Treating An Alzheimer's Disease Model in *Drosophila* with a Psychoplastogen

Jesus Quiroz
Lee Lab in the Molecular, Cellular and Developmental Biology Department
University of California, Santa Cruz

Alzheimer’s disease is a debilitating neurodegenerative disease

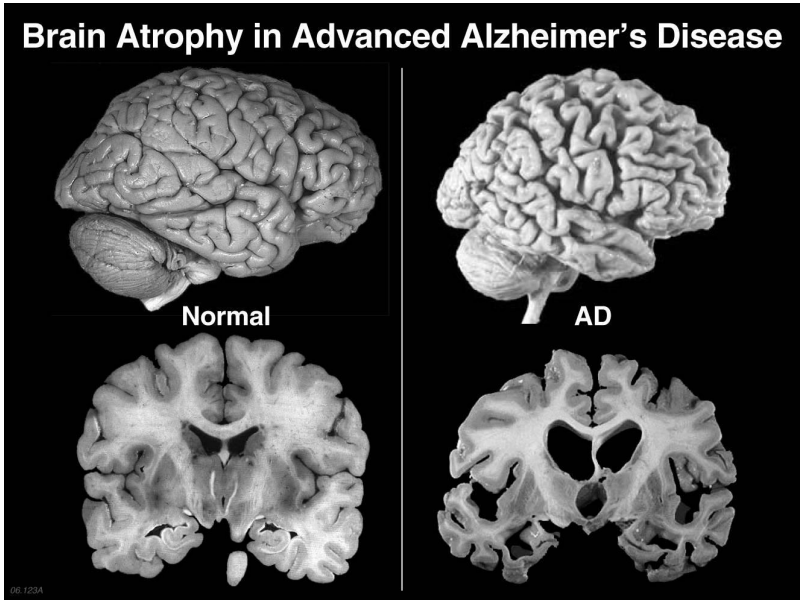


Figure 1: Pulled from Bagard et al., 2013.

According to the Alzheimer’s Association Report (2024), Alzheimer’s disease exhibits the following

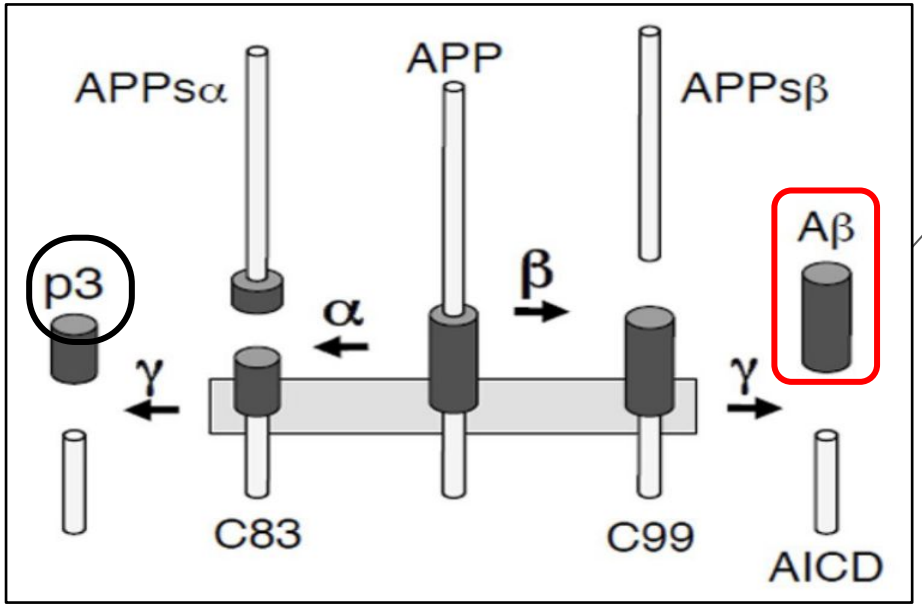
Symptoms

- **Early life deficits in memory, thinking, and language.**
- **Progressively degeneration leads to mobility issues.**

Hallmarks

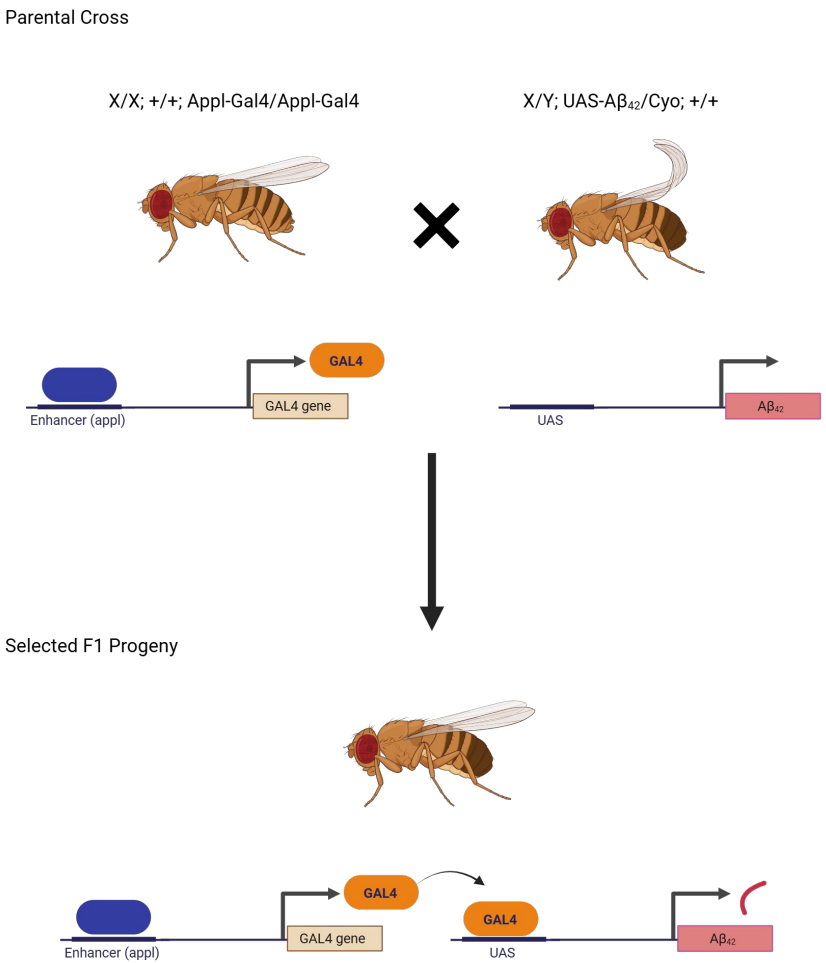
- **Beta-amyloid plaques form extracellularly, damaging neuron to neuron connections.**
- **Tau tangles from intracellularly, interfering with cellular processes.**

Aβ and Aα cleavage pathways from the Amyloid Precursor Protein (APP)



Deficits in lifespan, memory, and motor skills.

Previous Lee Lab Findings Using a *Drosophila* AD Model



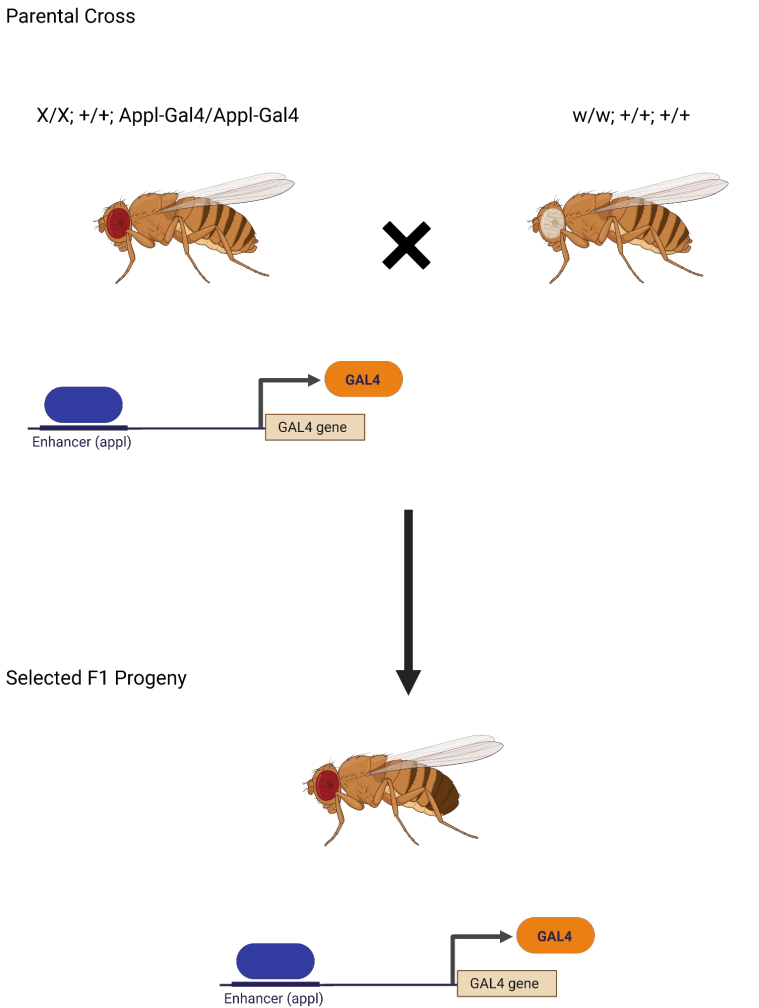


Figure 2: Gal4-UAS system used in my experiment. Left is AB42 cross. Right are controls

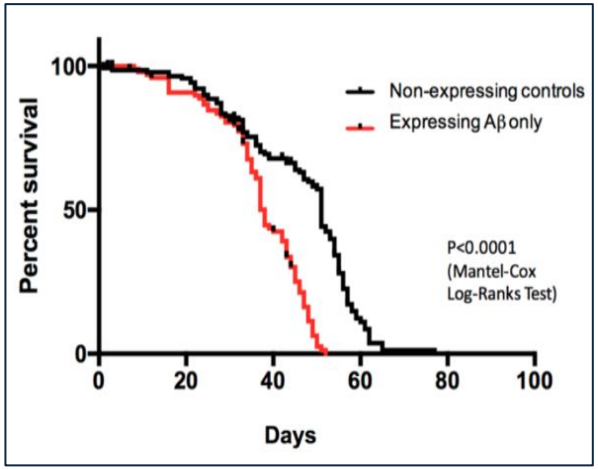


Figure 3: Previous Longevity assay, conducted in the Lee lab, compared pan-neuronal $A\beta_{42}$ expressing flies vs non-expressing. There is a significant lifespan deficit in $A\beta_{42}$ expressing flies compared to non-expressing.

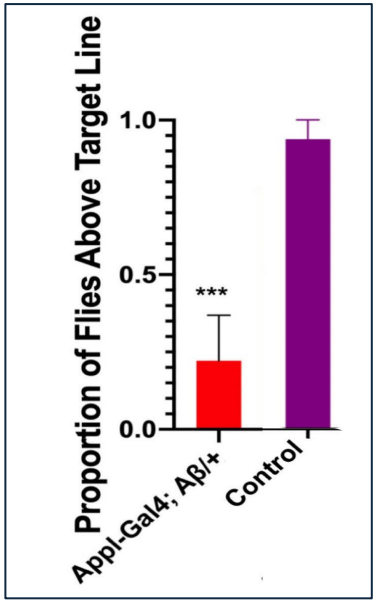


Figure 4: Previous Rapid Iterative Negative Geotaxis RING assay, conducted in the Lee lab, tested pan-neuronal $A\beta_{42}$ expressing flies vs non-expressing. There is a significant motor deficit in $A\beta_{42}$ expressing flies compared to non-expressing.

Gap In Knowledge About AD Research

According to the National Institute of Aging, current FDA treatments to manage symptoms employ:

- Cholinesterase inhibitors - inhibits the breakdown Acetylcholine whose levels are reduced in AD.
    - Helps with memory, thinking, & behavioral deficits
- Immunotherapy drugs- target cytotoxic $A\beta_{42}$ plaques for clearance.

But these aren't always effective, safe, or long lasting, and call into question approaches to understanding and thus treating the disease.

So, what if we treat synaptic dysfunction in the disease?

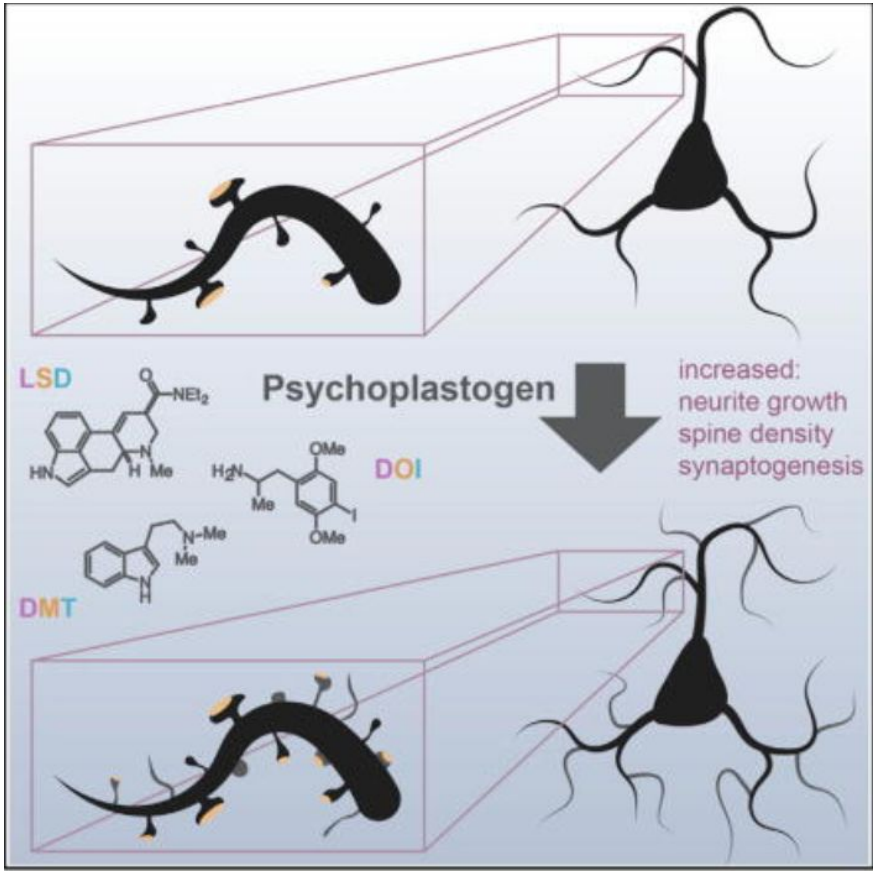
A gap of knowledge remains to systematically test molecules that reverse synaptic dysfunction and restore neuronal circuitry lost in AD

Could psychoplastogens alleviate symptoms in our AD fly model?

Psychoplastogens?

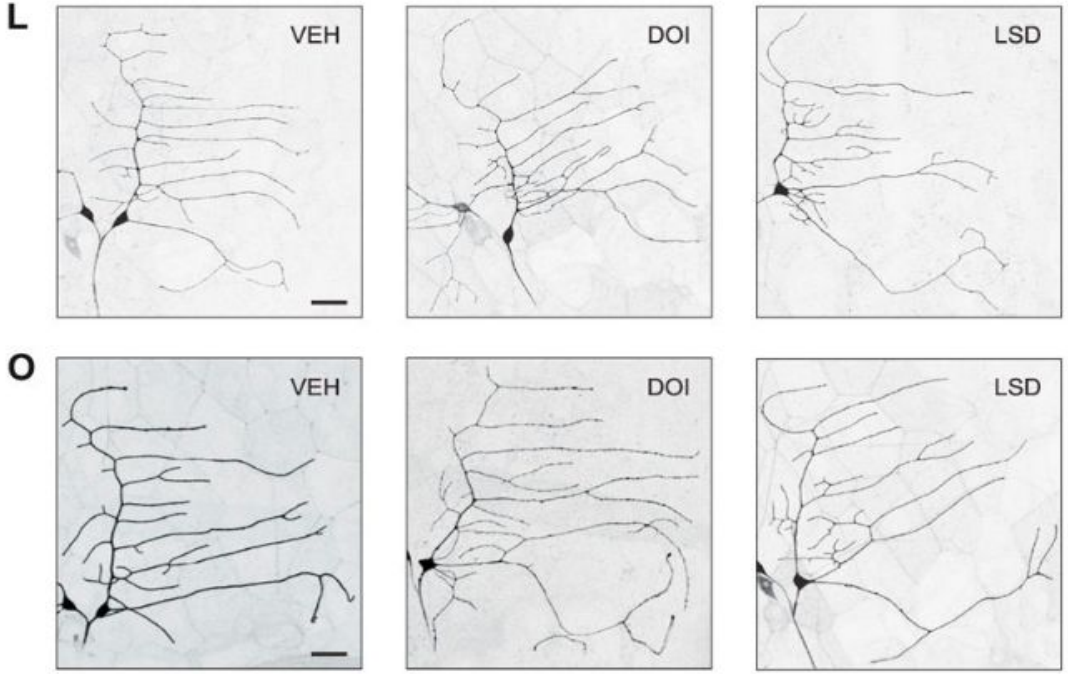
Quick definition: Psychedelics

Scientific definition: A term coined by Professor David Olson at UC Davis. In brief, psychoplastogens are small molecules that induce structural and functional changes in neurons that include but not limited to increased neurites, dendritic spines, and synapses. These changes are rapid and long lasting. Typically, they are studied in antidepressant research. This class of molecules isn't solely limited to 5HT2A agonists.



From Ly et al. 2018

Why could the psychoplastogen, DOI, work in flies?



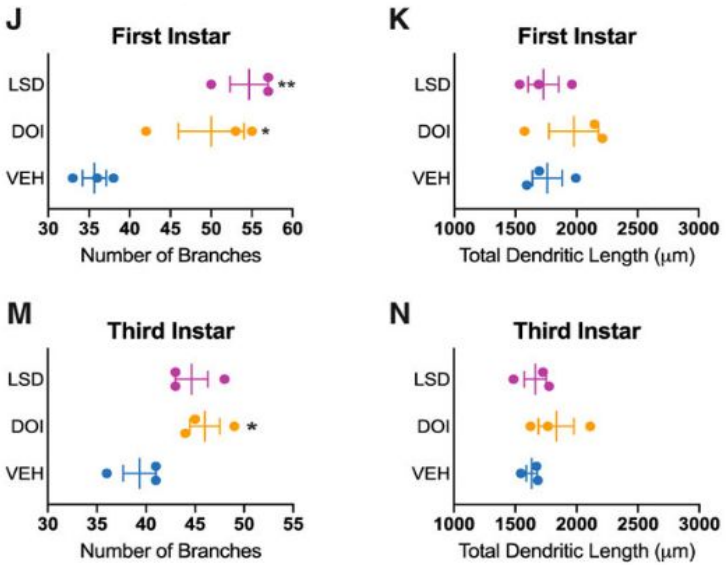
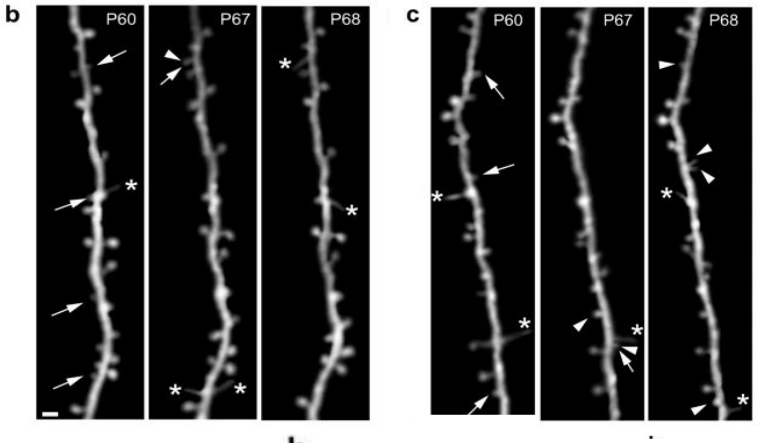
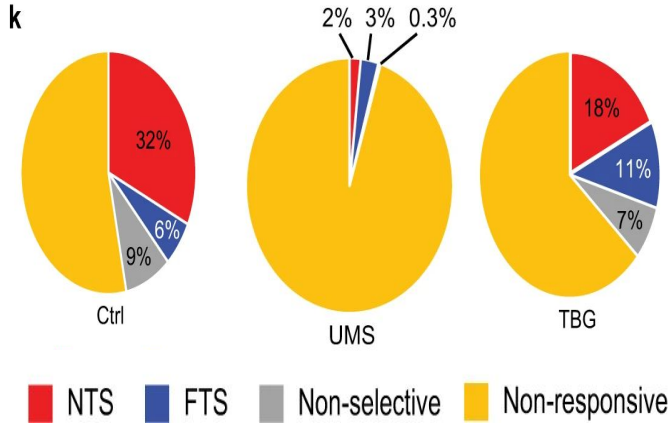
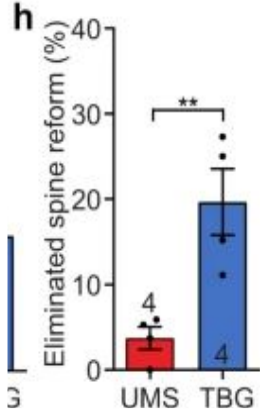


Figure 5 : Pulled from Ly et al, 2018. J, K & O represent dendrite observation at first instar. M, N, O represent dendrite observations at third instar.







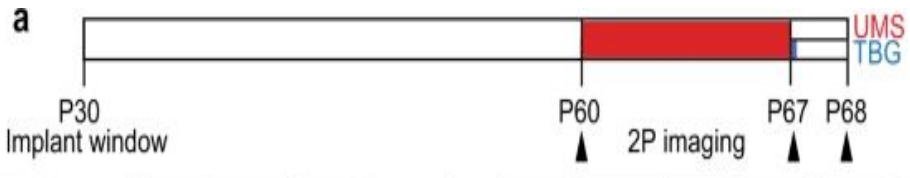


Figure 6: From paper published in Yi Zuo lab at UCSC, MCD department.(Lu J. et al 2021). *Thy1*-GFP-M *in-vivo* 2 Photon (2P) Microscopy Imaging of S1BF dendritic spines pre and post TBG administration. A) Experimental timeline, P stands for post-natal, Unpredictable Mild Stress(UMS) was conducted for 7 days from P60-P67. Imaging at P60, P67,& P68. B)S1BF spine imaging control. C) S1BF spine imaging of TBG treatment. h) Proportion of spine reformation with respect to those eliminated during UMS. K) Categorization of neurons, based on the ROC analysis, measured through Ca activity of S1BF L2/3 neurons during whisker texture interaction.

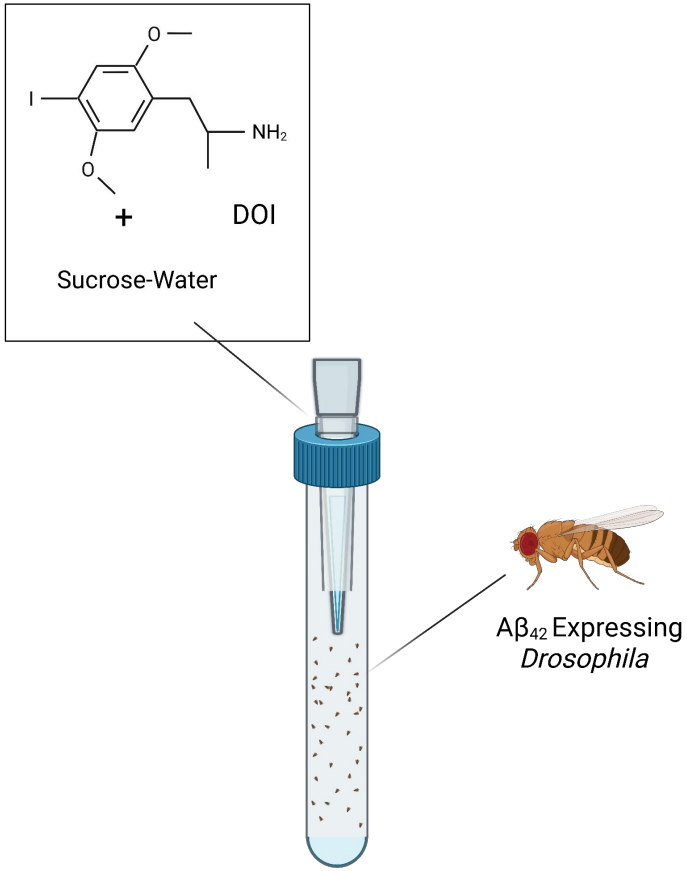
My central hypothesis:

Given the neurodegenerative phenotypic effects of Aβ42 in Drosophila, synaptic plasticity induced by DOI will restore neuronal circuitry thus rescue lifespan and motor skill deficits.

Aims & Approach

AIM 1: Rescue the lifespan deficits of *Drosophila* expressing $A\beta_{42}$ through a single DOI dosage treatment

AIM 2: Improve motor skill deficits over the lifespan of Drosophila expressing Aβ42 through a single DOI dosage treatment



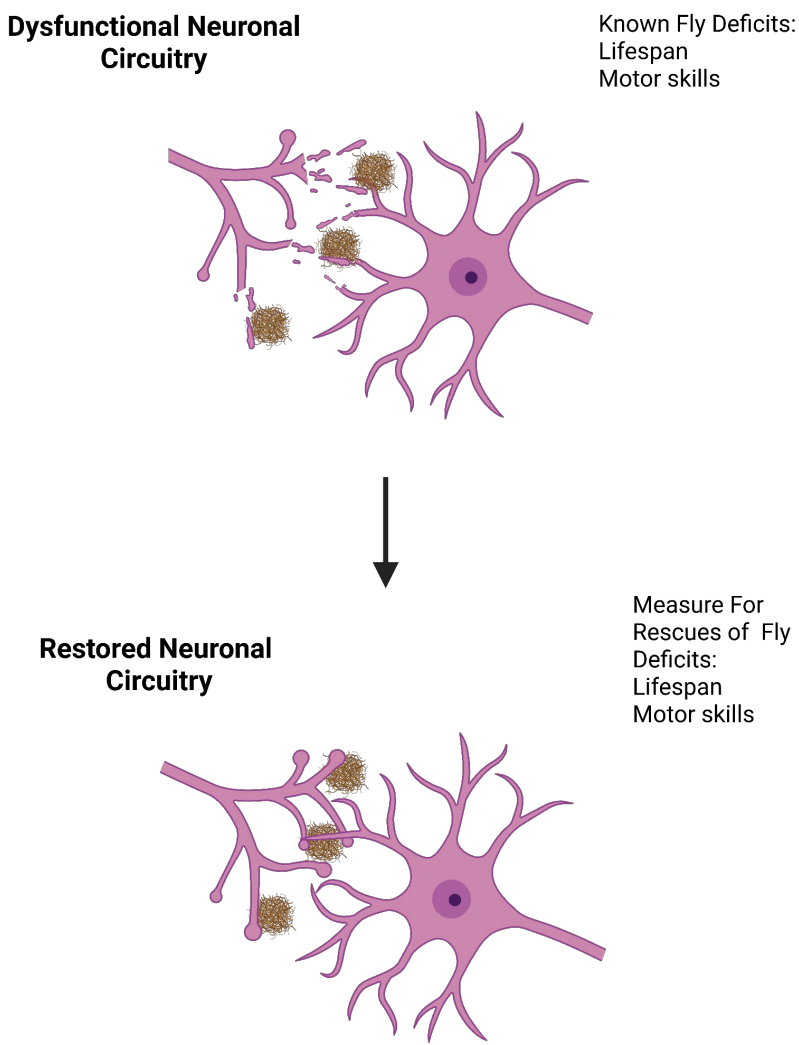


Figure 7: Left is dosing setup. Right is model for my hypothesis.

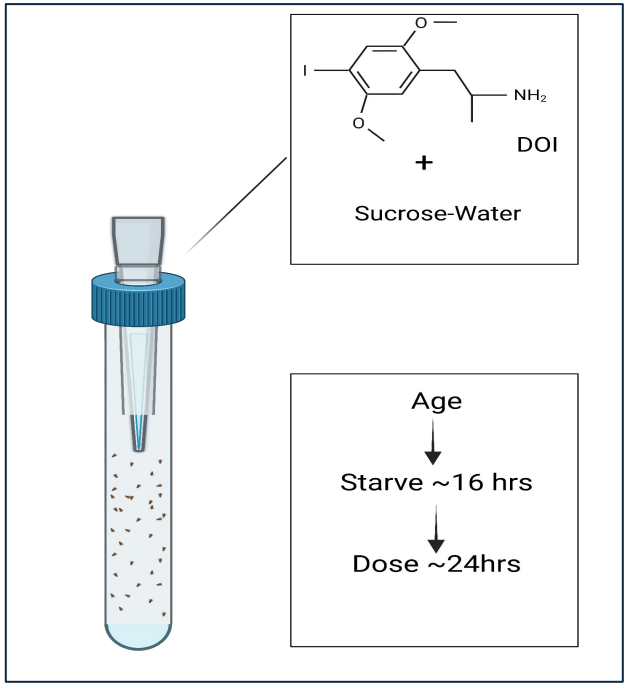


Figure 8: Modified CAFE setup for DOI administration setup to drip-feed a water-sucrose vehicle carrying dissolved 3 mM DOI. The meniscus line is marked and compared with evaporation control to confirm that the flies are consuming vehicle/DOI.

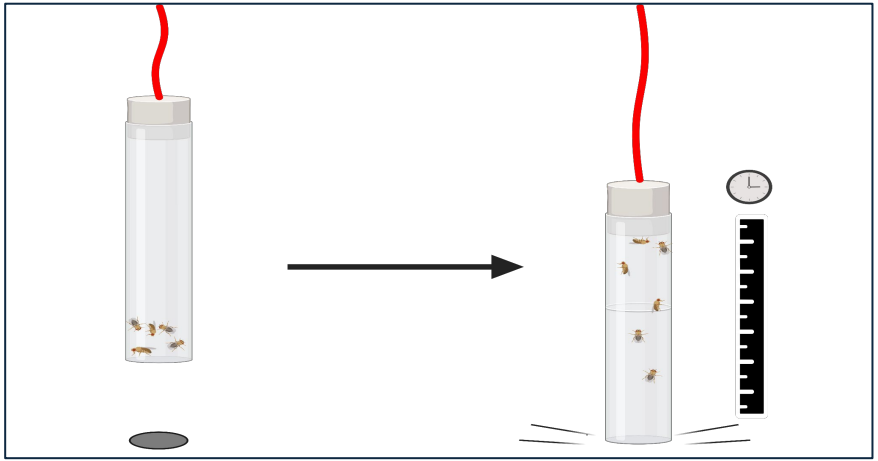


Figure 9: Rapid Iterative Negative Geotaxis(RING) assay to measure the motor abilities of flies at 20 days after eclosion (DAE) and 30 DAE.Velocity, distance, and time will be tracked with video tracking software.

Some Very Preliminary Data

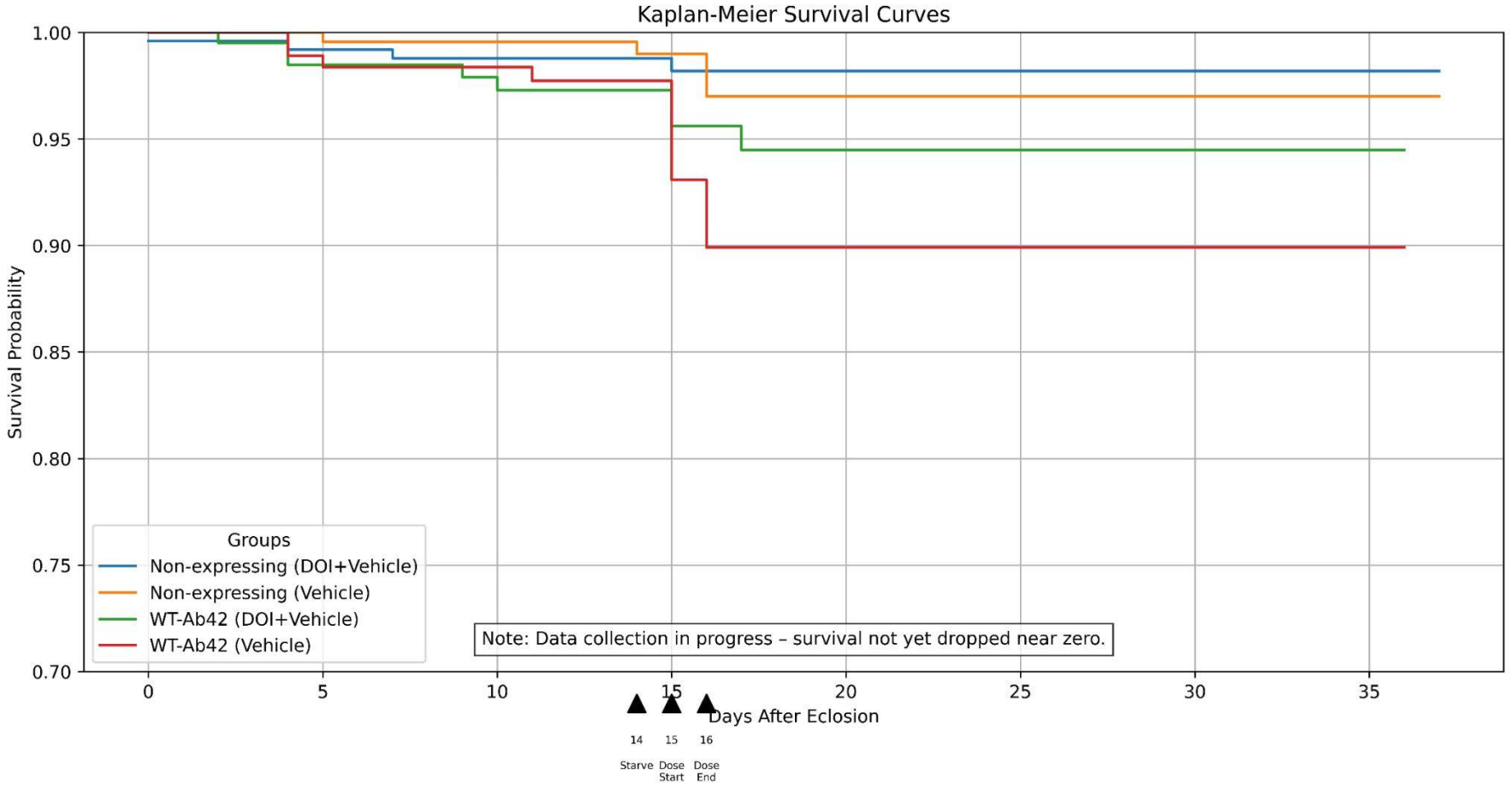
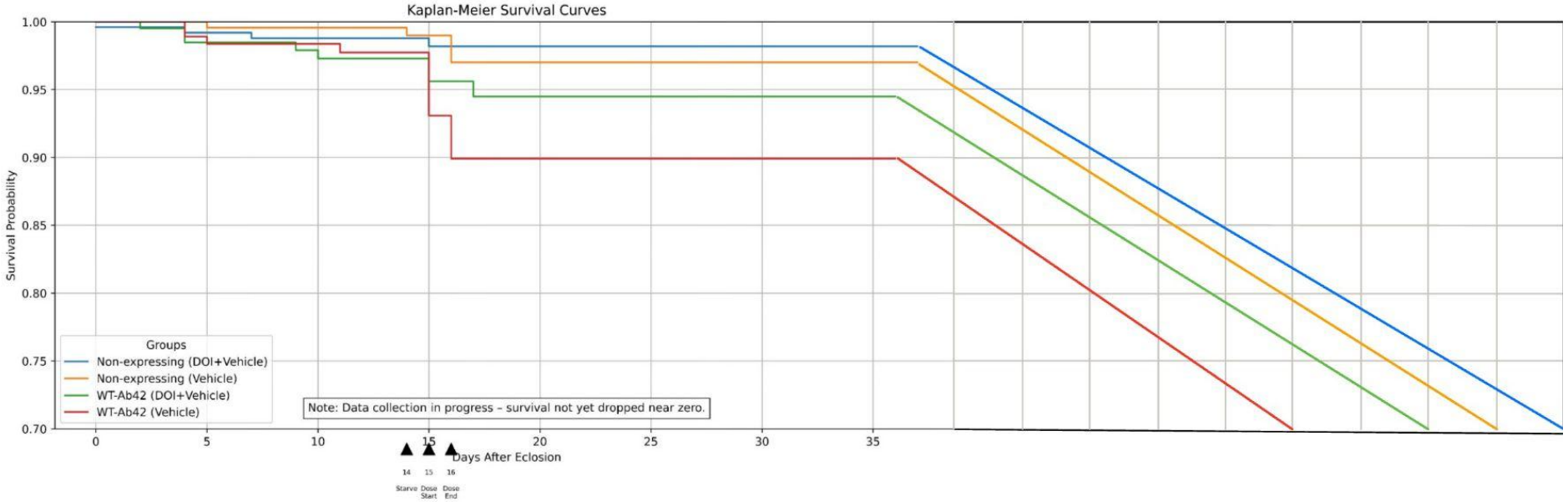
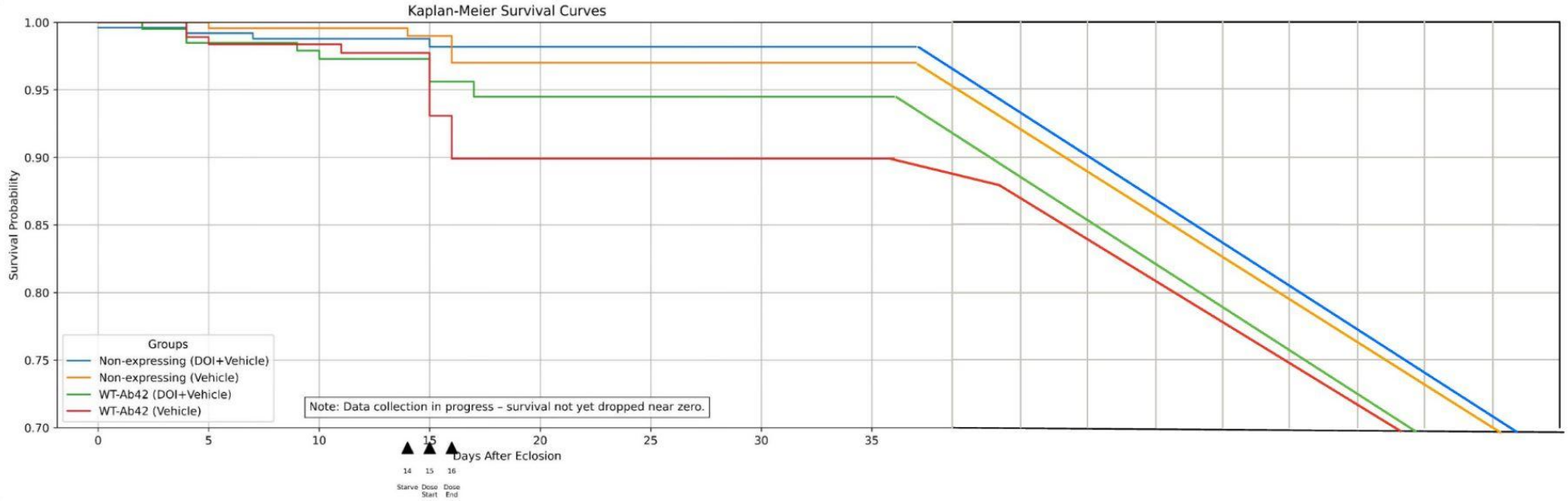


Figure 10: In progress longevity data generated 5/8/25. Data analysis inconclusive until last fly passes away.

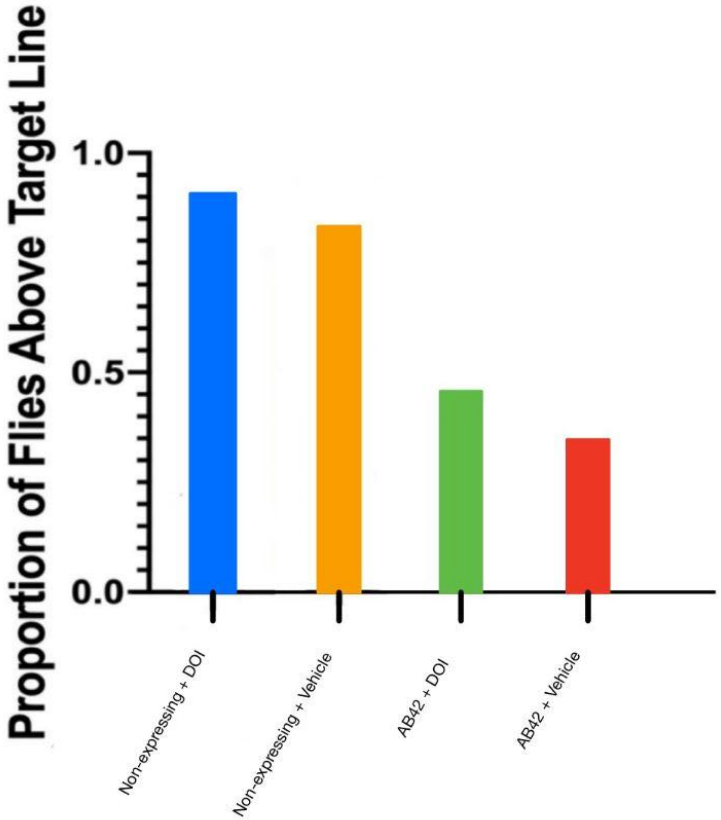
Possible Results

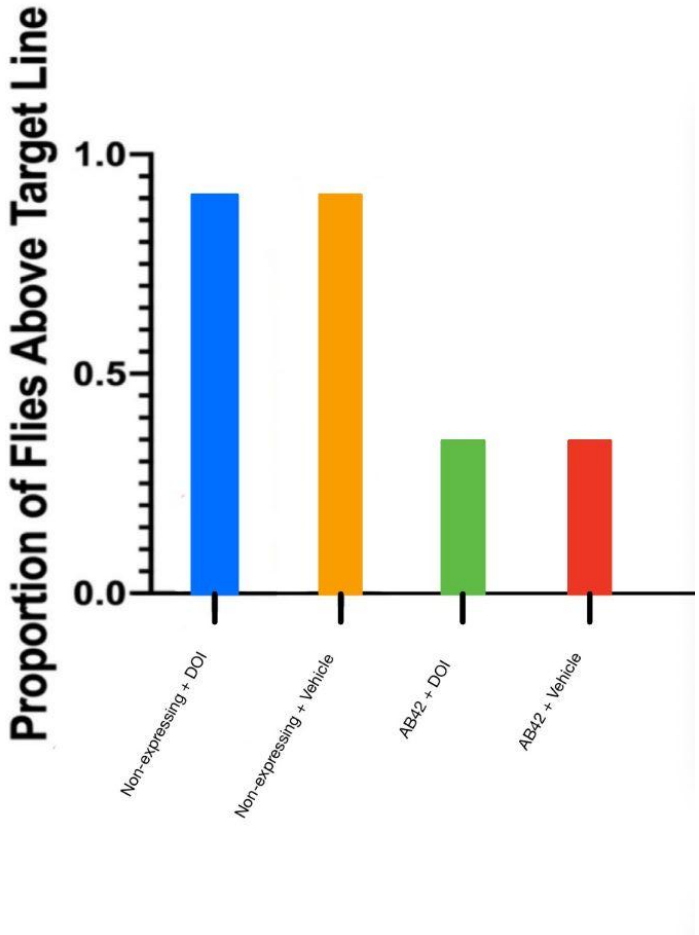


Successful Longevity



Unsuccessful Longevity





Left: Successful RING
Right: Unsuccessful RING

What Next? A lot.

Future plans include to uncover molecular details driving the hypothesized results:

(1)Does my drug alter $A\beta_{42}$ levels?

Conduct an ELISA or Western Blot at different lifespan points with antibodies specific for $A\beta_{42}$ for quantification.

(2)Does my drug alter gene regulation?

Conduct high throughput RNA sequencing to quantify and compare differential gene expression for hypothesized evidence of synaptic plasticity markers.

(3) Does my drug induce synaptic plasticity in the $A\beta_{42}$ expressing model?

Conduct *Drosophila* optogenetic studies using a pan-neuronal GAL4 driver and UAS-GFP to visualize hypothesized neuronal regeneration due to DOI administration.

(4) Are my results specific to DOI or other psychedelics? What would an antagonist do?

Screening of other 5-HT2 agonists such as psychedelics(psilocybin, DMT, TBG) and antagonists to measure their effects in similar behavioral, optogenetic, and biochemical studies to better understand the role of 5-HT2 receptor in a neurodegenerative context.

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References

[1] "2024 Alzheimer's disease facts and figures," Alzheimer's & Dementia, vol. 20, no. 5, pp. 3708–3821, 2024, doi: 10.1002/alz.13809.