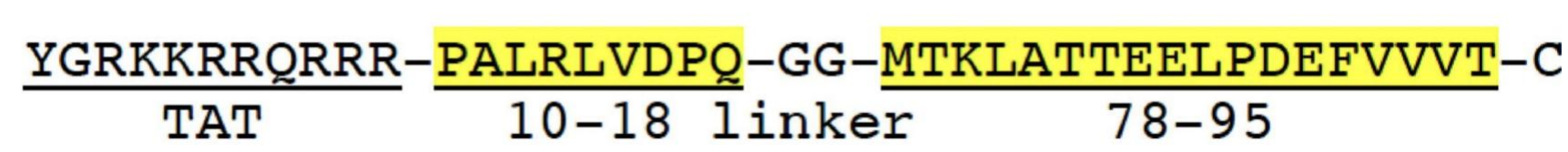
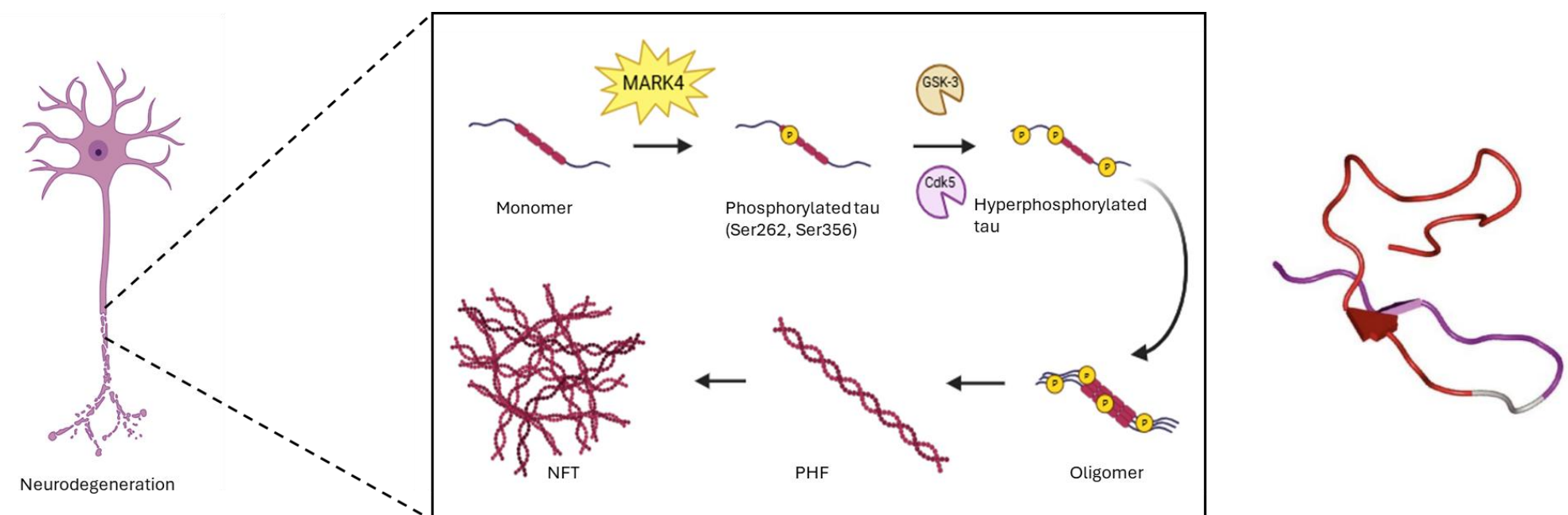


Mark4 Inhibitor Mitigates Tauopathy In A Mouse Model

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Introduction



- ◆ Microtubule affinity-regulating kinase 4 (MARK4) is critically involved in tau-mediated neurodegeneration.
- ◆ Targeting MARK4 may offer a disease-modifying strategy for tauopathies such as Alzheimer's disease.
- ◆ Due to high conservation of ATP-binding domains among MARK family members, most existing kinase inhibitors lack specificity.
- ◆ A peptide derived from SARS-CoV-2 Orf9b interacts specifically with MARK4 via an allosteric site.

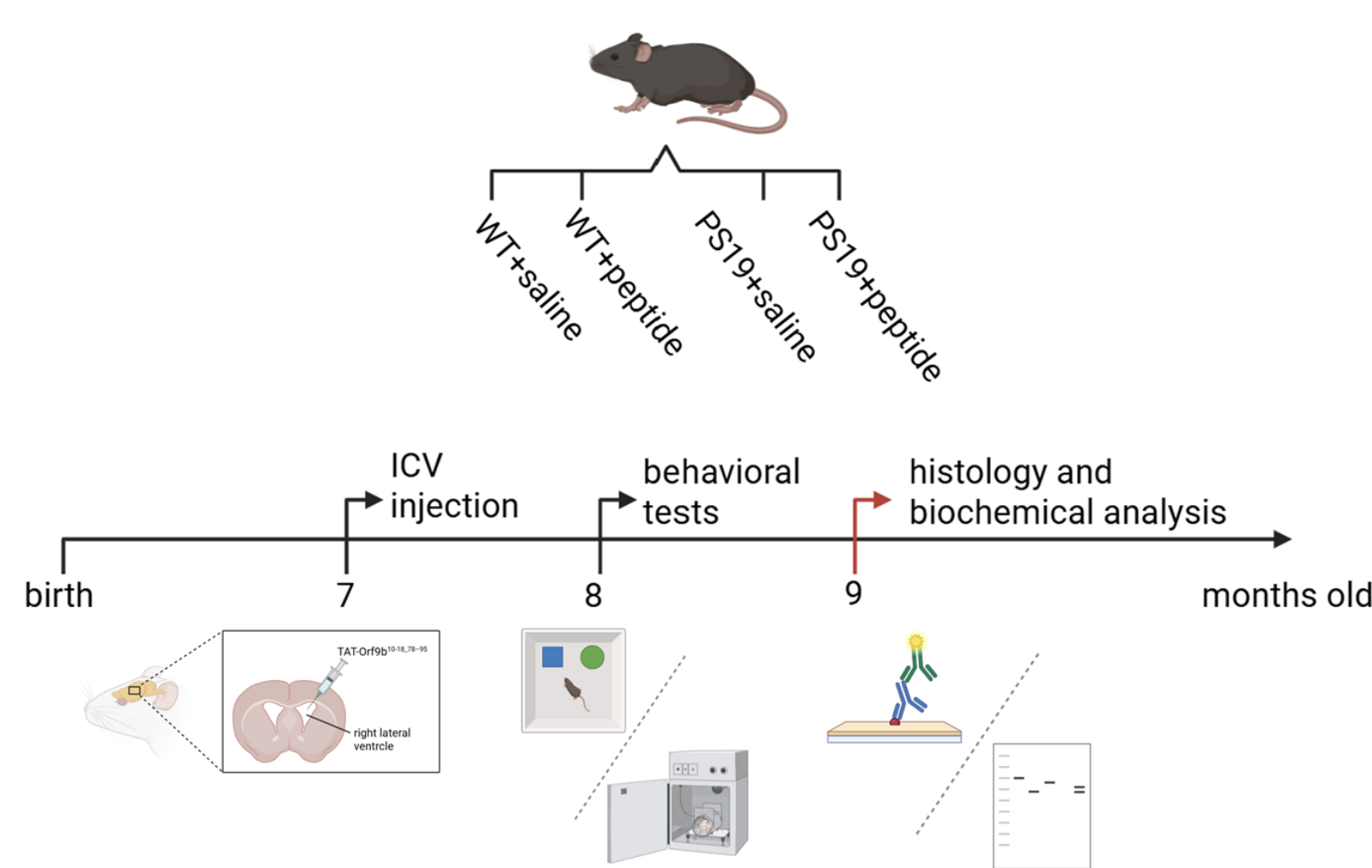
(Oba et al., 2023)

Figure created in BioRender.com

Objective

Investigating the effects of a peptide-based MARK4 inhibitor in a mouse model of tauopathy.

Methods



A total of 100 μ L of peptide (10 μ g/mL) was continuously infused into the right lateral ventricle over a period of 2 weeks using an ALZET osmotic pump.

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Conclusions

- ◆ Orf9b-derived peptide reduced tau phosphorylation at Ser262.
- ◆ Tau hyperphosphorylation at AT8 sites was decreased.
- ◆ Peptide-treated mice exhibited reduced GFAP expression, suggesting attenuation of astrocyte activation.
- ◆ Memory deficits in tauopathy mice was rescued, suggesting the potential of the peptide in tauopathy treatment.

Results

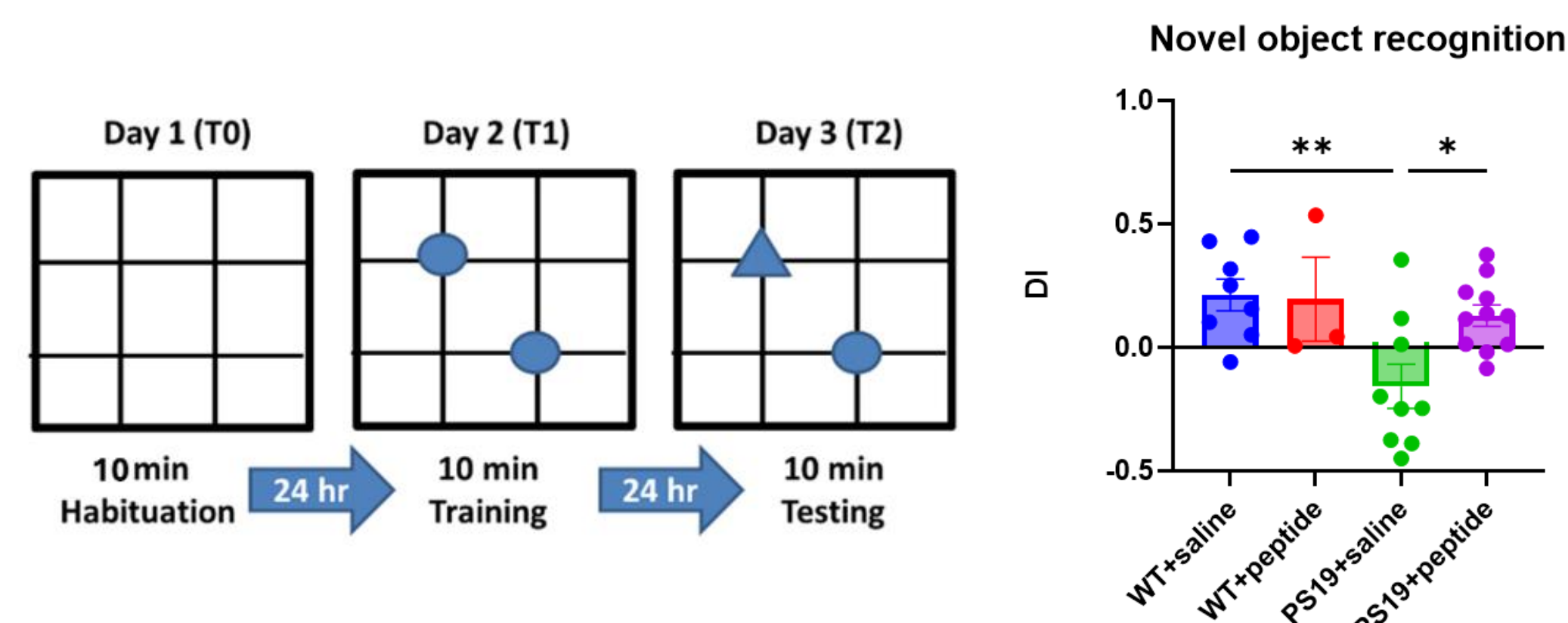


Fig 1. MARK4 inhibition rescued memory deficits in PS19 mice.

Novel object recognition (NOR) test was performed to measure the animal's ability to recognize the novel object from the familiar one. Discrimination index was quantified to assess recognition memory mice (Mean $\pm$ SD, N = 3 to 11, $*p < 0.05$, $**p < 0.01$ (One-way ANOVA followed by Tukey's multiple comparisons test)).

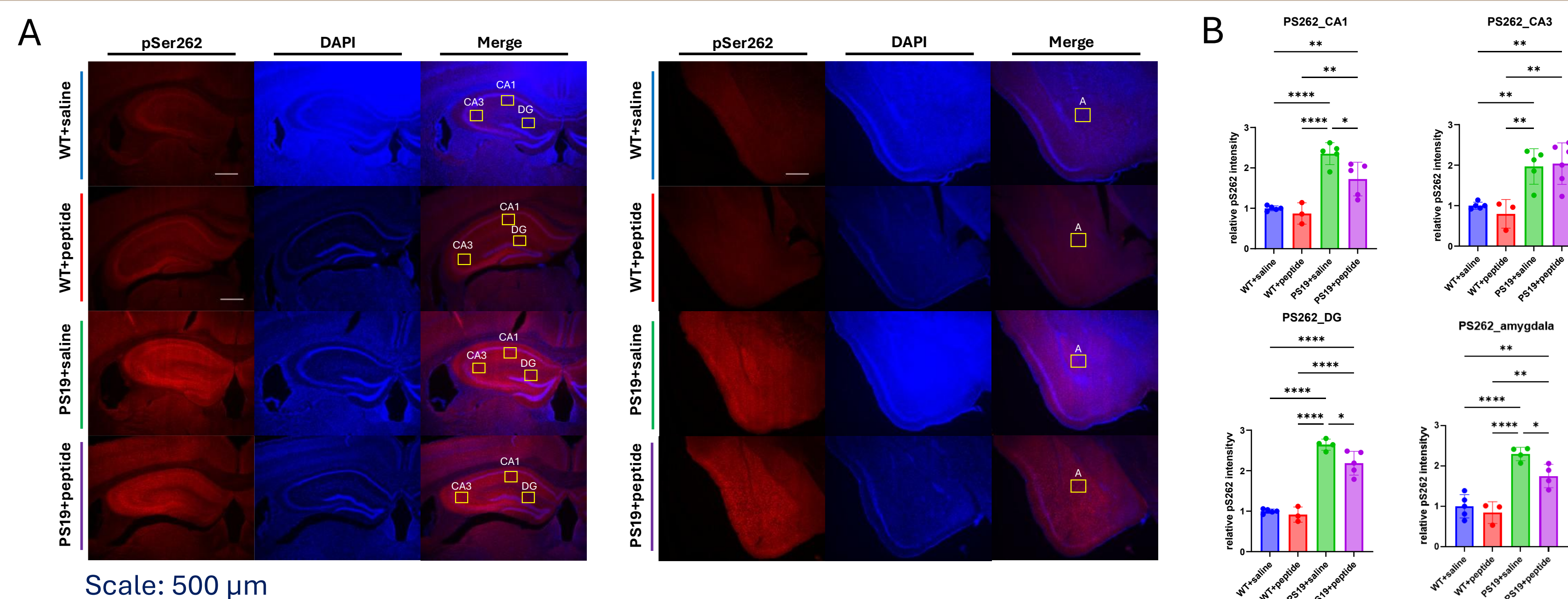


Fig.2 MARK4 inhibition decreased tau phosphorylation at Ser262.

(A) Representative images of pSer262 tau immunostaining in the hippocampus and amygdala. (B) Quantification of pSer262 integrated intensity (Mean $\pm$ SD, N = 3 to 6, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$ (One-way ANOVA followed by Tuckey's multiple comparisons test)).

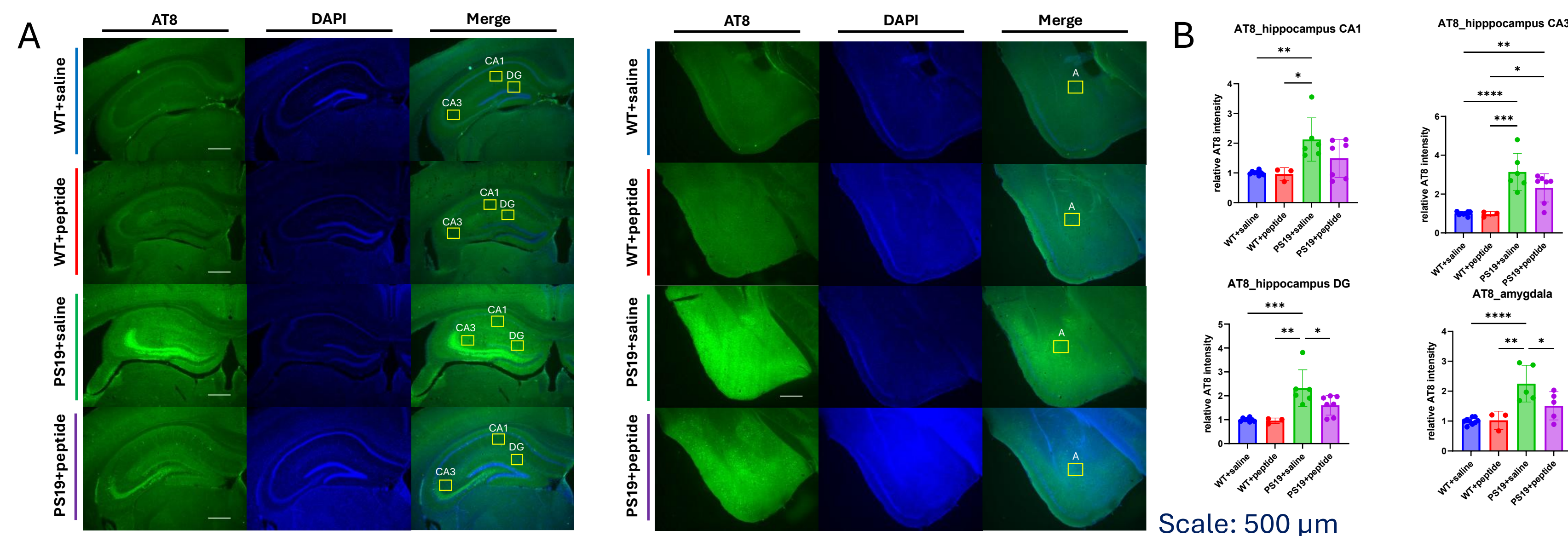


Fig.3 MARK4 inhibition decreased tau phosphorylation at AT8 sites. (A) Representative images of AT8 (pSer202/pThr205)immunostaining in the hippocampus and amygdala. (B) Quantification of AT8 integrated intensity (Mean $\pm$ SD, N = 3 to 9, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$ (One-way ANOVA followed by Tuckey's multiple comparisons test)). (C) Immunoblot of AT8 from brain lysates with integrated intensity quantification and normalization to HT7.

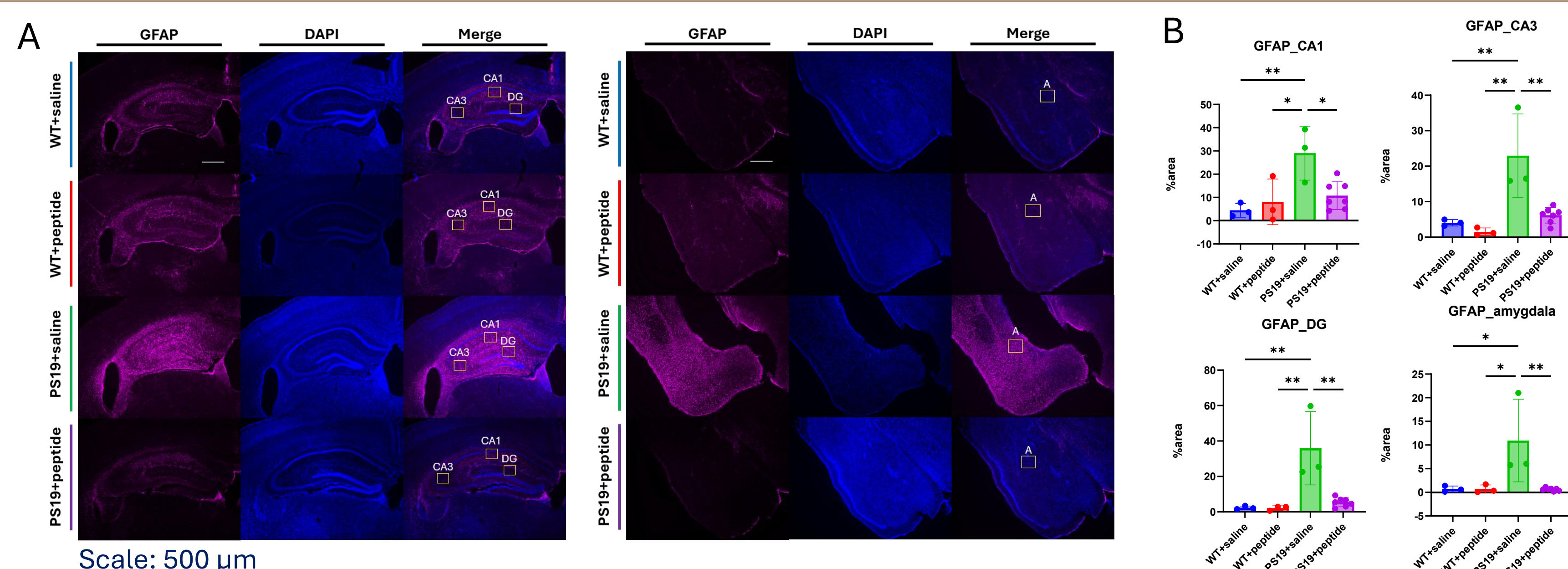


Fig.4 MARK4 inhibition reduced astrogliosis in PS19 mice.

(A) Representative images of GFAP immunostaining in the hippocampus and amygdala. (B) Quantification of the percentage of GFAP-positive area (Mean $\pm$ SD, N = 3 to 7, $*p < 0.05$, $**p < 0.01$, (One-way ANOVA followed by Tuckey's multiple comparisons test)).