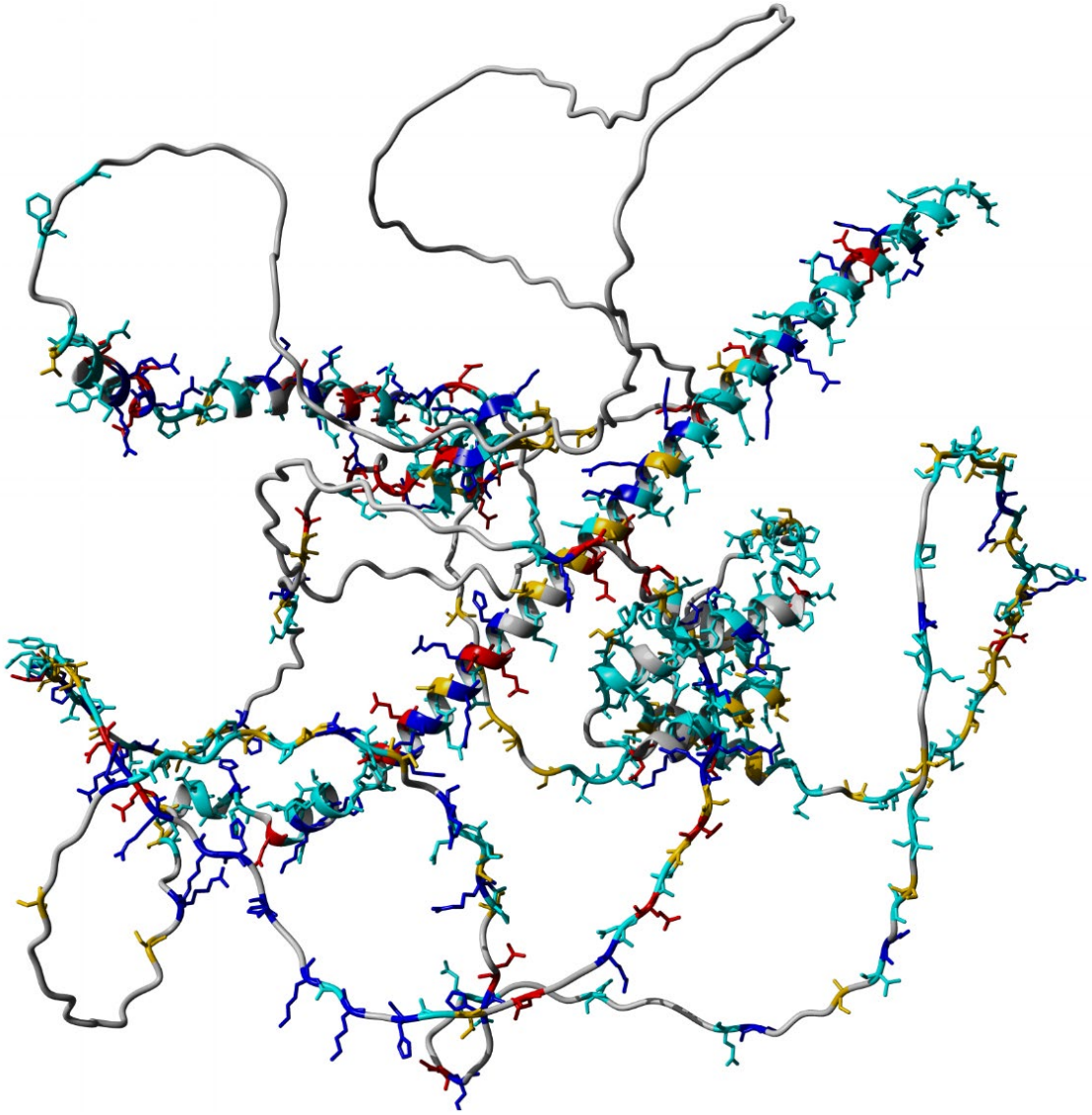
# DESSH Conference
# Sept 30th, 2023

**Daniel Vogt**
**Michigan State University**

## Animal models to understand DESSH

**Predicted shape of the WAC protein (using alpha fold)**



Rudolph et al., 2023

**Most Genetic changes in the *WAC* gene are loss of function/major recipe change**

Transcription Translation


**DNA** **RNA** **Protein**

Loss of function

Missense/single unit change

# Scientific advances require collaborative teams

| | |
|---|---|
| <u>Parent and patient advocates</u> | |
| Caitlin Piccirillo | Organization, leading, informing and connecting. |
| …and many here today! | |
| <u>Clinical guidance</u> | |
| Marwan Shinawi | Diagnosing and describing patient concerns and treatments. |
| <u>Research validation</u> | |
| Vogt lab | Mouse model of *WAC*. |
| Kim lab | Zebrafish model of *WAC.* |
| Gabel lab | Mechanisms by which *WAC* may function. |
| <u>Additional experts</u> | |
| Nord lab | RNA candidates (the copied recipes!) |
| Jeong lab | Craniofacial analyses of WAC mouse model. |
| UCI MRI institute | MRI assessment of WAC mouse model. |

# What does the *WAC* recipe look like?

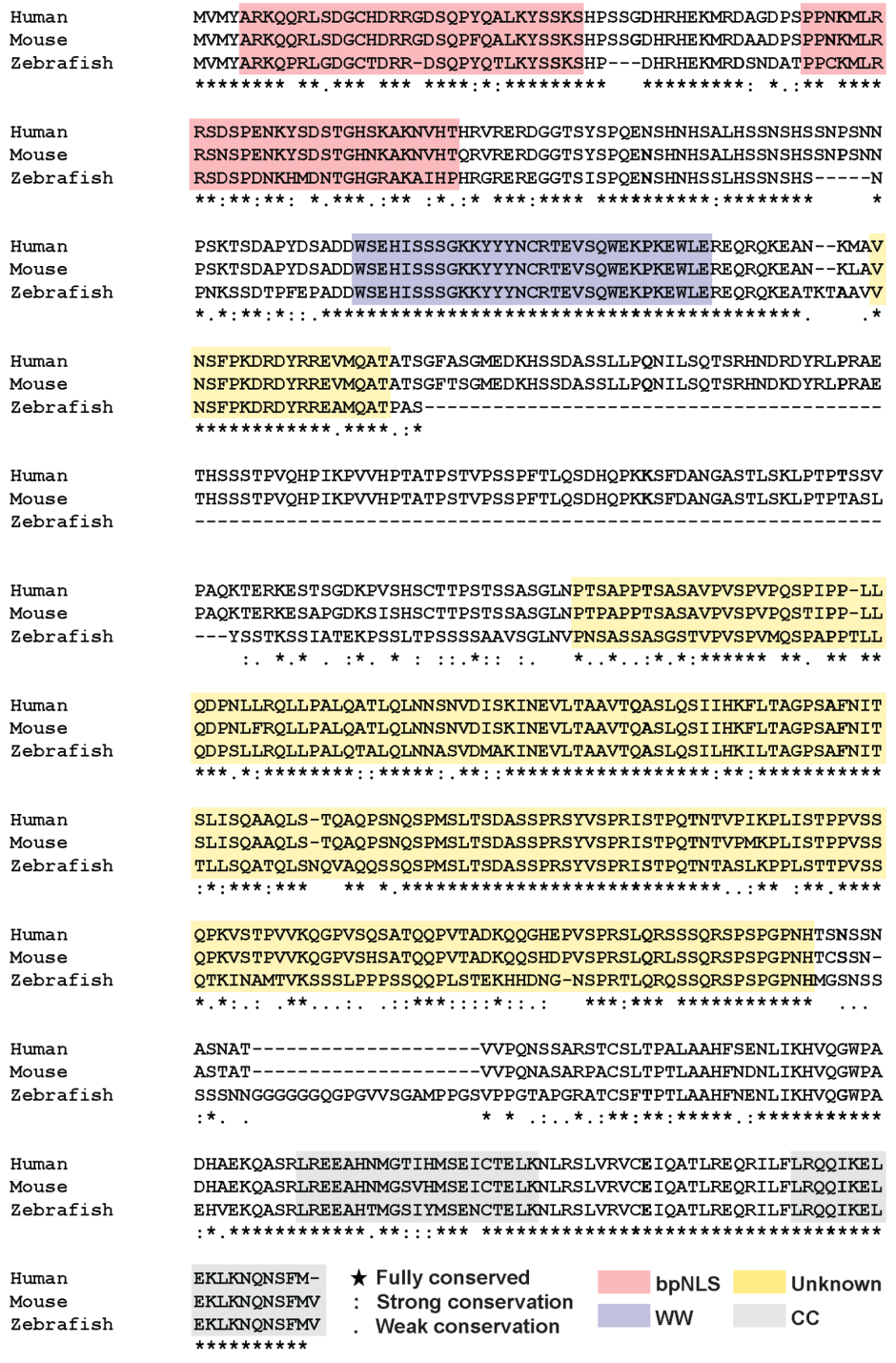
# Can we find some common ingredients?

Very important protein parts will be the same in many species, can use this to our advantage…

Known ingredients include the WW and coiled coil domains, as well as a nuclear targeting domain: these interact with other proteins or direct a protein where to go.

Some regions are highly conserved but do not have a known function.

These domains are conserved between species

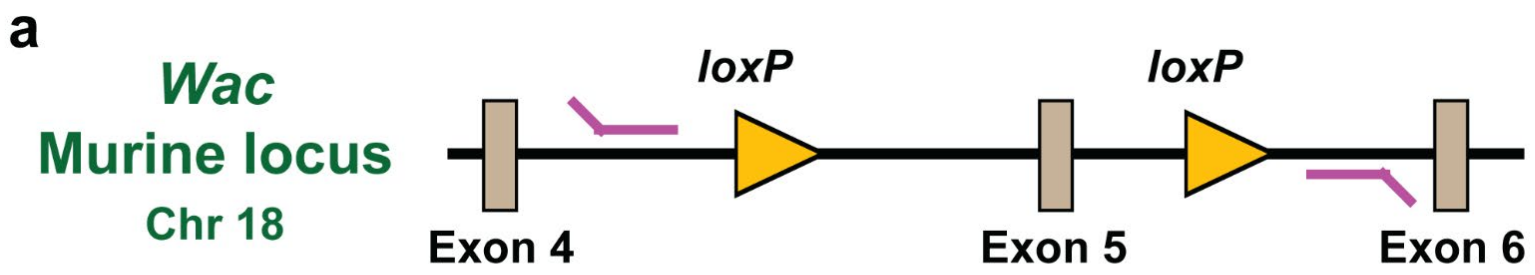


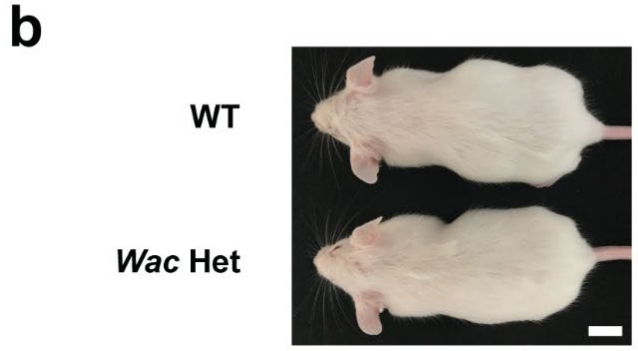
We and the Kim lab successfully generated mice and zebrafish (recipes) that lacked a copy of the *WAC* gene

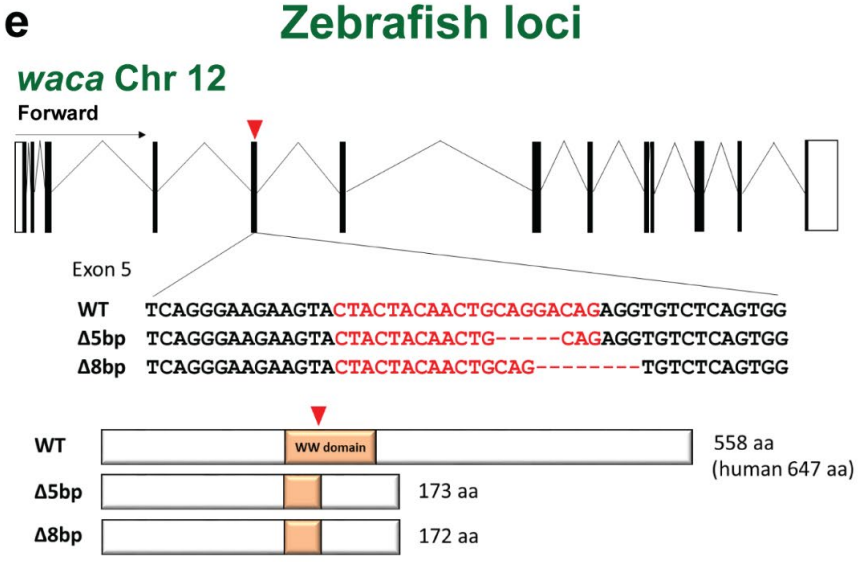
Animals developed normally at first

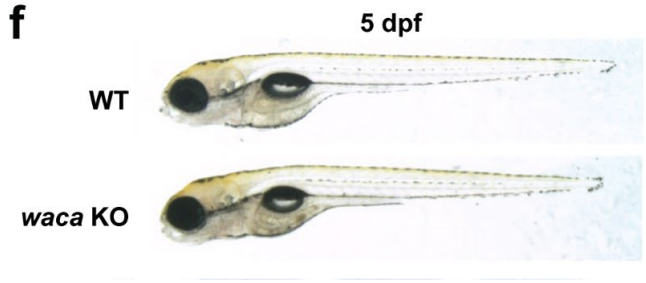
Mouse Het
and
Zebrafish *waca* ko

Are the same in *Wac* gene dose
= ½ of normal WAC protein made



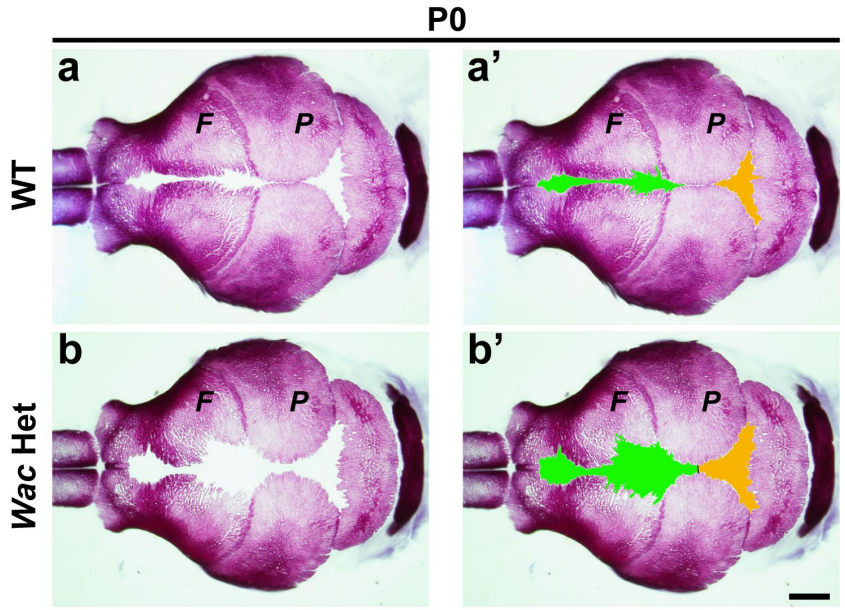
# Predictions and findings

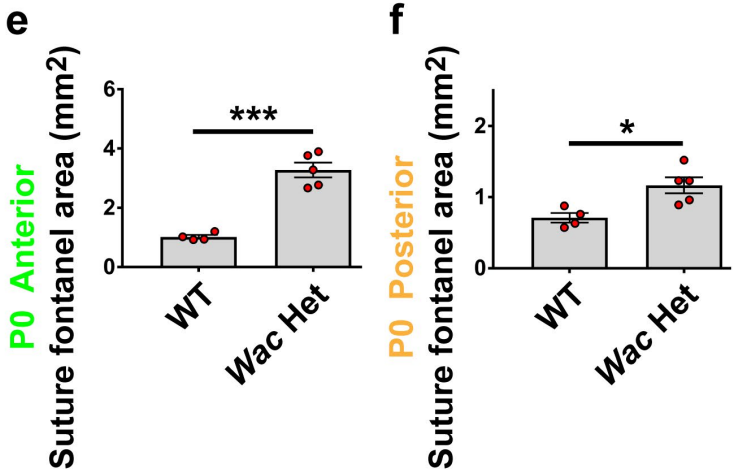
| Clinical reports | Mouse model | Zebrafish model |
|---|---|---|
| Craniofacial | Yes | Yes |
| Behaviors | Yes | Yes |
| Hypotonia | NT | NT |
| Seizures | Yes | NT |
| Gastrointestinal | NT | NT |
| Blood glucose | Yes | NT |

NT not tested

# What do these changes look like?

**Craniofacial changes were observed early (Neonatal)**

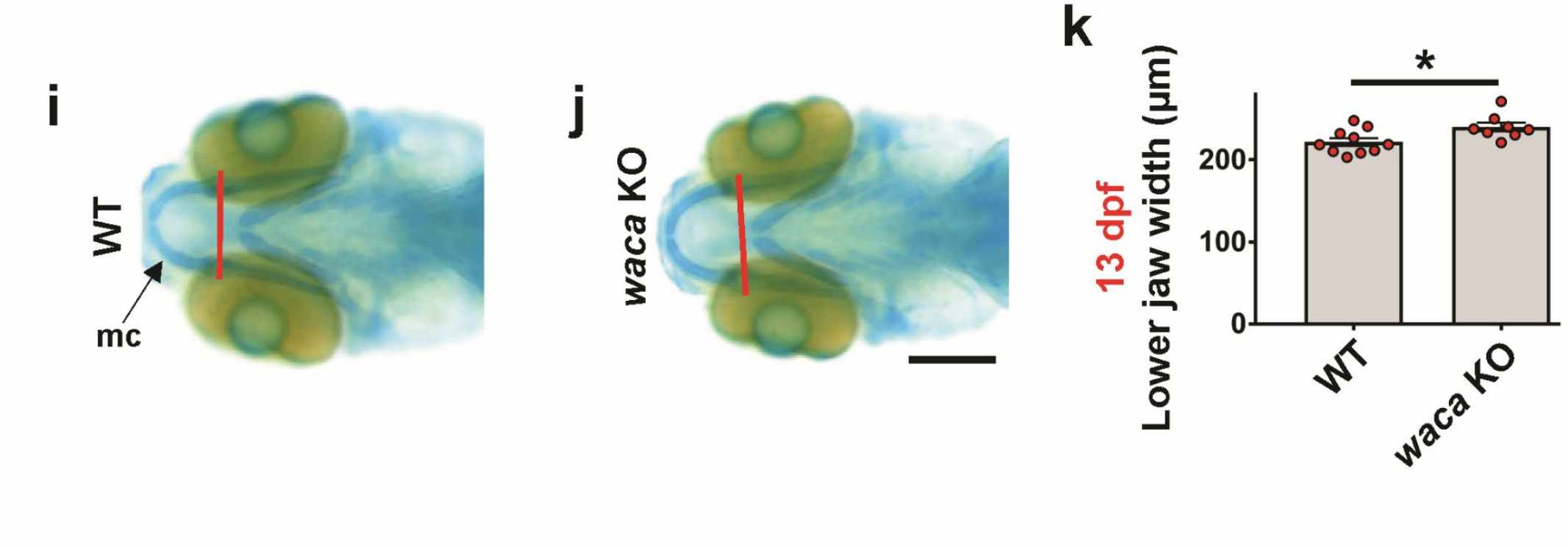


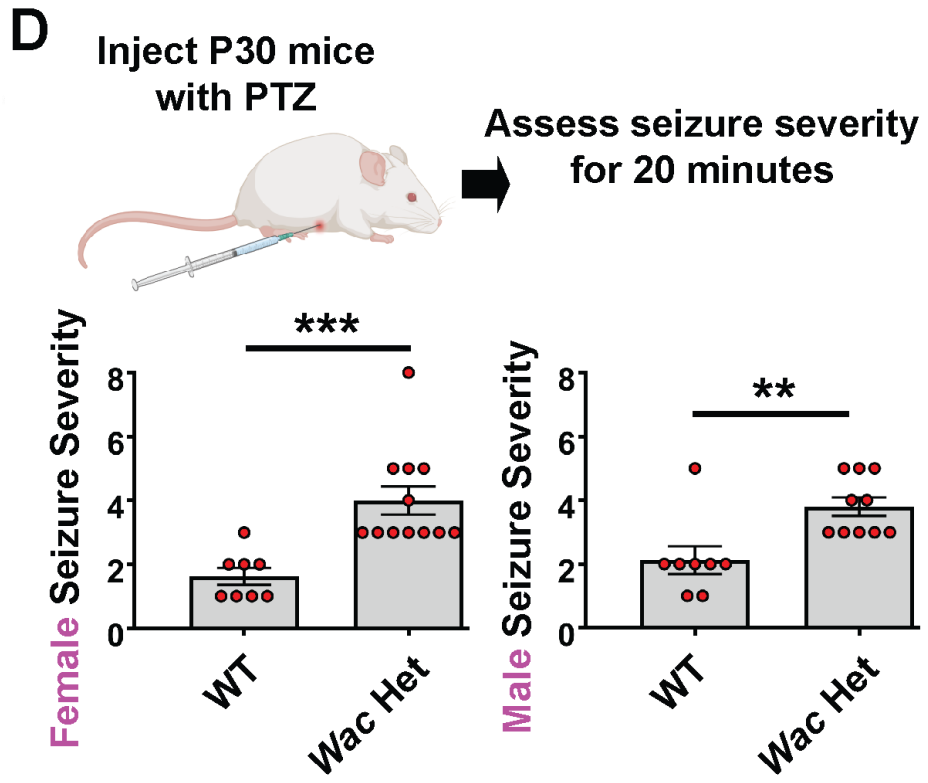

Work performed by:
Maria Pacheco and Juhee Jeong

New York University

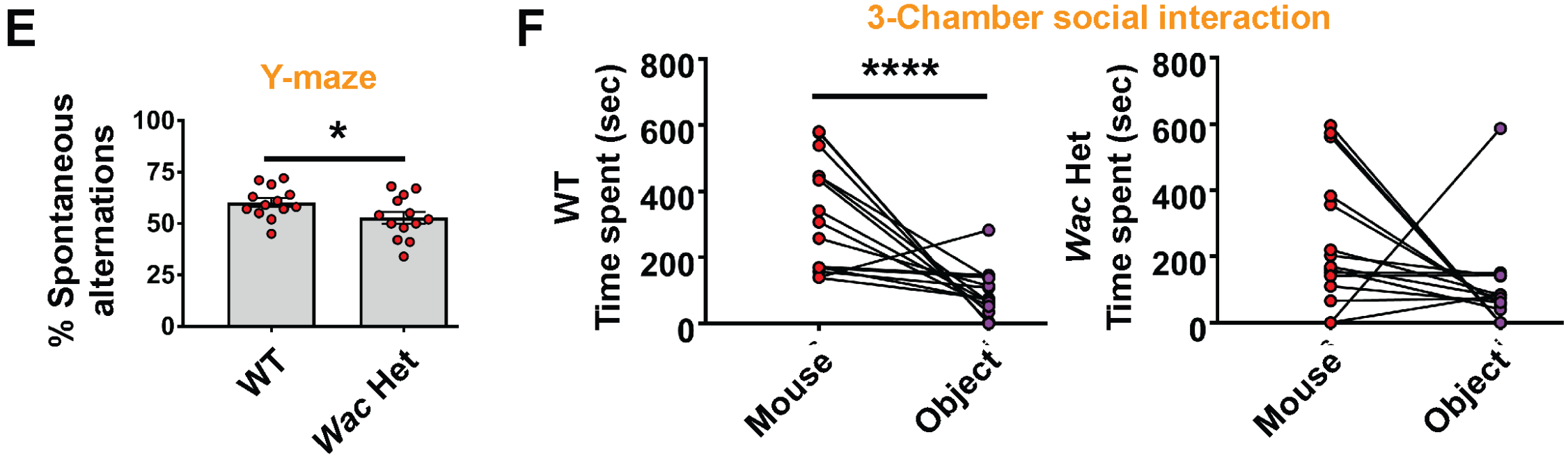
# Zebrafish jaws are wider when there is a decrease in *wac*



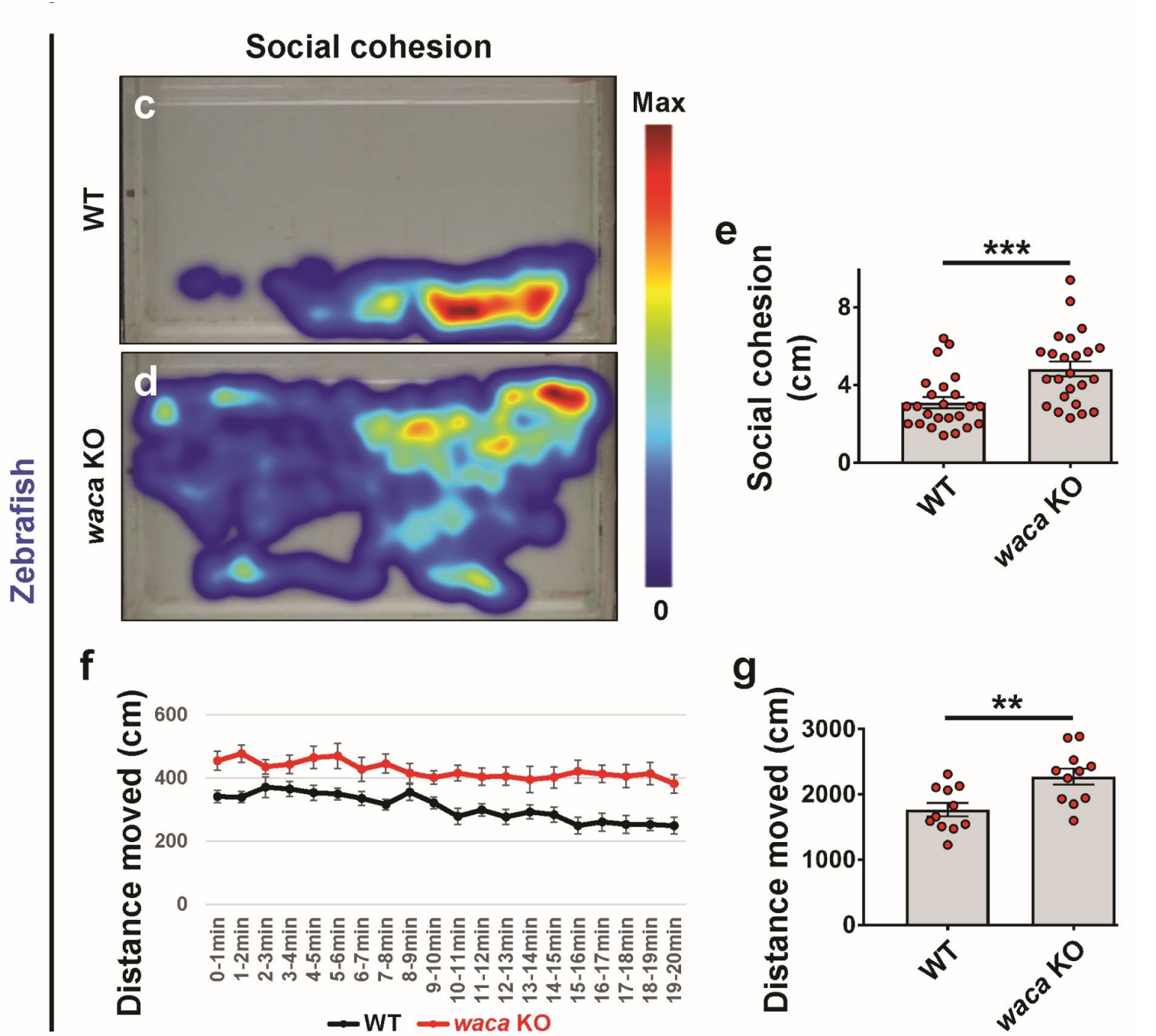
# Challenging *Wac* Hets with a seizure causing drug leads to greater response



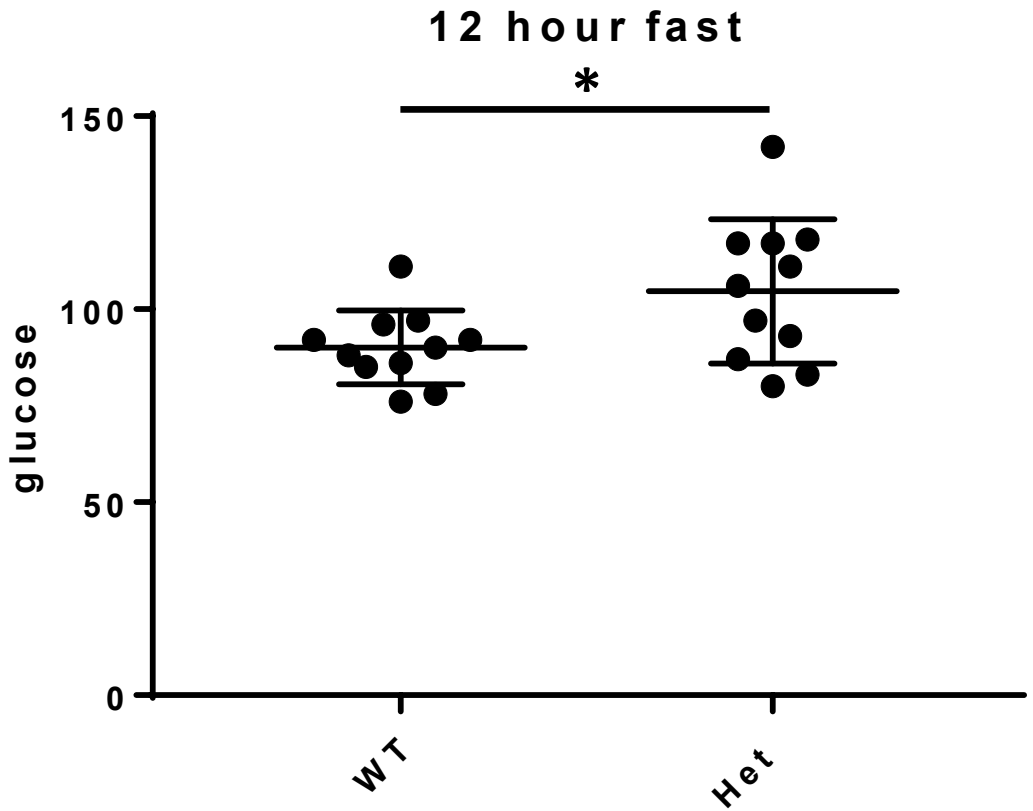
# Some behaviors relevant to social interactions and short-term memory were altered in *Wac* Hets



# Decreased *wac* in Zebrafish leads to less social behavior and hyperactivity



# At young adult ages, *Wac* hets exhibit elevated blood glucose levels




However, low blood glucose observed in young pups (still collecting data)

# Part one conclusions

Both mouse and zebrafish *WAC* models exhibit relevant craniofacial and behavior outcomes; mice also have a susceptibility to seizures, and potential glucose alterations.

Still many DESSH symptoms to test

- This is beyond our abilities, please ask your doctors if they know researchers that would be interested in helping?
- We have the mice and are happy to provide to any lab that wants to investigate.

What are some mechanisms/cell types that we could be targeting to treat DESSH symptoms?

# Our brains are balanced to transmit information using neurons

Each part of the brain forms a circuit made up of different cells

Dysfunction of any cell type can often alter the function of a circuit

Which *brain regions* are impacted by loss of *WAC*?

How are different *cell types* effected?

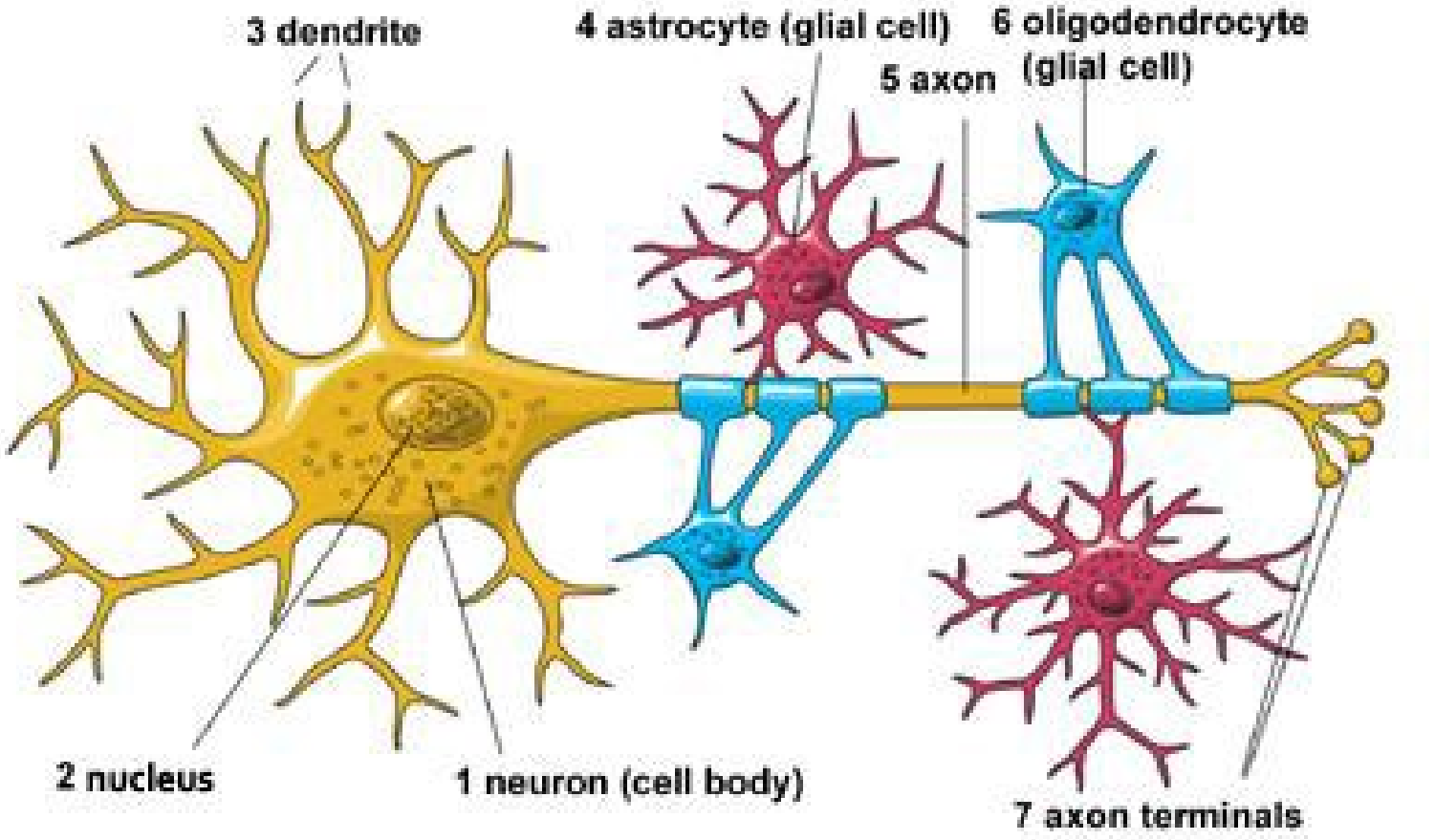


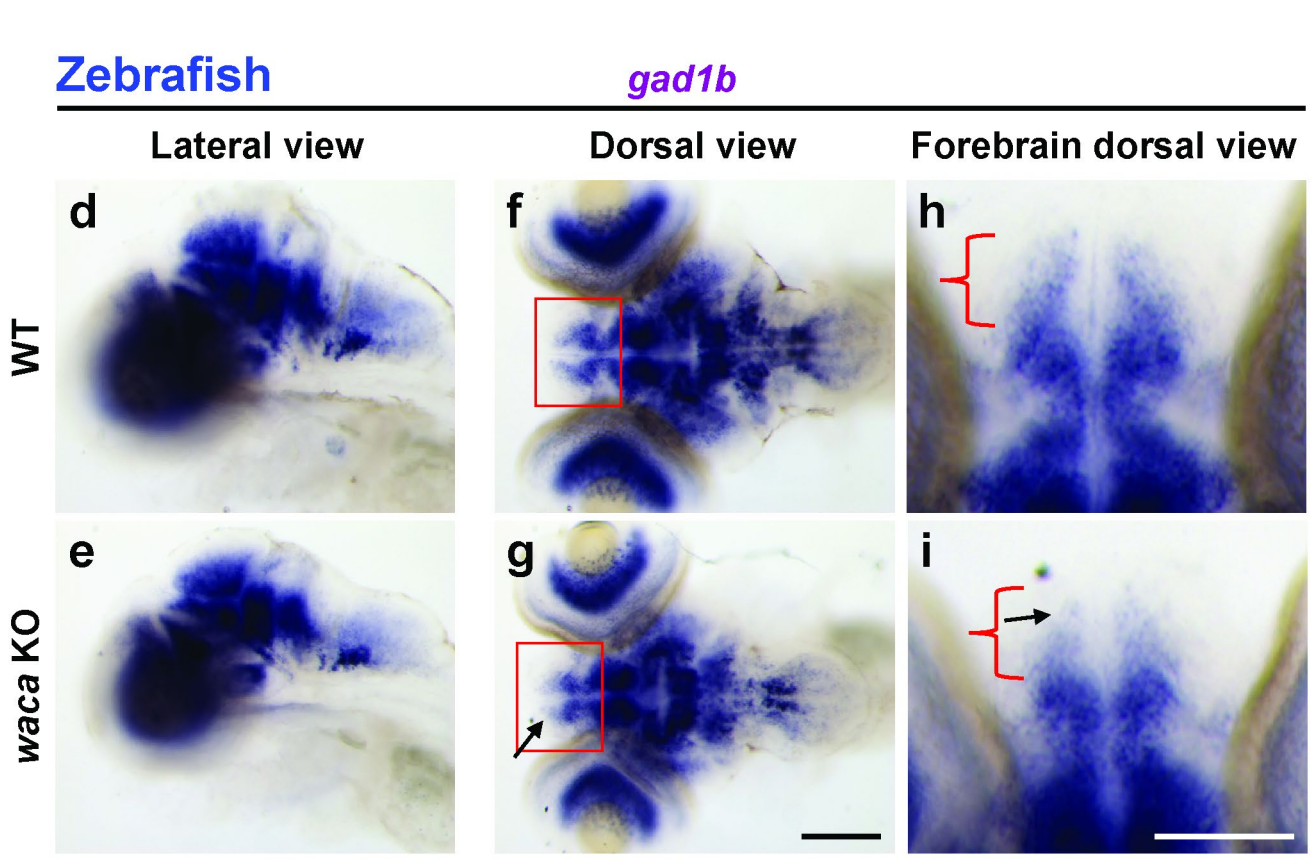

Image from NINDS

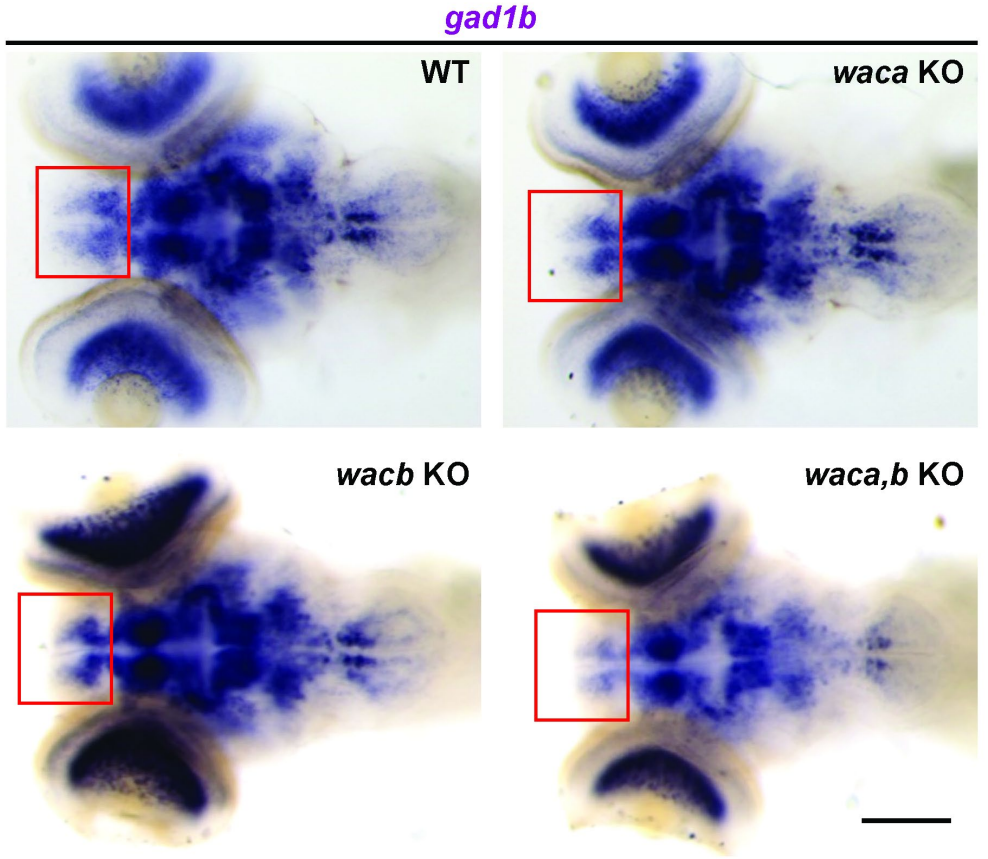
# Most major brain cell types are present

**a** **P30 Somatosensory Cortex Cell Counts**

| Cell classification | Marker | WT Cells/mm$^2$ (SEM) | Het Cells/mm$^2$ (SEM) |
|---|---|---|---|
| Neuron (General) | NeuN | 3324 (±179) | 3380 (±48) |
| Oligodendrocyte | OLIG2 | 725 (±9) | 752 (±7) |
| Astrocyte | S100beta | 606 (±8) | 599 (±8) |
| Microglia | IBA1 | 431 (±15) | 440 (±30) |
| Interneuron | PROX1 | 185 (±10) | 186 (±11) |
| Interneuron | Somatostatin | 129 (±9) | 121 (±8) |
| Interneuron | Parvalbumin | 171 (±6) | 141 (±6) * |
| Interneuron | LHX6 | 326 (±15) | 323 (±15) |

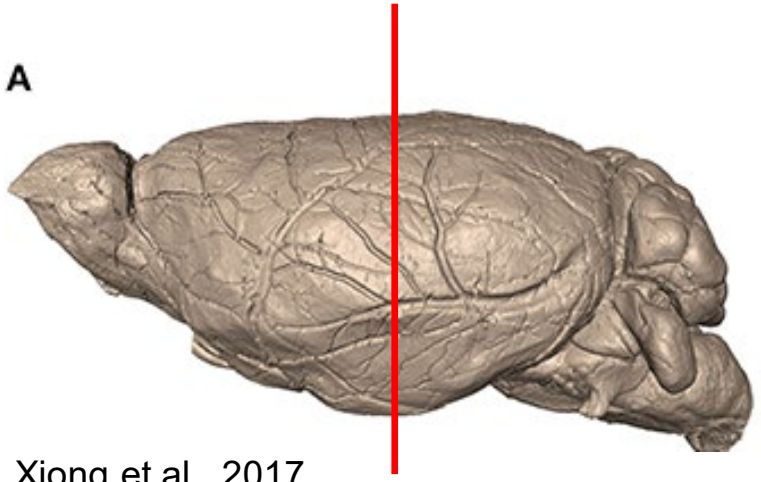
# GABAergic cell types are altered in Zebrafish as well



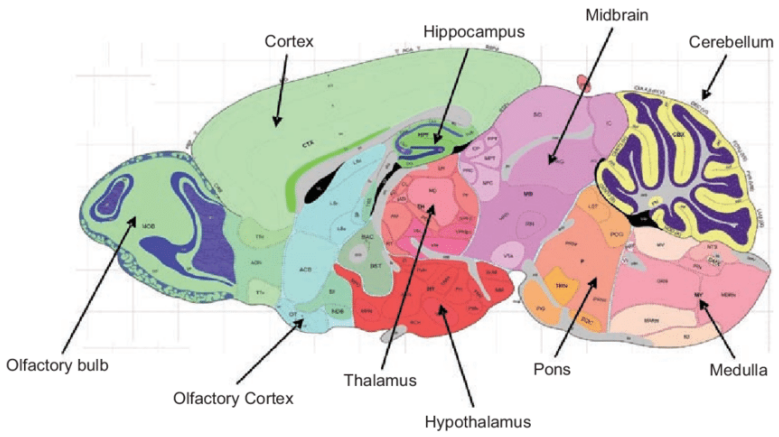



# Our previous data were very targeted, can we be unbiased?

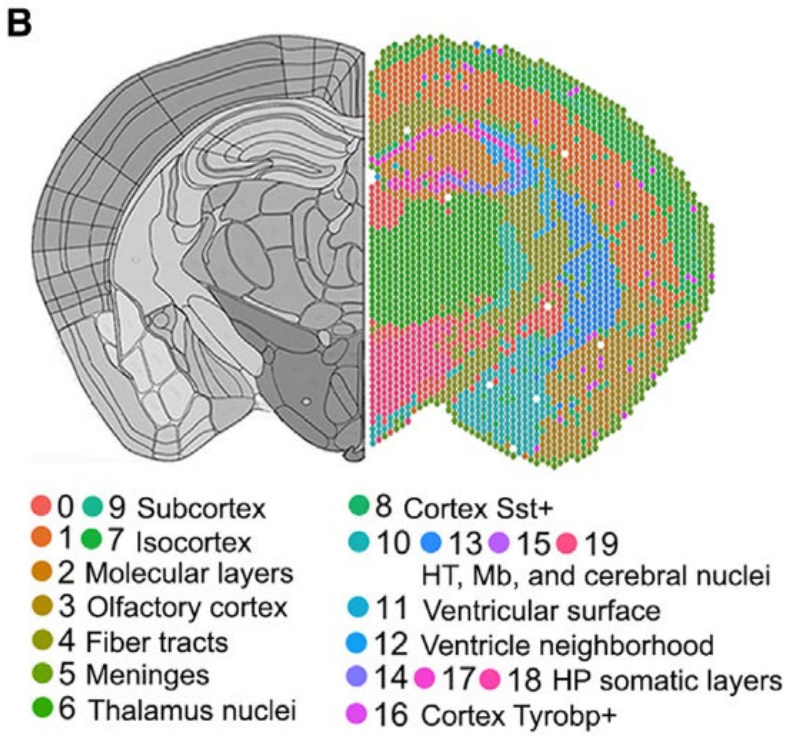
## New techniques allow us to view the whole menu (recipes being used by a cell)




Xiong et al., 2017




Heydel et al., 2010

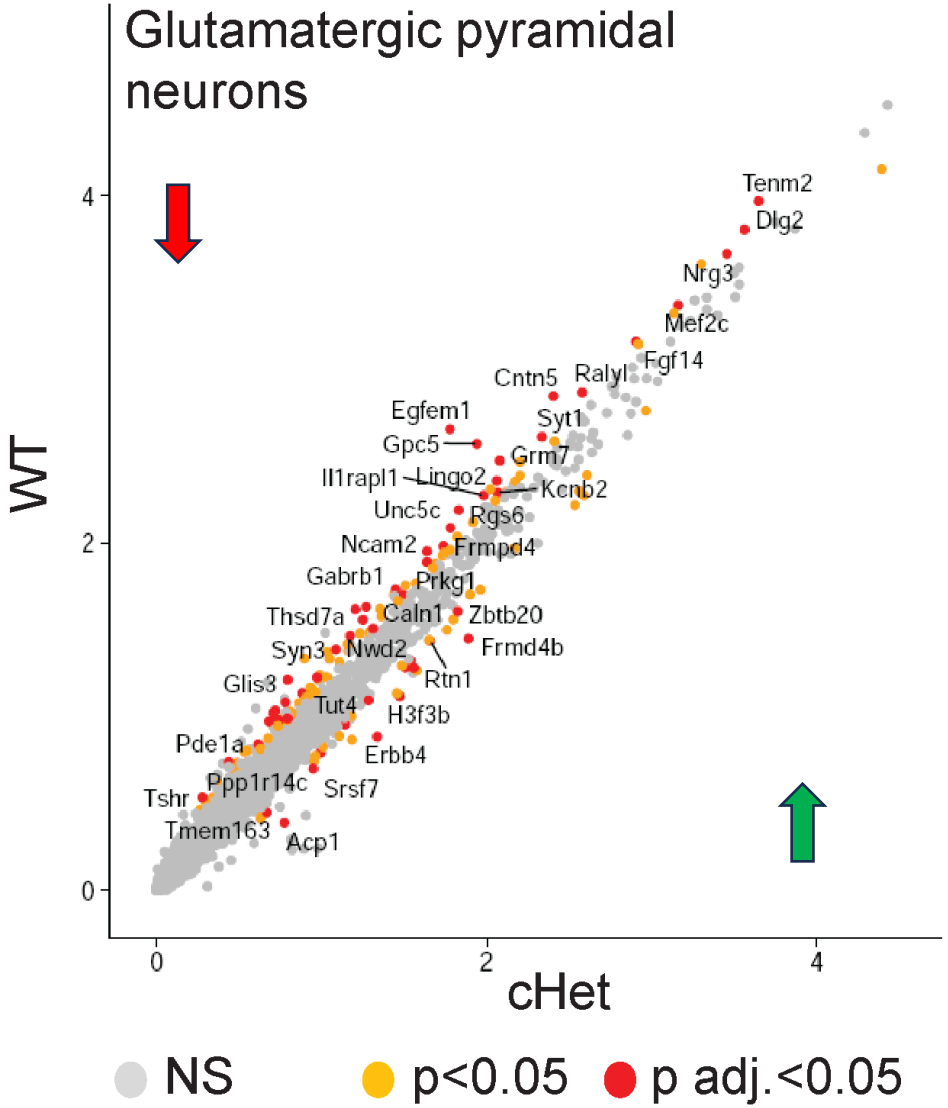


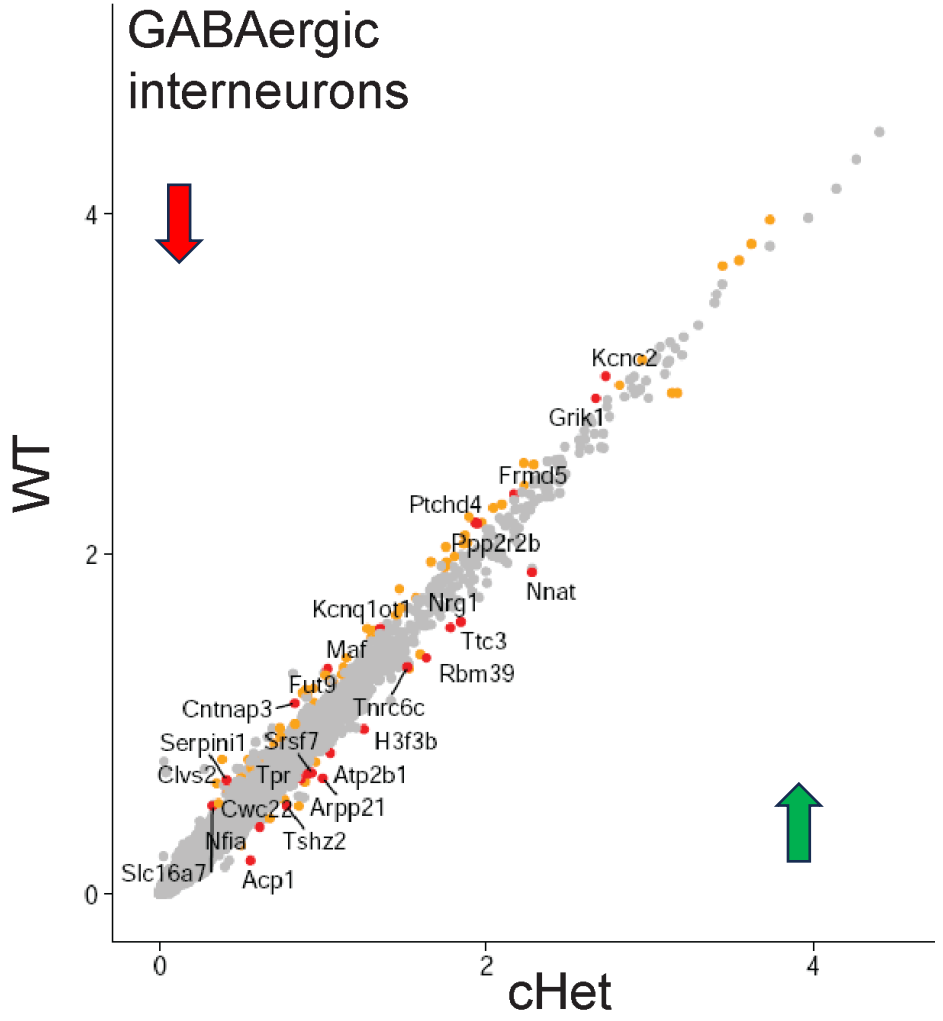
# Can investigate changes in all brain cell types at the menu/RNA level

**Excitatory (Glut) and inhibitory (GABA) neurons were the most impacted cells**

Gene is reduced

Gene is increased

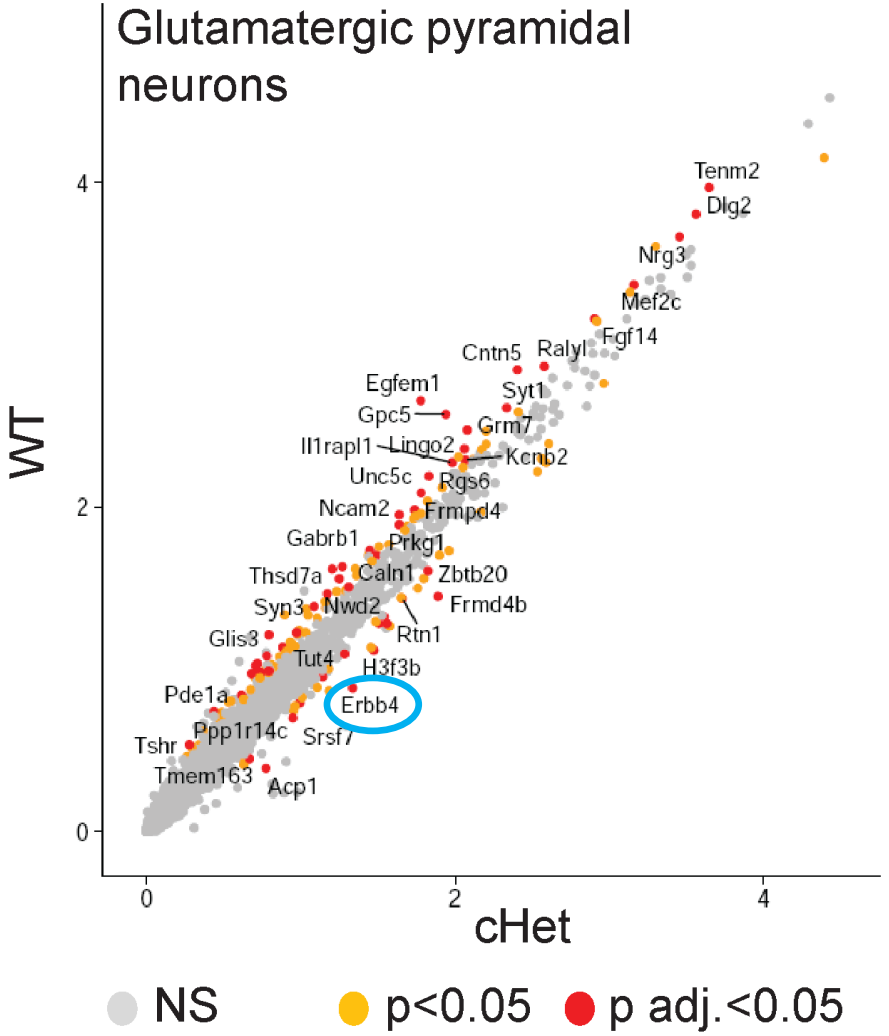


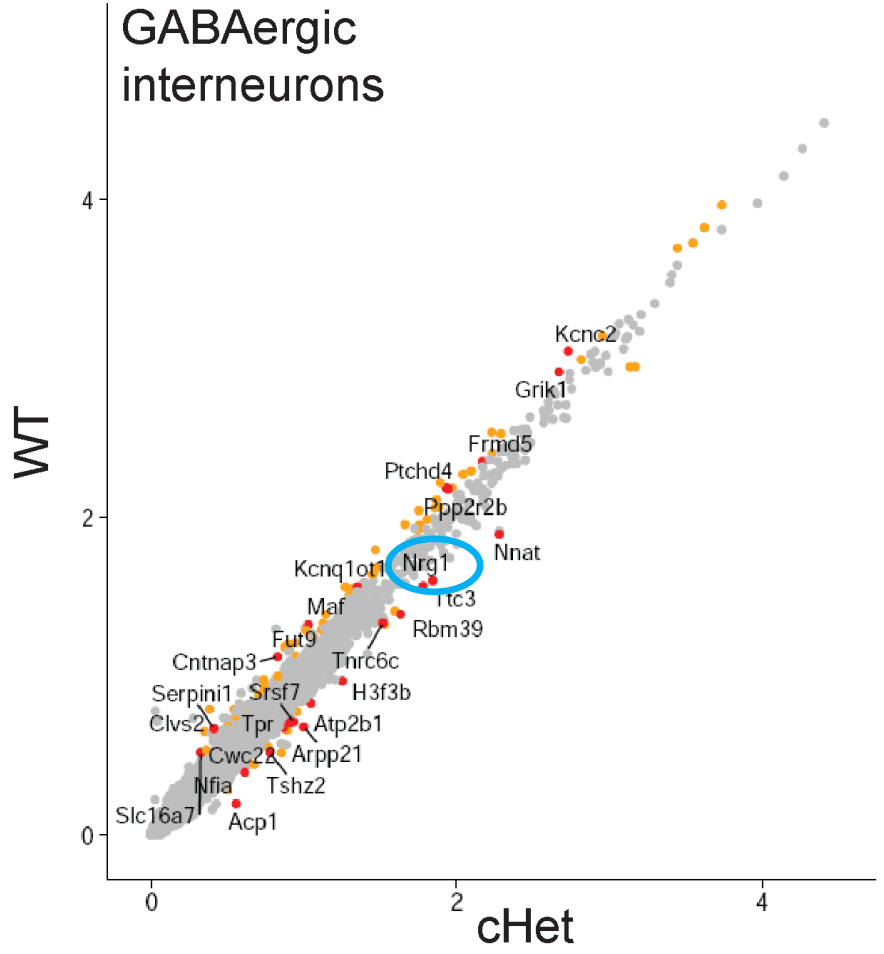



# Now validating candidates to see which RNA-menu is used by each cell

*Dariangelly Pacheco-Cruz, (Graduate Student)*

Some candidates have FDA-approved drugs to test
-- Now being investigated



# Ongoing and future work

Collaboration with Kim and Gabel labs

Cell specific loss of function; using engineered mice to study
- Inhibitory neurons
- Excitatory neurons and glia

Unbiased screen to profile RNA abundance in single brain cells
(Alex Nord lab, UC Davis)

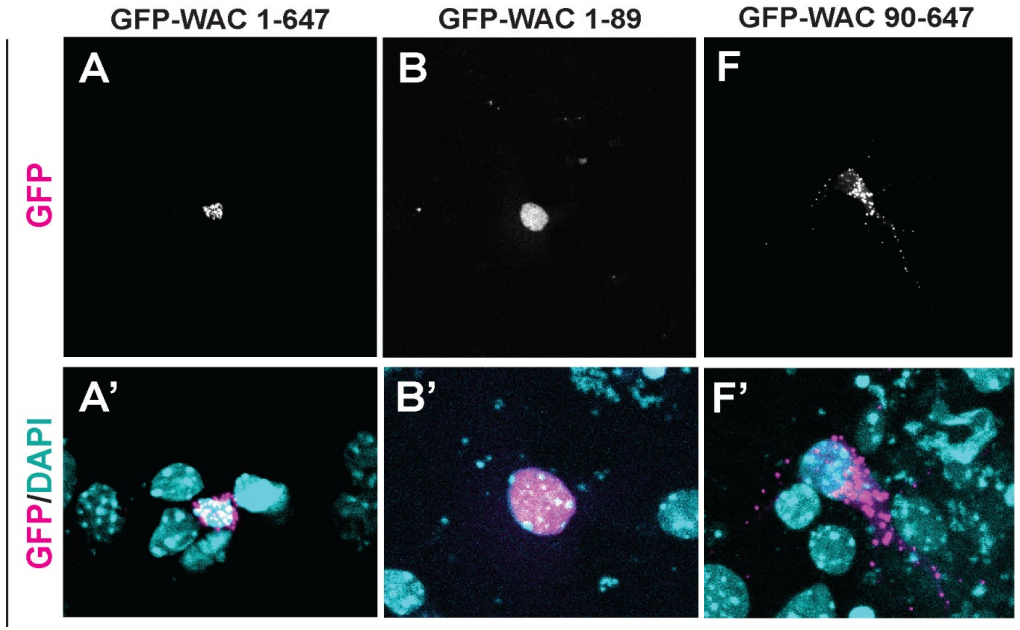
Any labs interested in trying out ideas/therapeutics?

# Funding and thanks

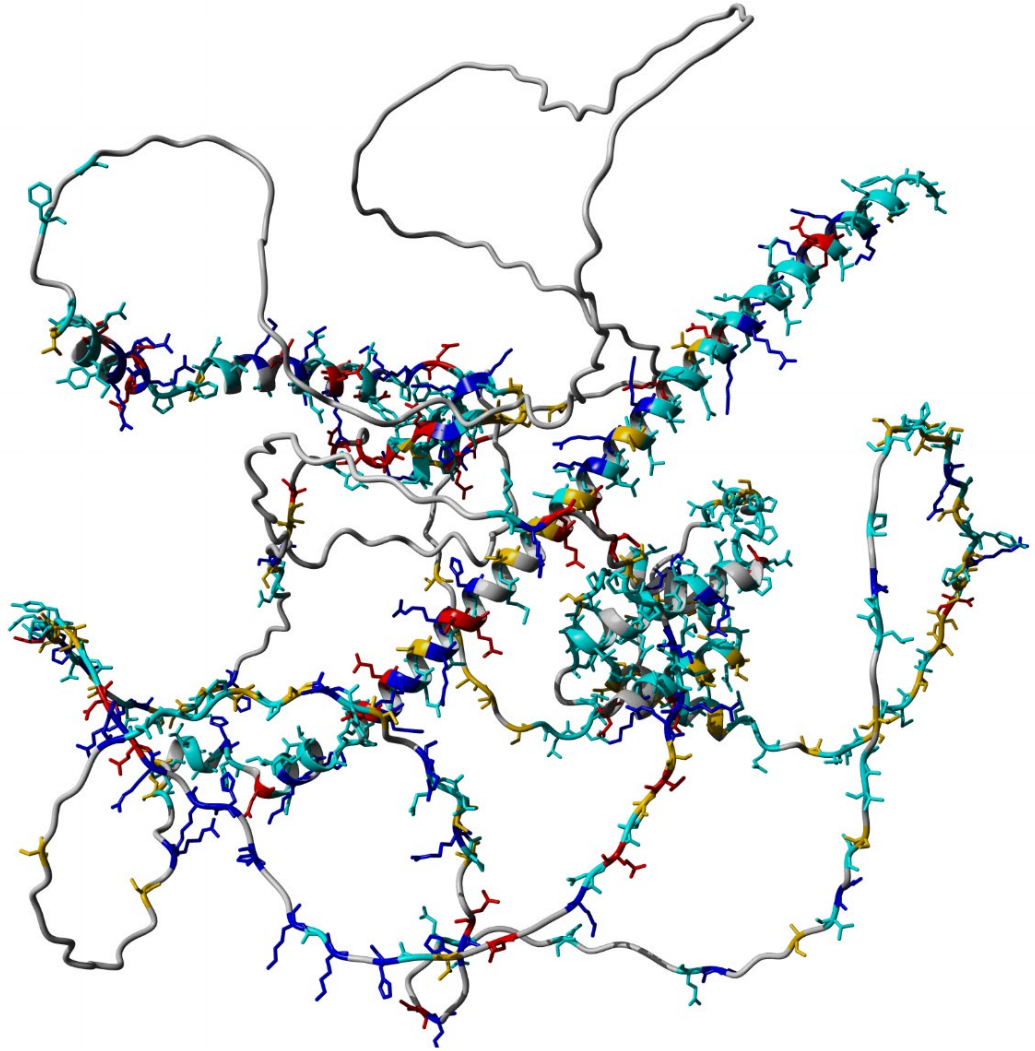
Spectrum Health – Michigan State University Alliance

Michigan State University IPSTP NIH training grant
To Dariangelly Pacheco-Cruz

Lab manager, April Stafford (generated the mouse *WAC* mice)




Rudolph et al., 2023



# Questions?

1. Can DESSH be diagnosed in utero?
   -- This is possible, but may need good indication to attempt

2. Are researchers looking at the gene therapy treatments in utero?
   -- Our lab is attempting to introduce a full-length human WAC gene to rescue symptoms

3. Is there hope for treatment in the future?
   -- Yes, but depends on finding druggable targets and/or therapeutics

4. Will cell manipulation work for DESSH?
   -- Let's discuss

5. Have you researched targeted cell therapy? Have you researched gene therapy or protein replacement?
   -- Let's discuss

6. Can WAC protein be synthesized? Has anyone tried?
   -- This is possible, but I am not aware of anyone who has synthesized the WAC protein