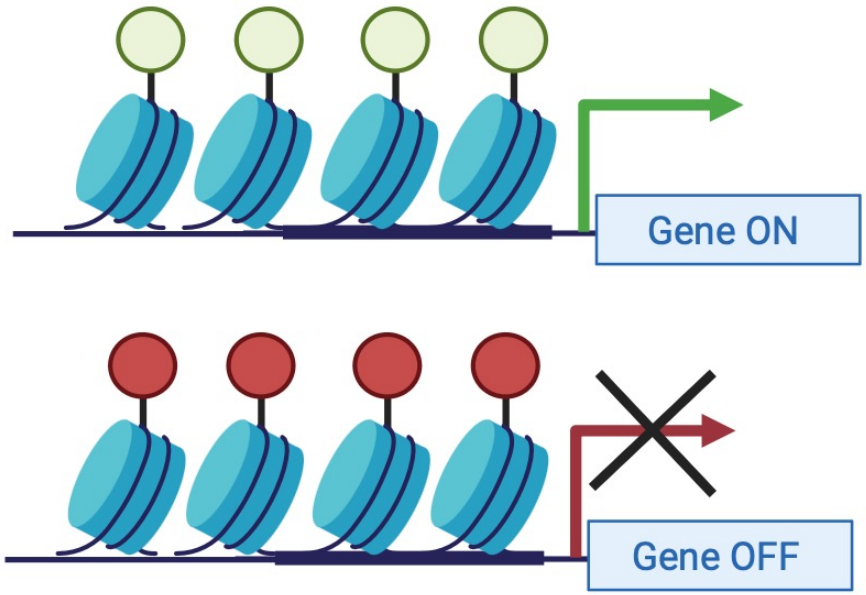
Cell lines

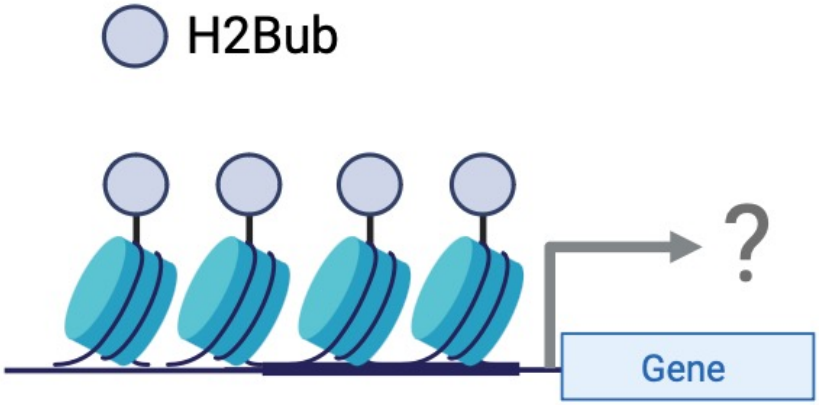




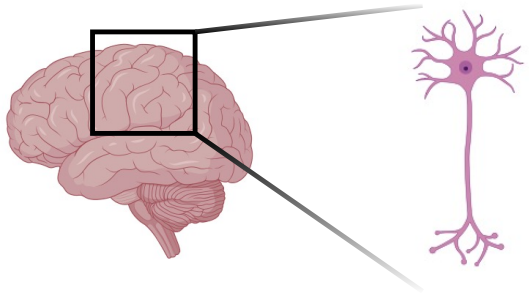
Neurons in the brain?

H2B monoubiquitin (H2Bub) is a modification that affects gene expression





Important to determine if/how WAC affects H2Bub and gene regulation in neurons in the brain



Goal: study the effects of a **complete WAC knockout** on:

- H2Bub

- Neuronal gene transcription

Why complete knockout?

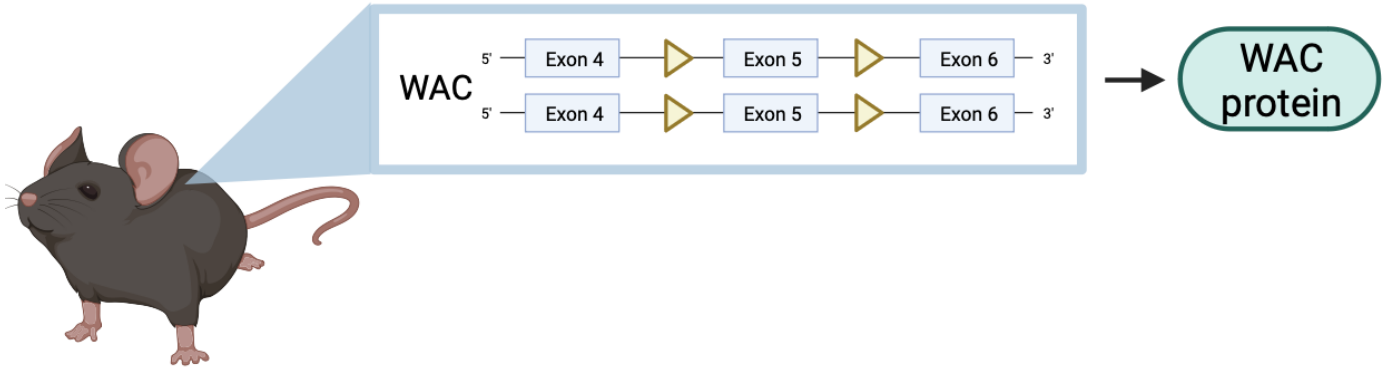
- Allows us to determine core functions of WAC

- Effects are larger, discoveries in a complete knockout tell us where to look in heterozygous knockout

How to make a complete knockout of WAC?

In mice, if both copies of Wac are deleted, the mouse will not live to birth

We use a **conditional knockout mouse**



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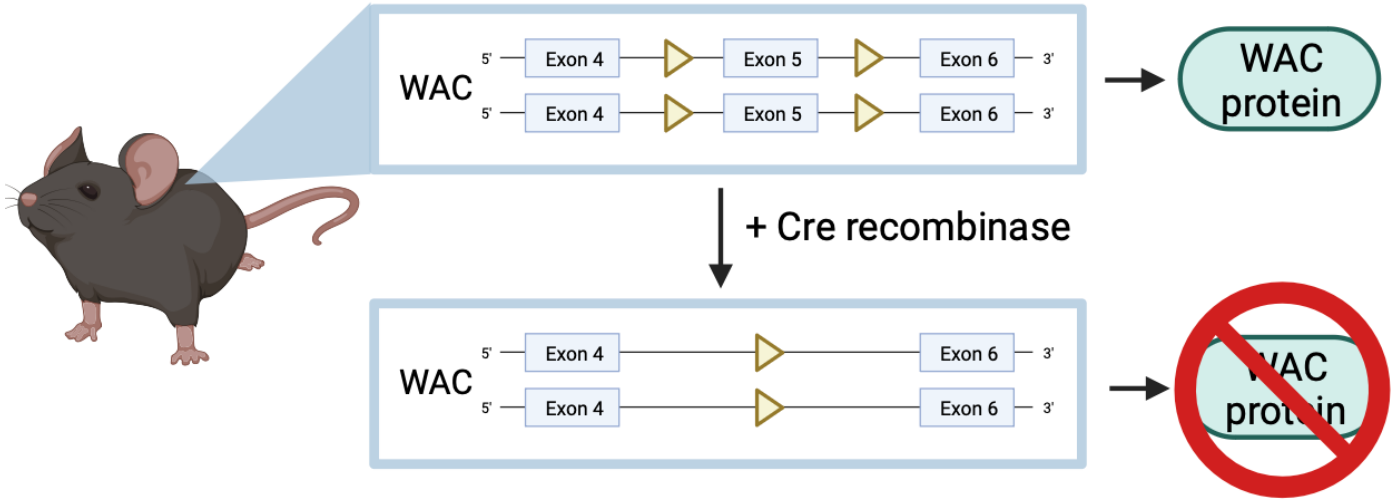
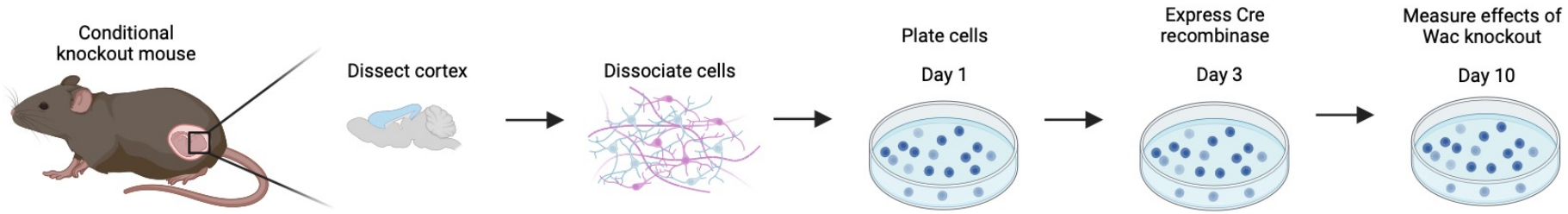


Cultured neurons allow for manipulation

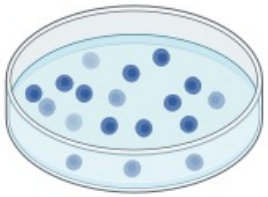
Can easily treat with Cre recombinase to delete WAC



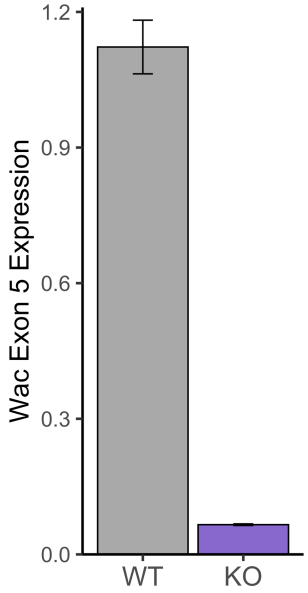
Now we can ask: does WAC affect H2Bub in neurons?

Measure effects of Wac knockout

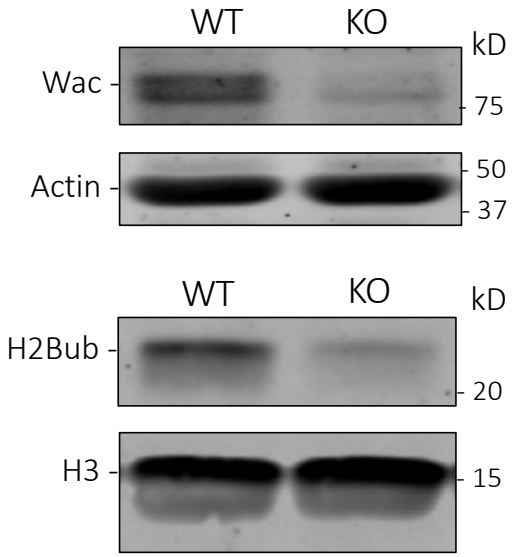
Day 10



Confirm loss of WAC



Measure amount of H2Bub



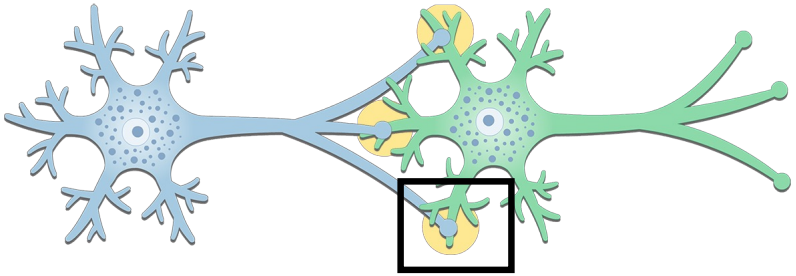
Gene pathways related to **synaptic function** are dysregulated

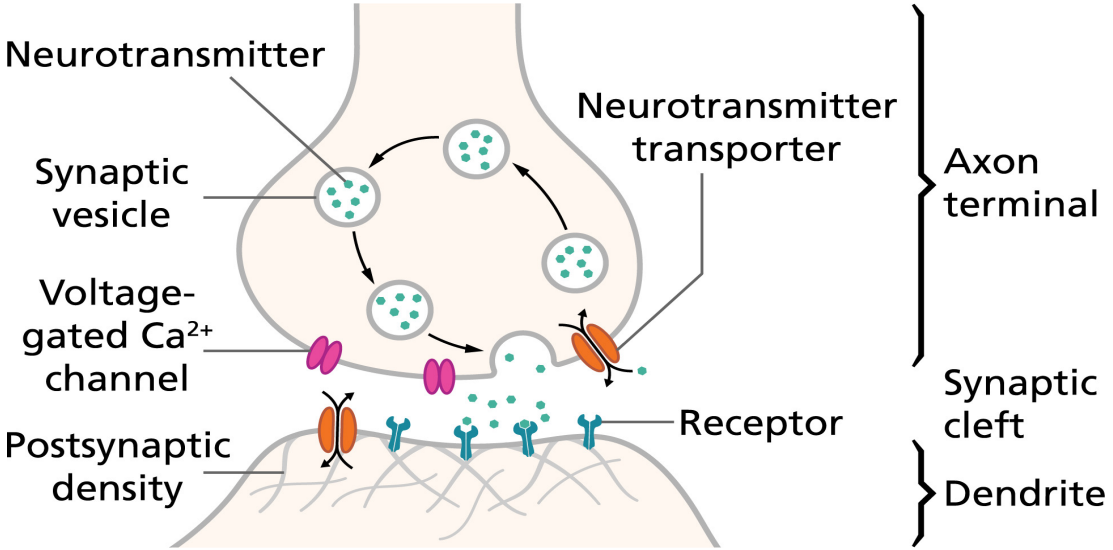
~400 genes are dysregulated in Wac KO

What does this mean for neuron function?

There is an enrichment for dysregulated genes to be involved in **synaptic function**

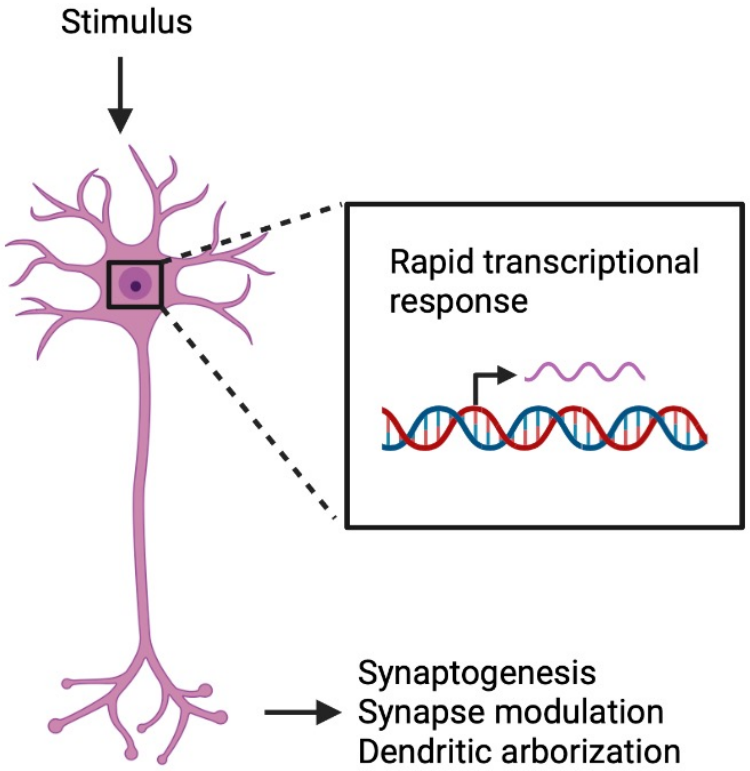
Neurons send and receive signals at their synapses, and this requires complex and precise regulation





https://qbi.uq.edu.au

How is loss of WAC affecting synaptic function?

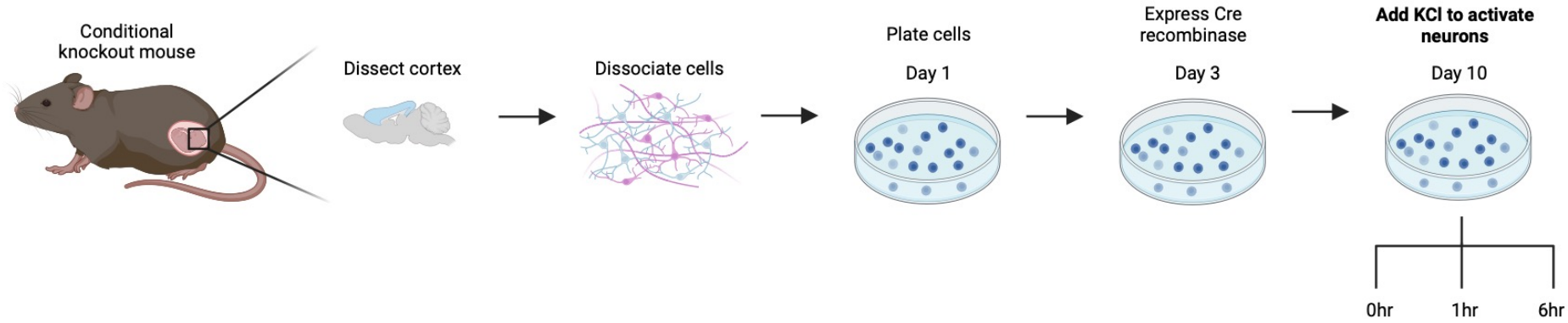


H2Bub is important for rapid gene expression in other systems

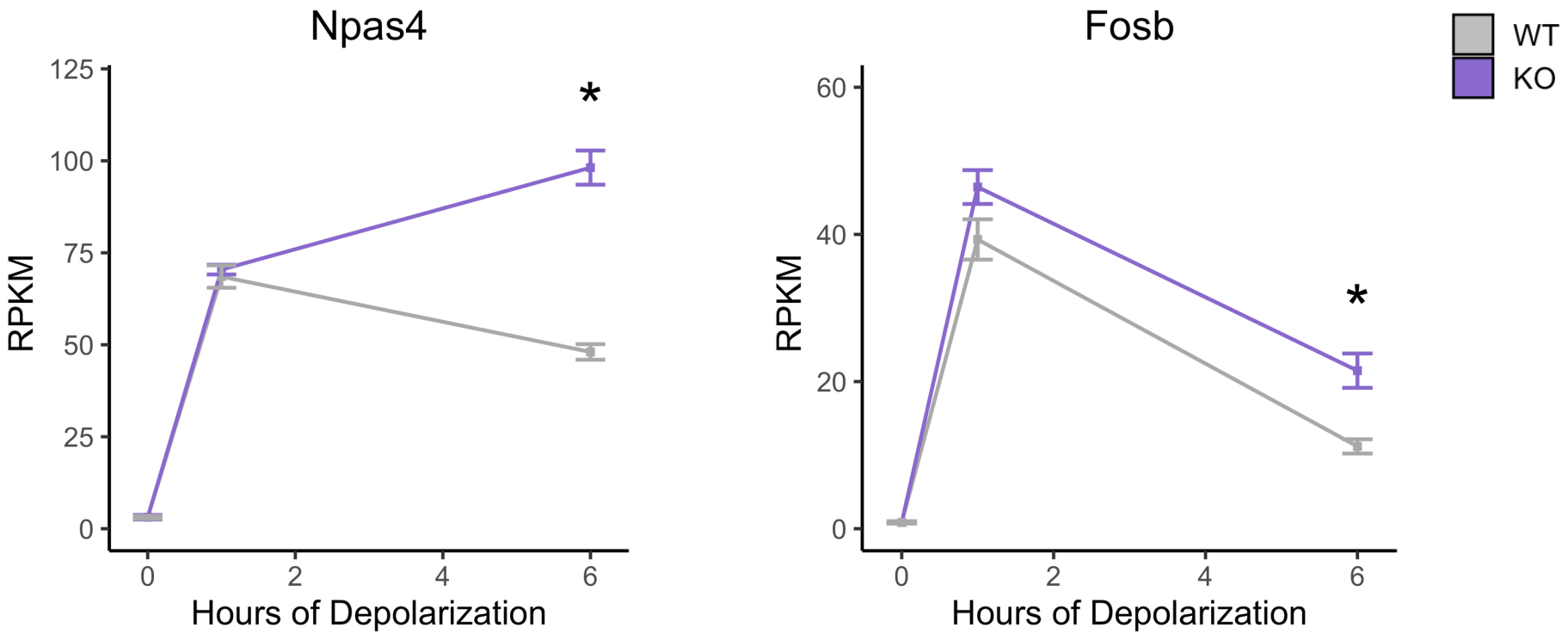
Is it necessary for neurons to respond to synaptic activity?

Is WAC necessary for activity-dependent transcription?

KCl can be used to induce neurons to depolarize so that neuronal activity can be studied

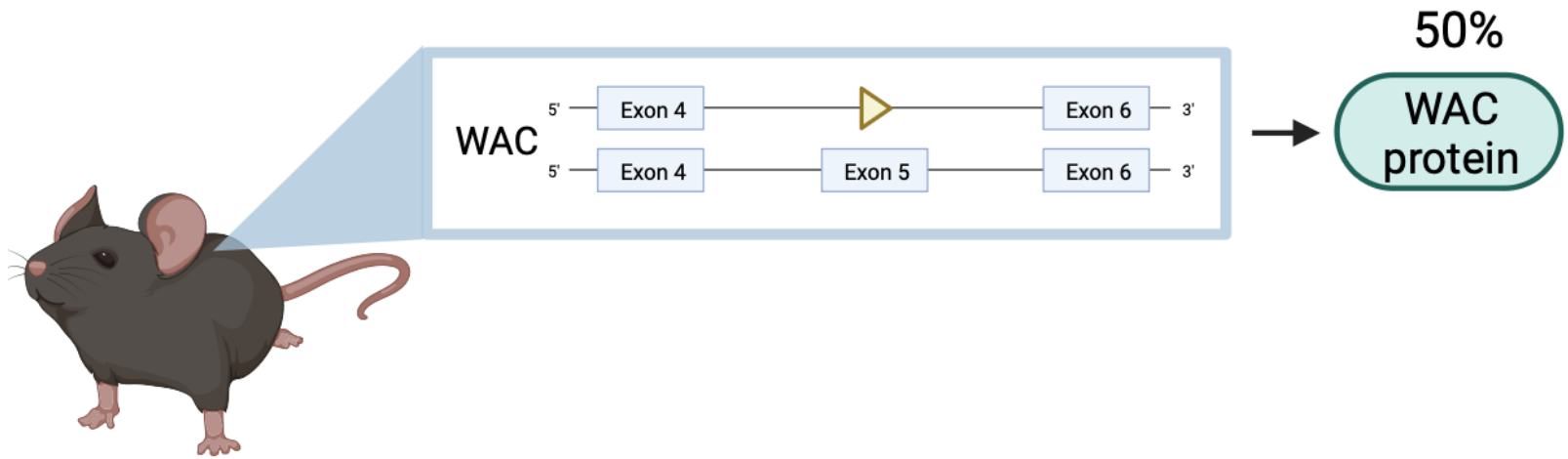


WAC knockout causes over-induction of several activity genes

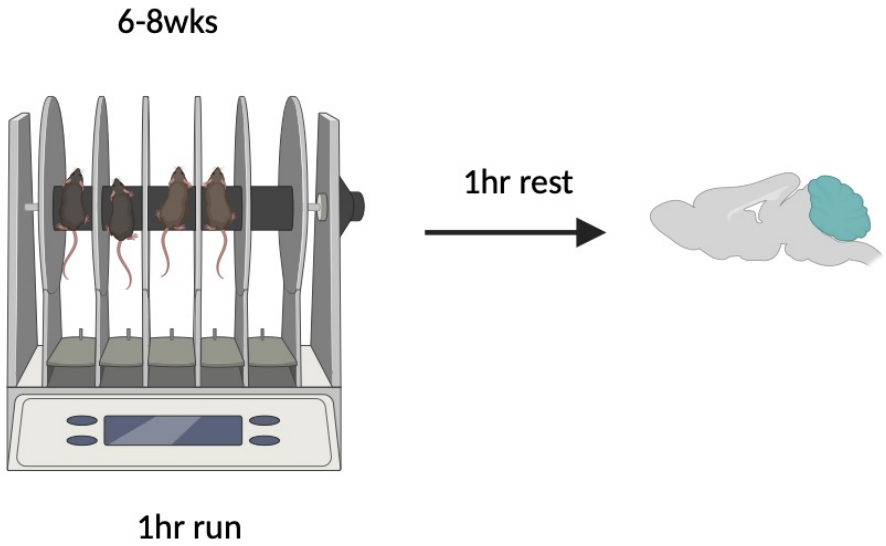


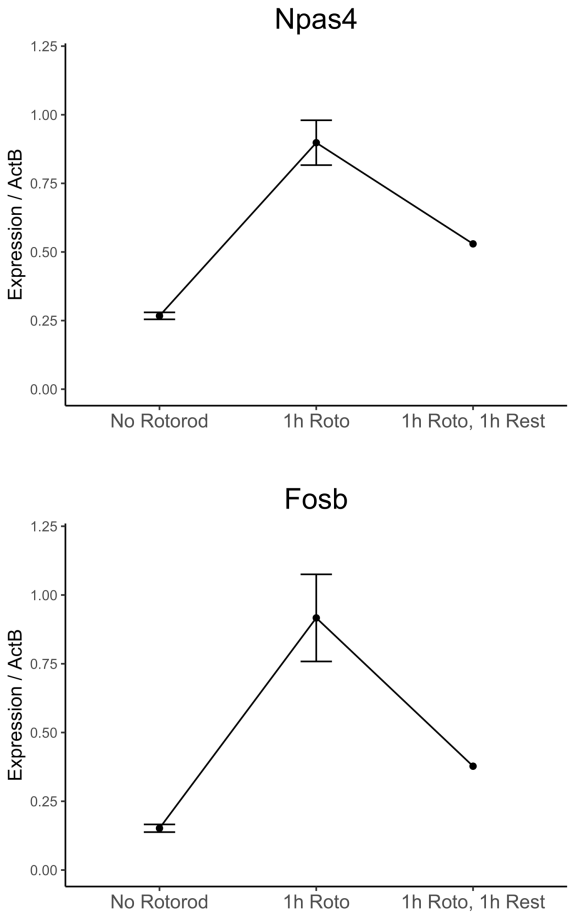
Future direction: is activity-dependent transcription disrupted *in vivo* in a DESSH model?

DESSH mouse model: **heterozygous WAC knockout**



Example: use motor activity to study induced expression

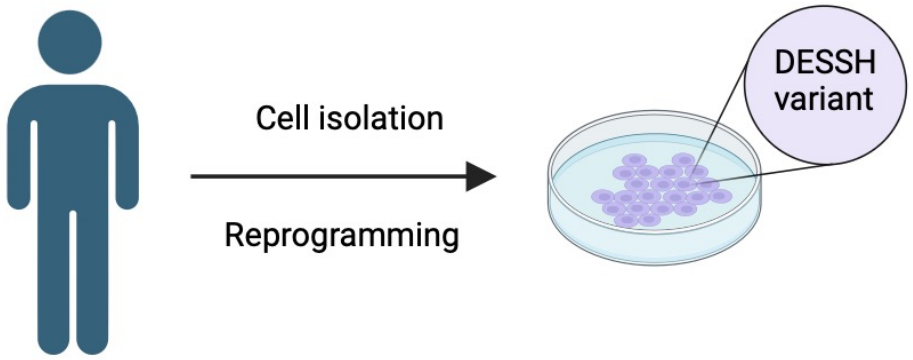




Future direction: is activity-dependent transcription disrupted in neurons with DESSH variants?

Skin cells from individuals with DESSH can be reprogrammed to neurons

Can use these neurons to test whether H2Bub, gene regulation, and activity-dependent transcription are affected by specific DESSH variants



Conclusions from our initial studies of WAC in neurons

- We have established a system where we can study complete neuronal knockout of WAC, helping us to define its function

- WAC regulates global H2Bub levels and affects gene expression in neurons

- WAC is necessary for proper activity regulated gene expression, particularly silencing following activation

Future directions: is activity-dependent transcription disrupted *in vivo* in the bain of the DESSH mouse model or cultured neurons with DESSH variants?

Acknowledgements

Gabel Lab

Alyssa Erickson
Nicole Hamagami
Kim Boua
Diana Beard
Mati Nemera
Ladan Abbasi
Rinaldo D'Souza
Yasmin Razia
Shawn Covarrubias

WashU DBBS

Dept. of Neuroscience

Dr. Marwan Shinawi
Dr. Amanda Smith