

INVESTIGATING THE ROLE OF HUMAN TAU IN SYNAPTIC LOSS AND COMPENSATION

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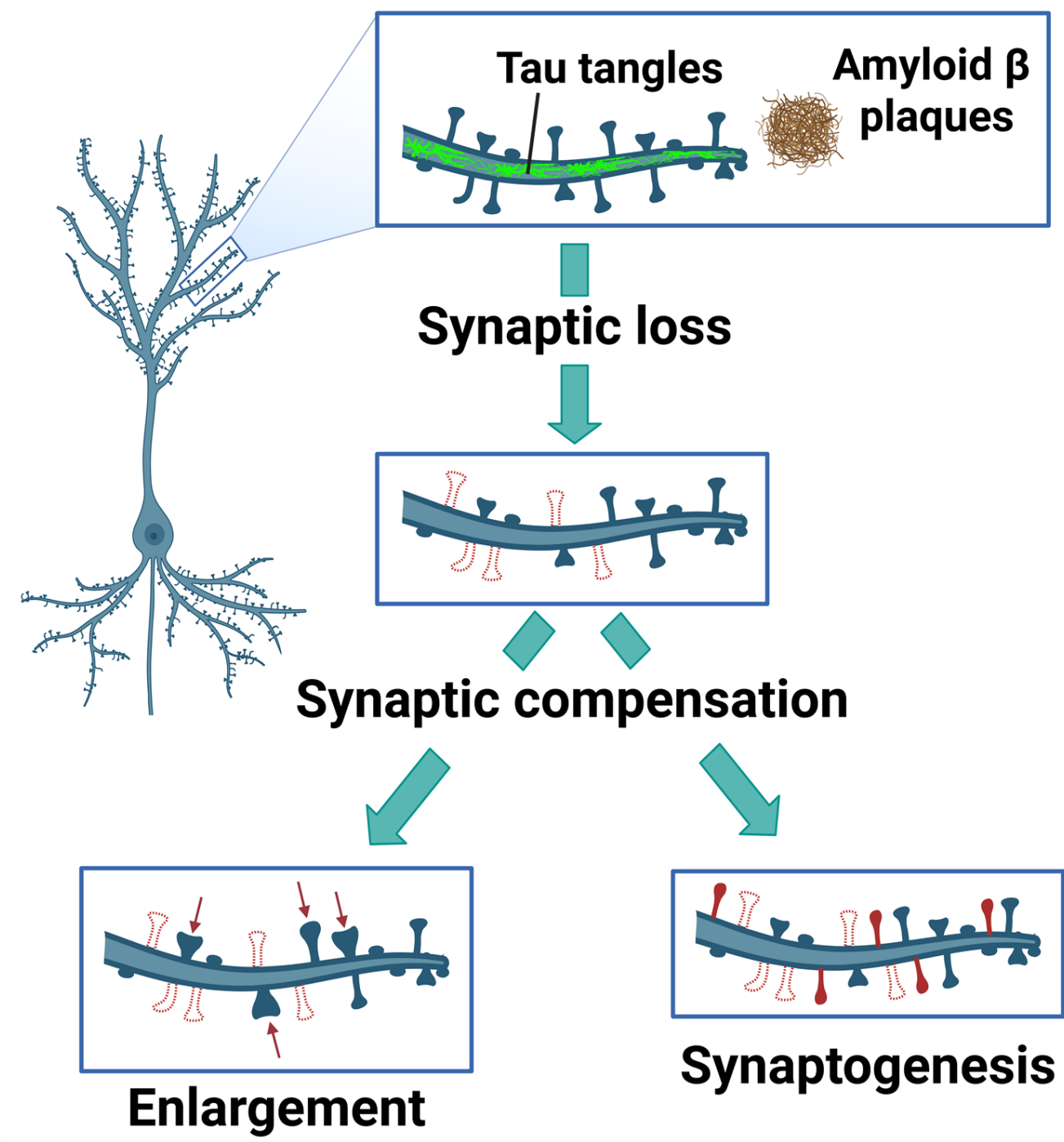
1. SYNAPTIC COMPENSATION IN ALZHEIMER'S DISEASE

BACKGROUND

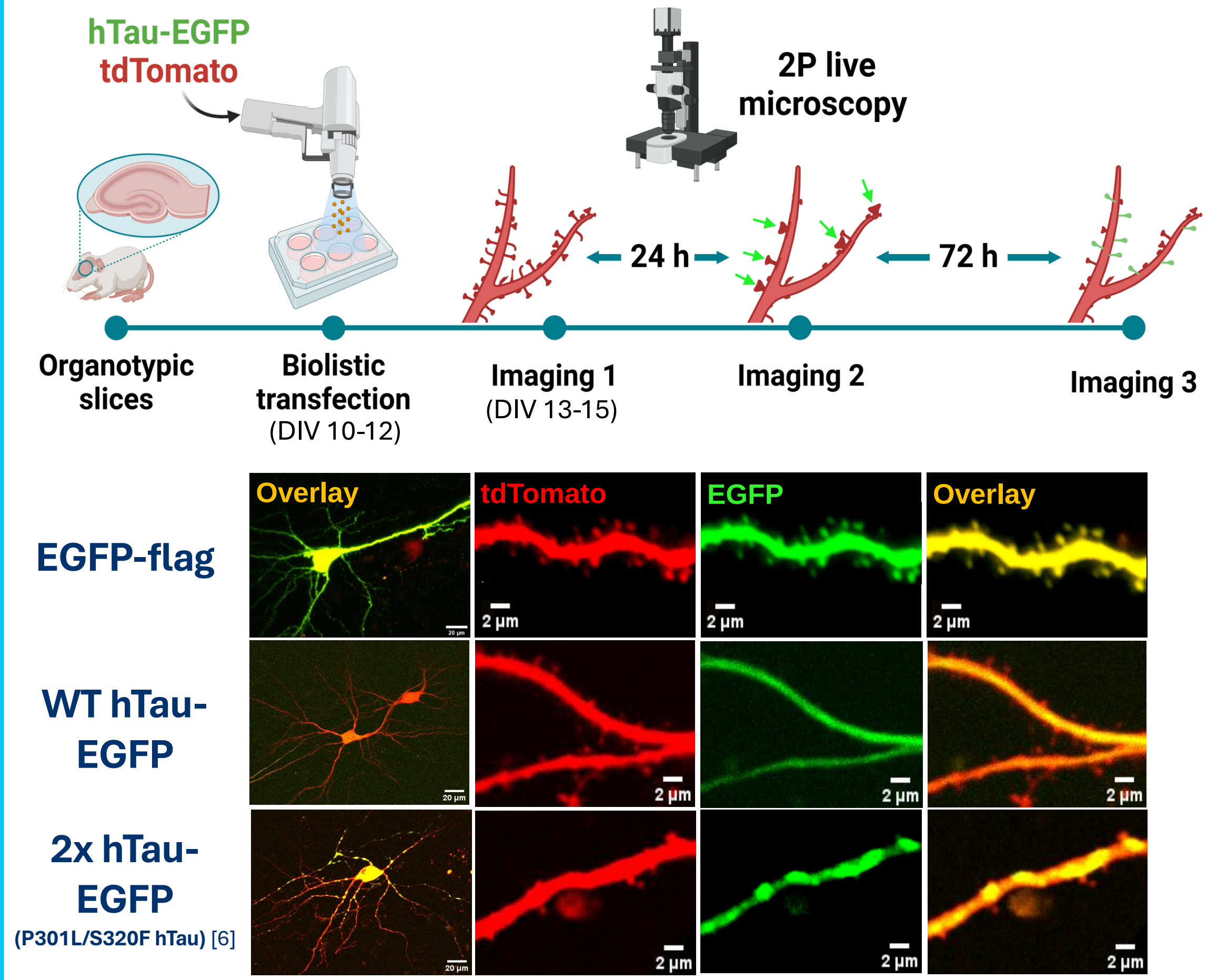
- **Synapse loss** is the best correlate of **cognitive decline** in Alzheimer's disease (AD). [1]
- **Compensatory mechanisms**, like **synapse enlargement** and increased **synaptogenesis**, might counteract synapse loss in early AD. [2-4]
- Tau is physiologically expressed at low concentrations at the post-synapse and plays a role in **synaptic plasticity** and **spinogenesis**. [5]

HYPOTHESES

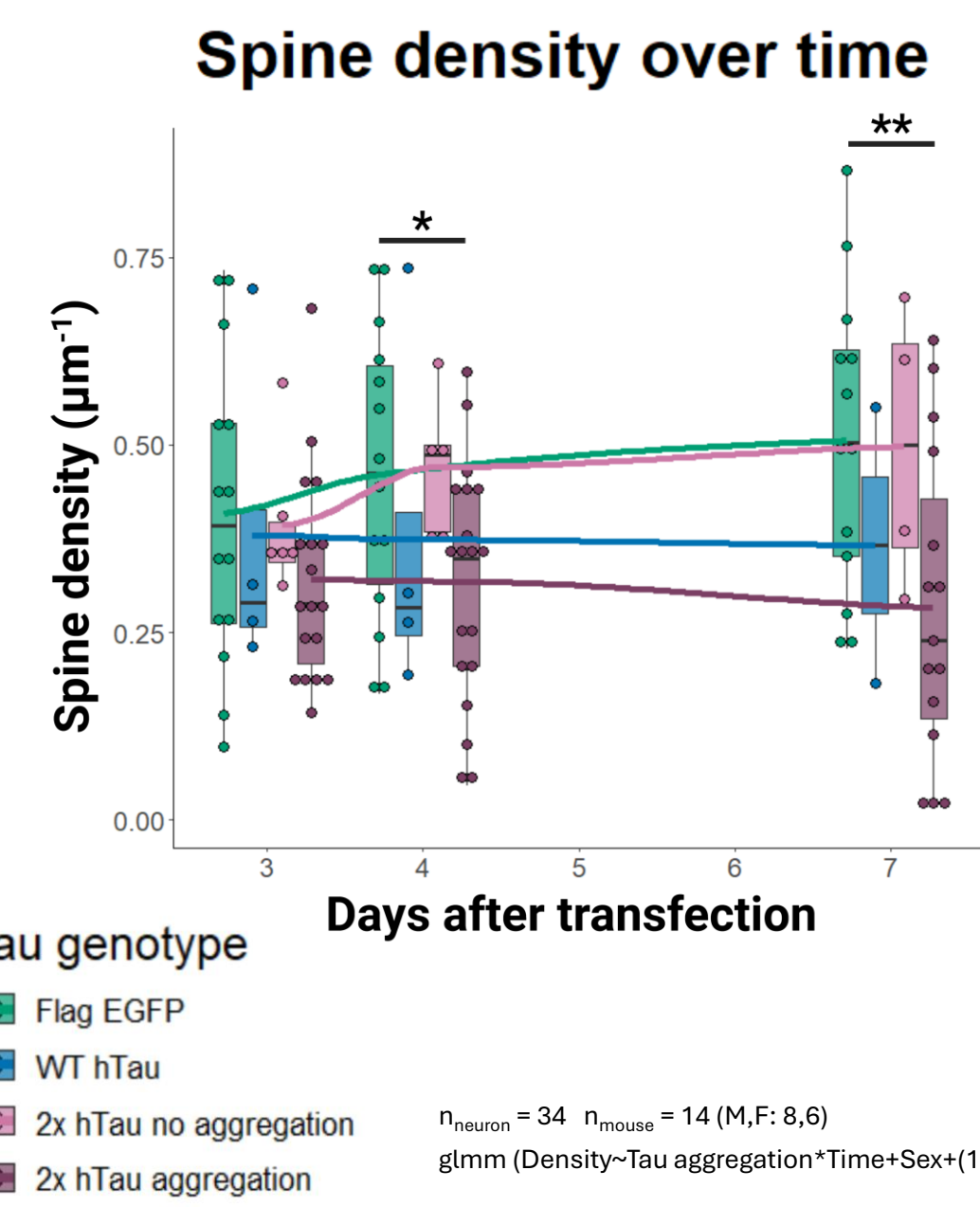
- Synaptic **compensation** might emerge in the context of **tau aggregation**.
- Under **physiological** conditions, tau might be involved in **synaptic compensation**.



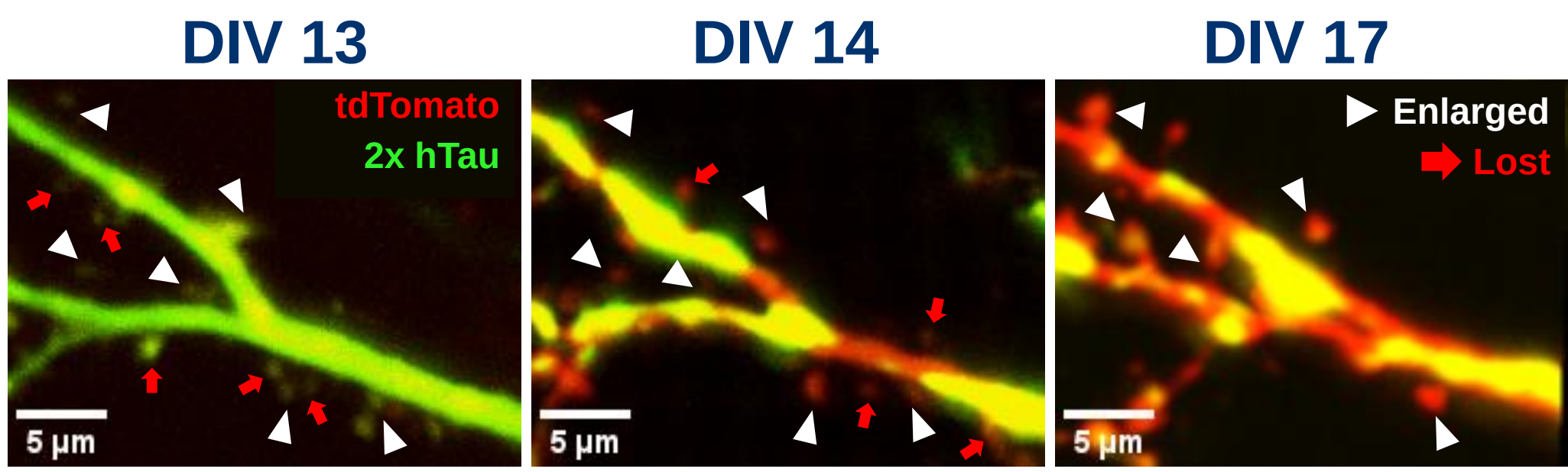
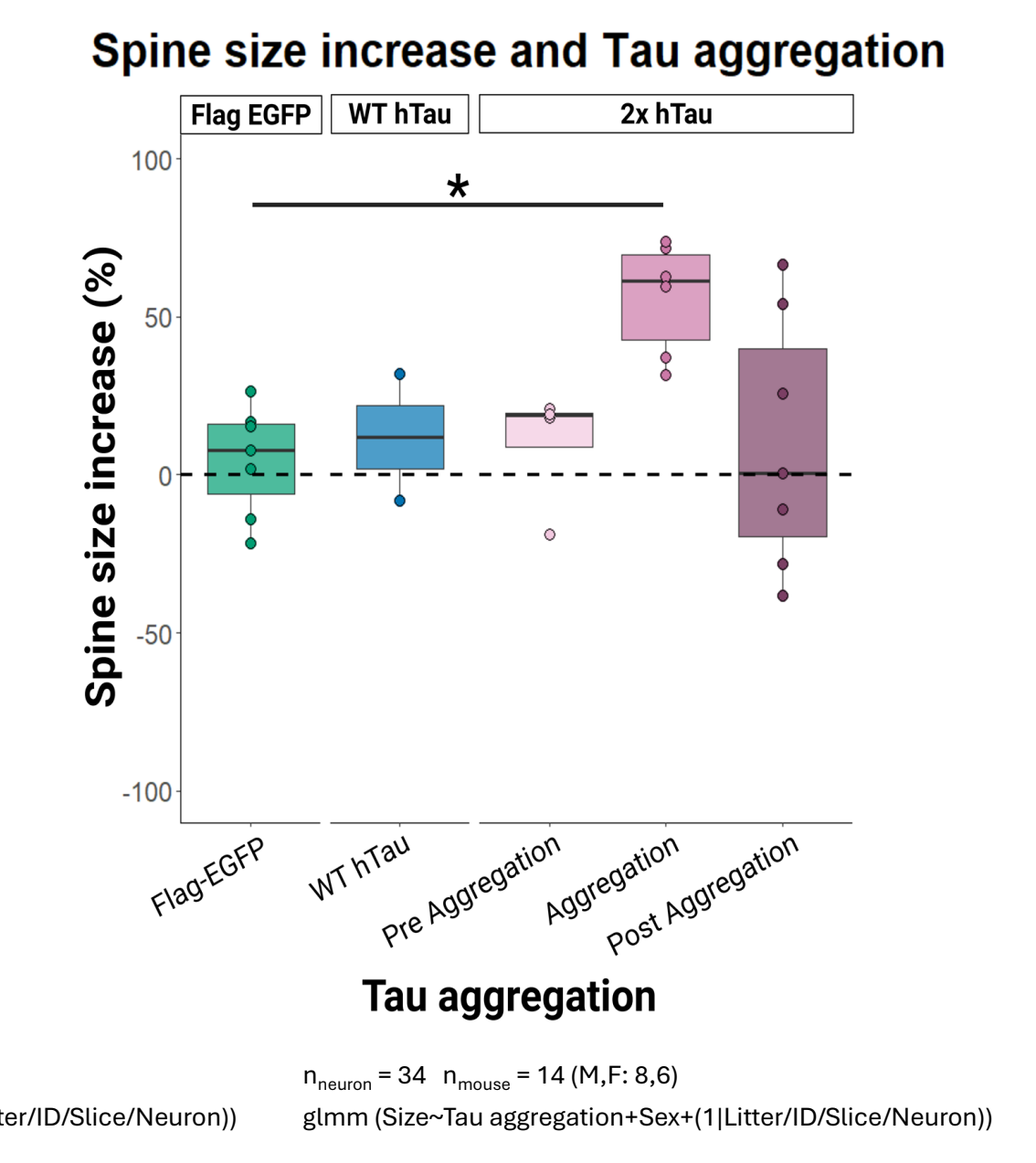
2. SPINE LOSS AND COMPENSATORY ENLARGEMENT OCCUR DURING TAU AGGREGATION



2x hTau AGGREGATION INDUCES SPINE LOSS



RETAINED SPINES ENLARGE DURING TAU AGGREGATION



5. CONCLUSIONS

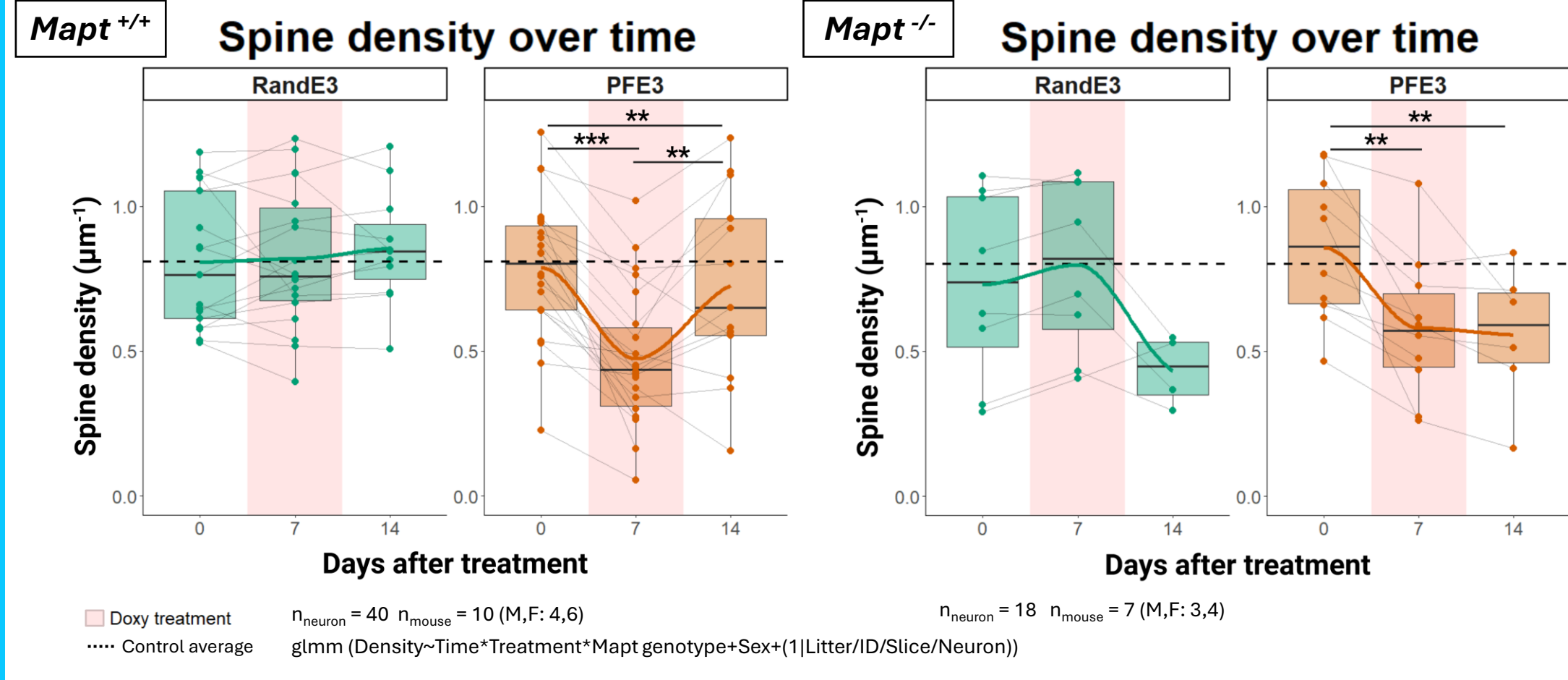
- Spine loss and compensatory **enlargement** occur at the onset of human **tau aggregation** in **mouse** hippocampal slices. Preliminary evidence suggests that this may also occur in **human** cortical slice cultures.
- Spine loss, compensatory spine enlargement and spinogenesis are triggered by **PFE3** in **Mapt^{+/+}** mouse hippocampal slices.
- PFE3-induced compensatory spine enlargement and spinogenesis are **abolished** in **Mapt^{-/-}** neurons, suggesting that **tau** is **necessary** for both these compensatory mechanisms.

6. FUTURE DIRECTIONS

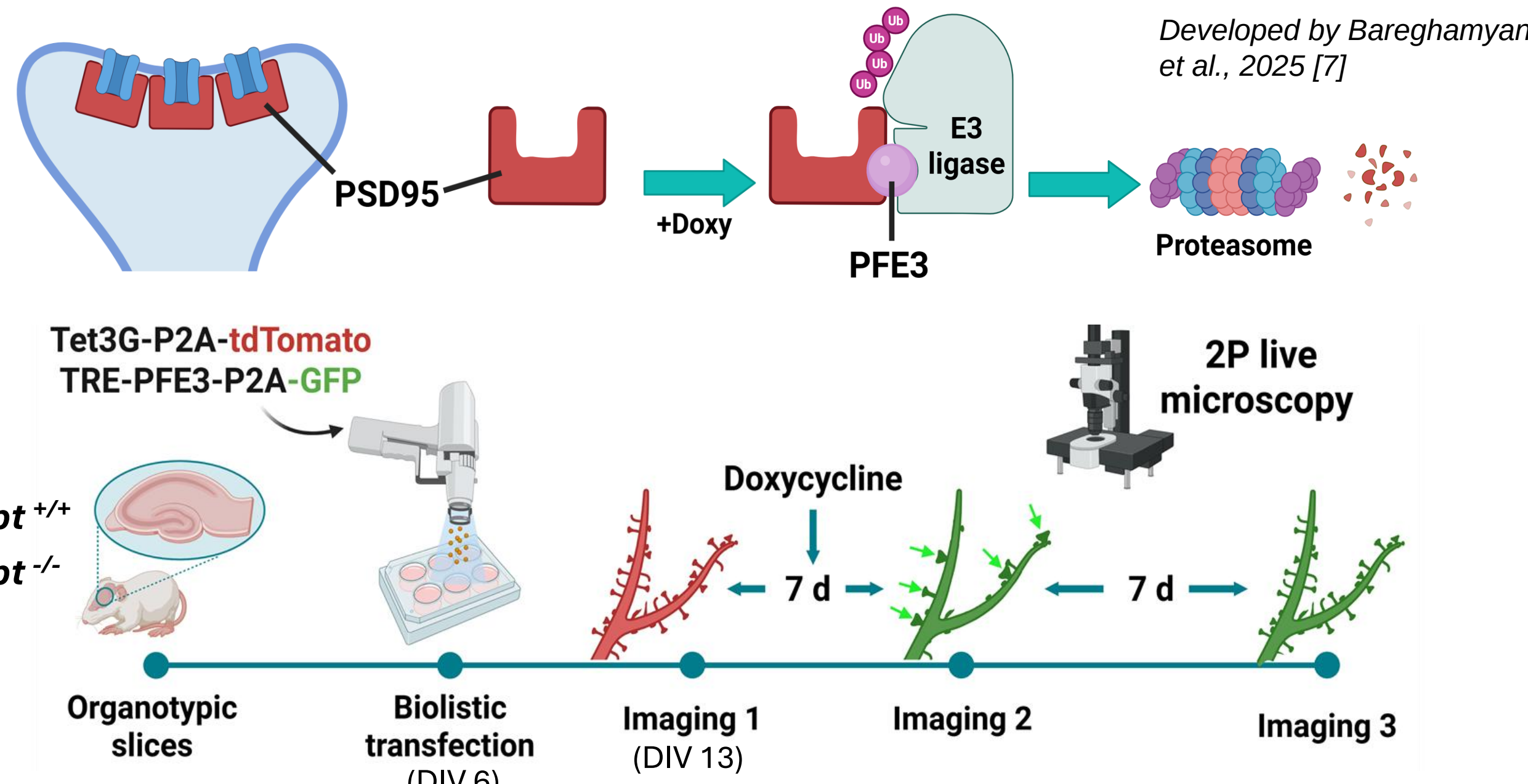
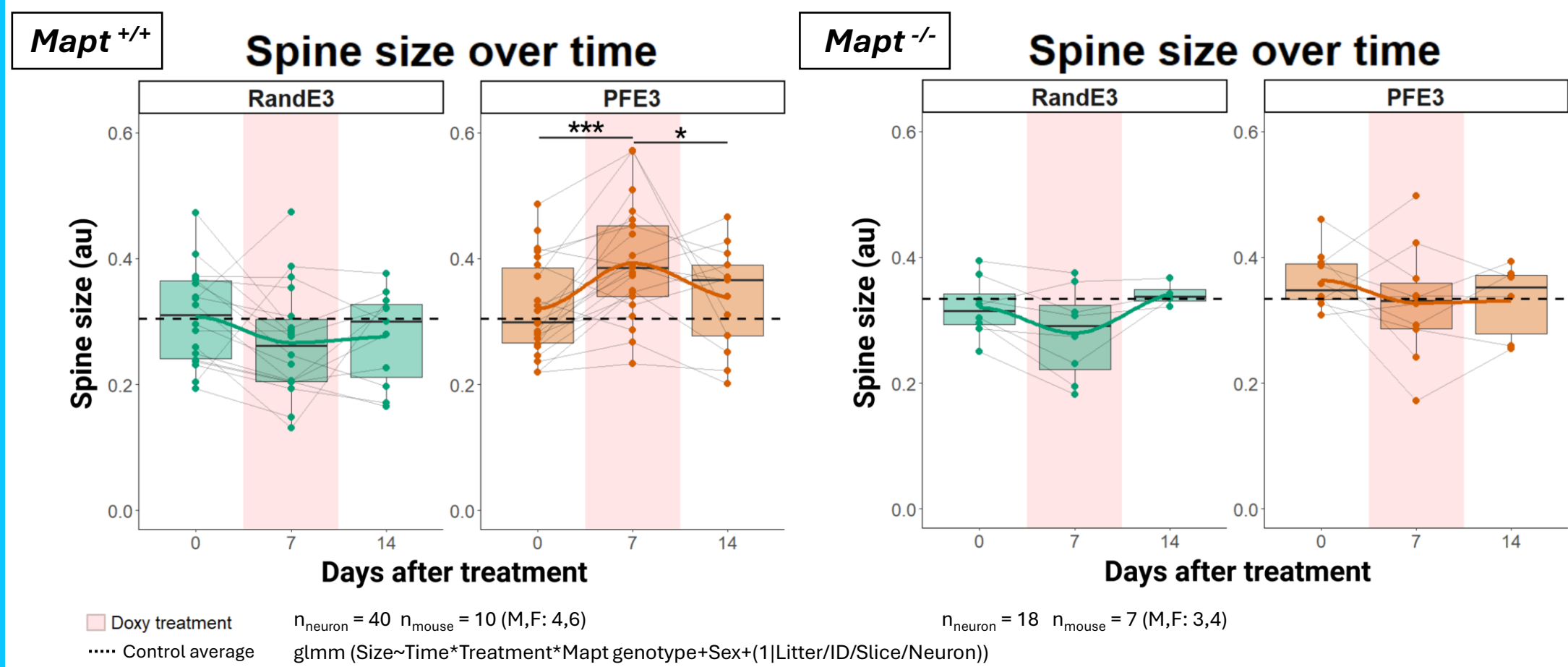
- Test whether **endogenous tau** is necessary for compensatory spine enlargement in the context of **tau aggregation**-induced spine loss, transfecting **2x hTau** into **Mapt^{-/-}** neurons.
- Test whether spine enlargement and spinogenesis coincide with **functional compensation**, complementing the pipeline with **calcium imaging**.
- Increase sample size for **tau aggregation**- and **PFE3**-induced spine loss and compensation in **human brain slices** cultures.

3. TAU IS NECESSARY FOR SYNAPTIC COMPENSATION

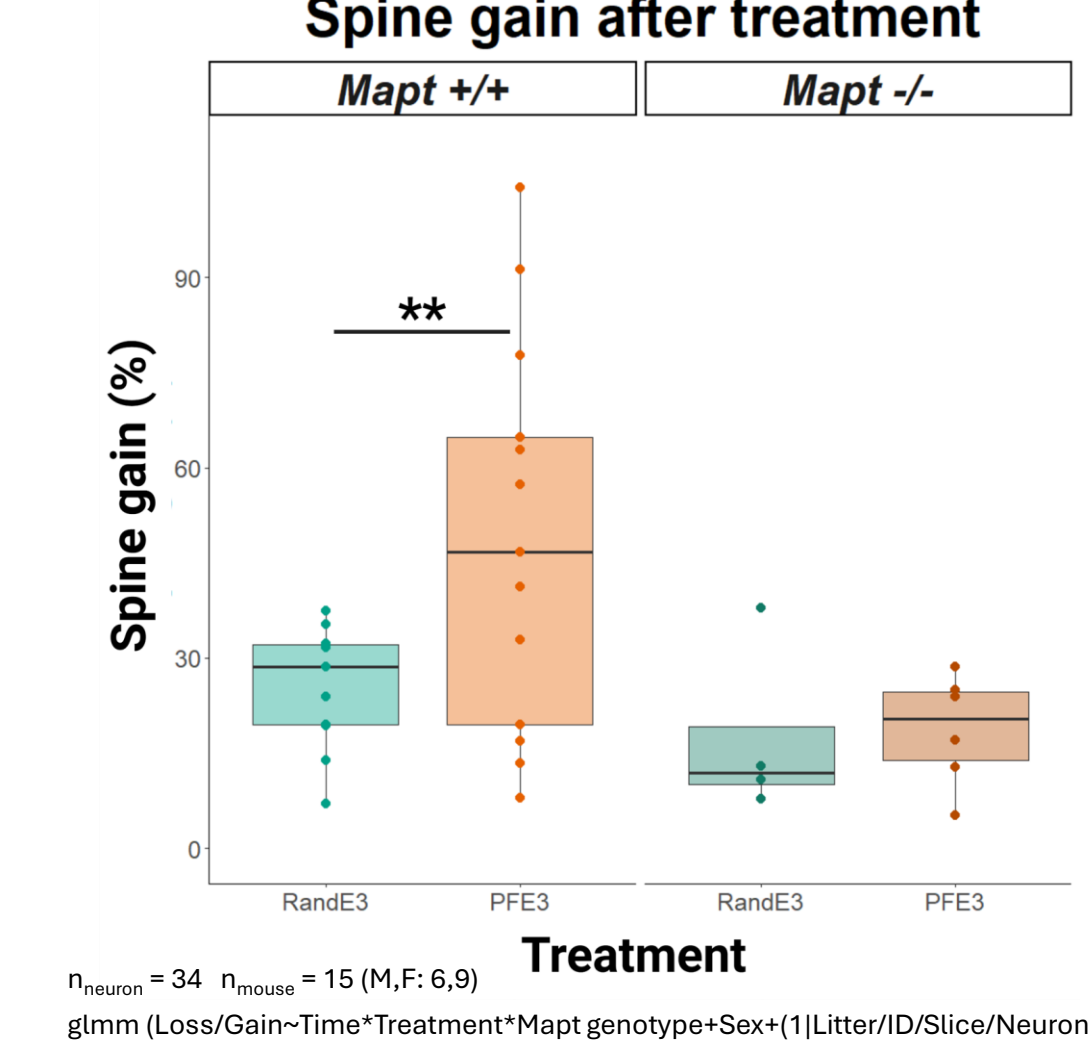
PFE3 ACTIVATION INDUCES SPINE LOSS



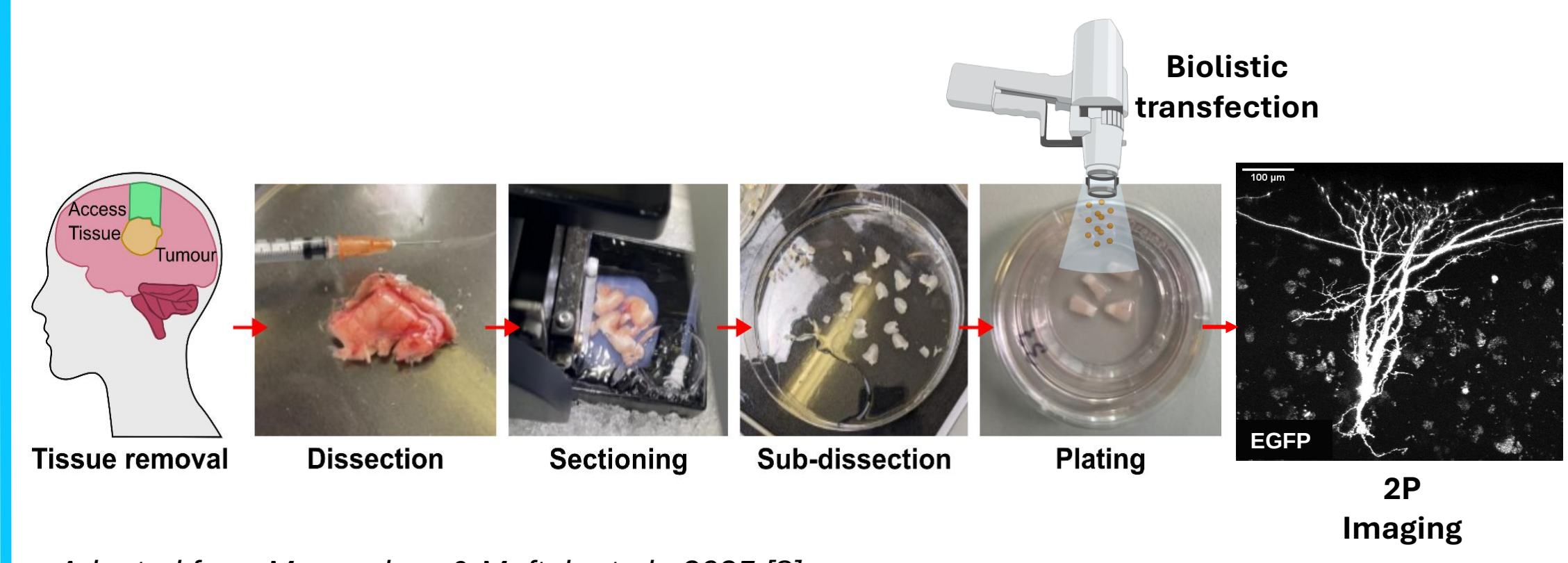
TAU IS NECESSARY FOR PFE3-INDUCED COMPENSATORY SPINE ENLARGEMENT



TAU IS NECESSARY FOR PFE3-INDUCED SPINOGENESIS

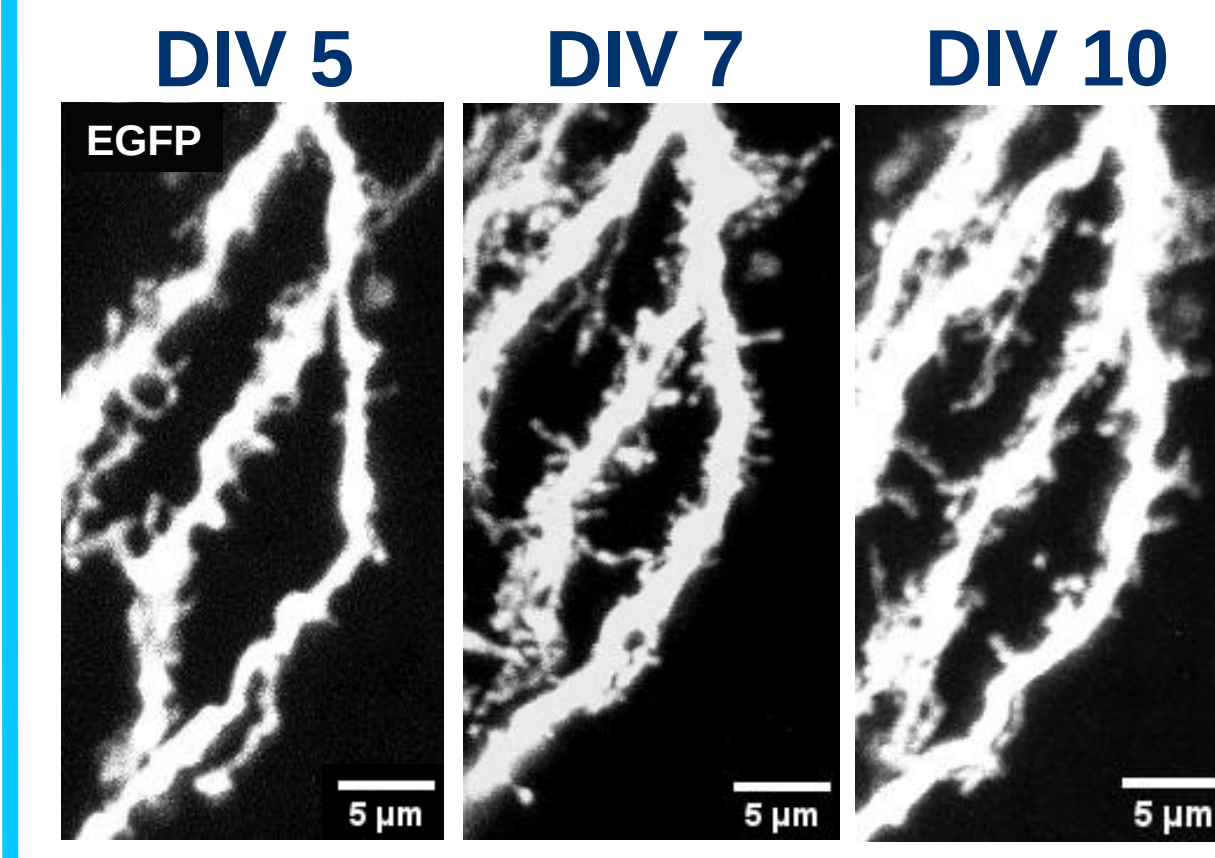


4. HUMAN BRAIN SLICE CULTURES TO INVESTIGATE CLINICAL RELEVANCE

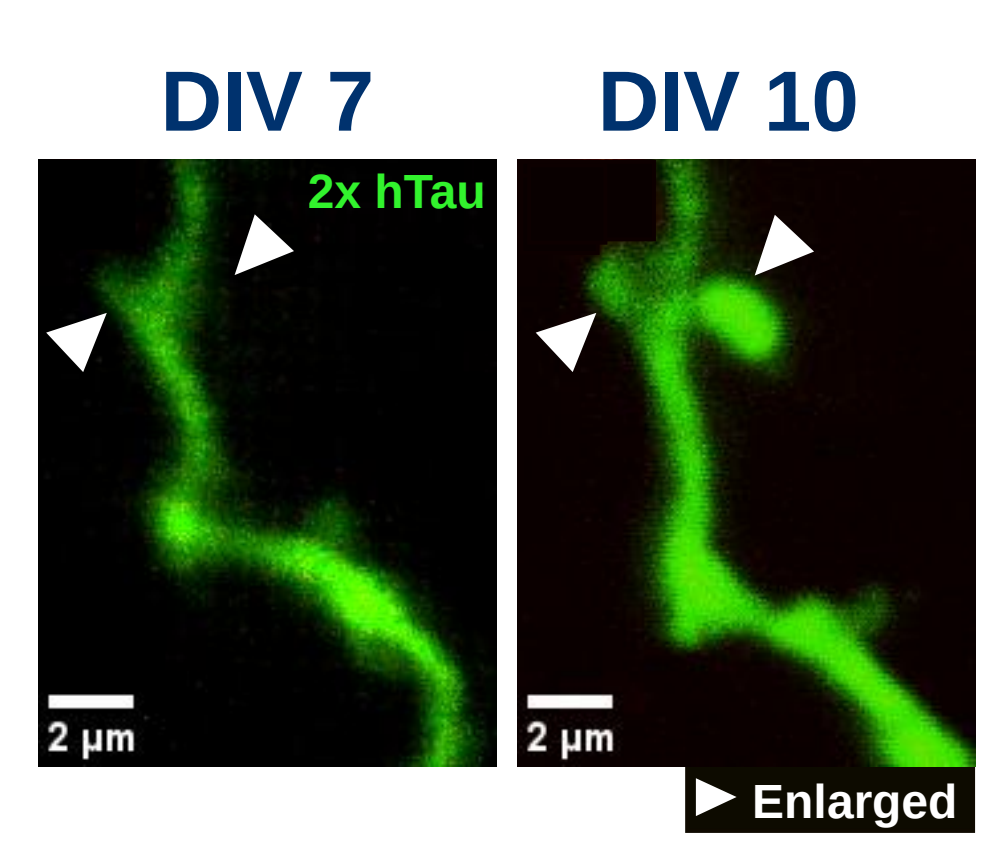


Adapted from McGeachan & Meftah et al., 2025 [8]

HUMAN DENDRITE LIVE IMAGING



TAU-MEDIATED HUMAN SPINE ENLARGEMENT



REFERENCES

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