

Targeting Pyk2 to Modulate Osteoporosis-Associated Alzheimer's Disease Pathology

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KEY TAKEAWAY Pyk2 inhibition simultaneously normalizes bone resorption (Type I Collagen) and reduces amyloid pathology (serum Aβ42 and plaque), identifying Pyk2 as a dual-target node of the bone–brain axis in Alzheimer's disease.

INTRODUCTION

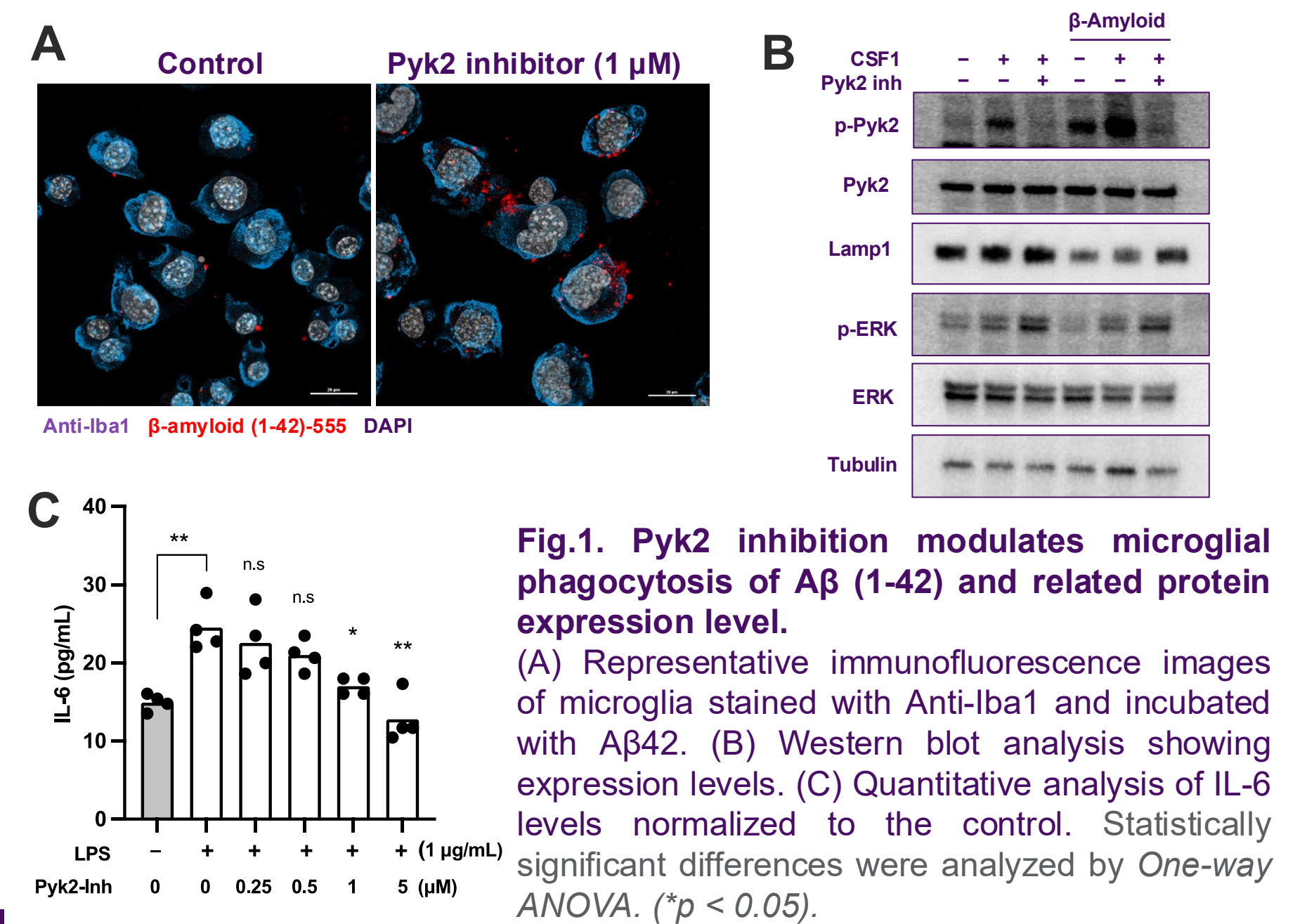
- Osteoporosis and Alzheimer's disease (AD) are linked age-related disorders. In postmenopausal women, bone loss is associated with increased AD risk, pointing to a shared mechanism [1].
- Genome-wide association studies identify ***PTK2B*** (encoding PYK2) as a shared risk gene for both conditions [1]. Pyk2 regulates immune-cell signaling and inflammation and modulates microglial function [2].
- We tested whether **PYK2 inhibition can simultaneously ameliorate bone loss and AD pathology** — a dual-target strategy across the bone–brain axis.

METHODS

- **In vitro.** HMC3 human microglia were stimulated with Aβ42, then treated with the Pyk2 inhibitor PF-431396. Pro-inflammatory cytokine mRNA (*TNFα*, *IL-1β*, *IL-6*) was measured by RT-qPCR; pPyk2 and Lamp1 were assessed by Western blot.
- **In vivo.** Ovariectomy (OVX) on *App^{NL-F}/Psen1^{P117L}* mice modeled osteoporotic AD; the Pyk2 inhibitor was given at low and high doses, with sham controls. Serum CTX-I and Aβ42 were measured by ELISA; brain Aβ and microglia (Iba1) were quantified by immunofluorescence.
- **Serum proteomics.** LC-MS/MS profiling to identify bone–brain axis biomarkers — **ongoing**.

RESULTS

Pyk2 inhibition modulates microglial phagocytosis



Pyk2 inhibition lowers serum Aβ42 & CTX-I

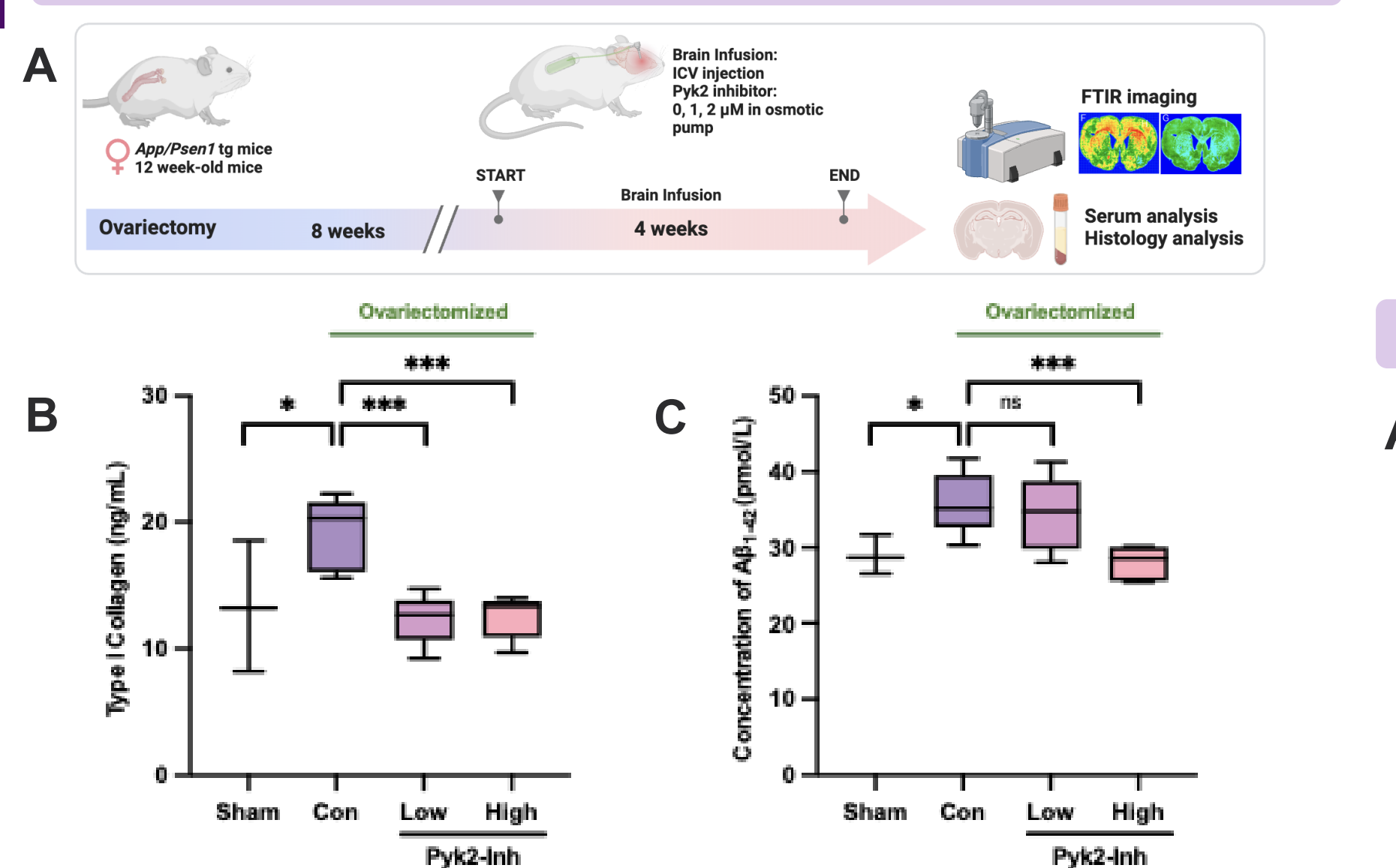


Fig. 2. Pyk2 inhibition attenuates bone resorption and Aβ42 accumulation in ovariectomized App/Psen1 transgenic mice. (A) Experimental schematic illustration. (B) Quantitative analysis of serum Type I Collagen levels (ng/mL) as a marker for bone resorption among Sham, Ovariectomized Control (Con), and Pyk2-Inh treated groups (Low and High doses). (C) Quantitative analysis of serum Aβ42 concentration (pmol/L) across the experimental groups. One-way ANOVA with Tukey's HSD multiple comparisons. *p<0.05; n.s., not significant.

CONCLUSIONS

- Pyk2 inhibition acts on both arms of the bone–brain axis: in microglia it lowers pro-inflammatory cytokine expression and NF-κB signaling; in OVX-AD mice it reduces serum CTX-I (bone resorption) and serum Aβ42.
- Brain immunofluorescence is consistent with fewer Aβ deposits and greater microglia–Aβ contact (representative).
- Together, these nominate Pyk2 (*PTK2B*) as a candidate dual target linking skeletal and neural pathology, warranting further study as a disease-modifying strategy for AD.
- Serum proteomic profiling (LC-MS/MS) is **ongoing** to identify bone–brain axis biomarkers.

REFERENCES

[1] Lee JW, Lee IH, Iimura T, Kong SW. Two macrophages, osteoclasts and microglia: from development to pleiotropy. *Bone Res.* 2021;9:11.

[2] Lee JW, Mizuno K, Watanabe H, et al. Enhanced phagocytosis associated with multinucleated microglia via Pyk2 inhibition in an acute β-amyloid infusion model. *J Neuroinflammation.* 2024;21:196.

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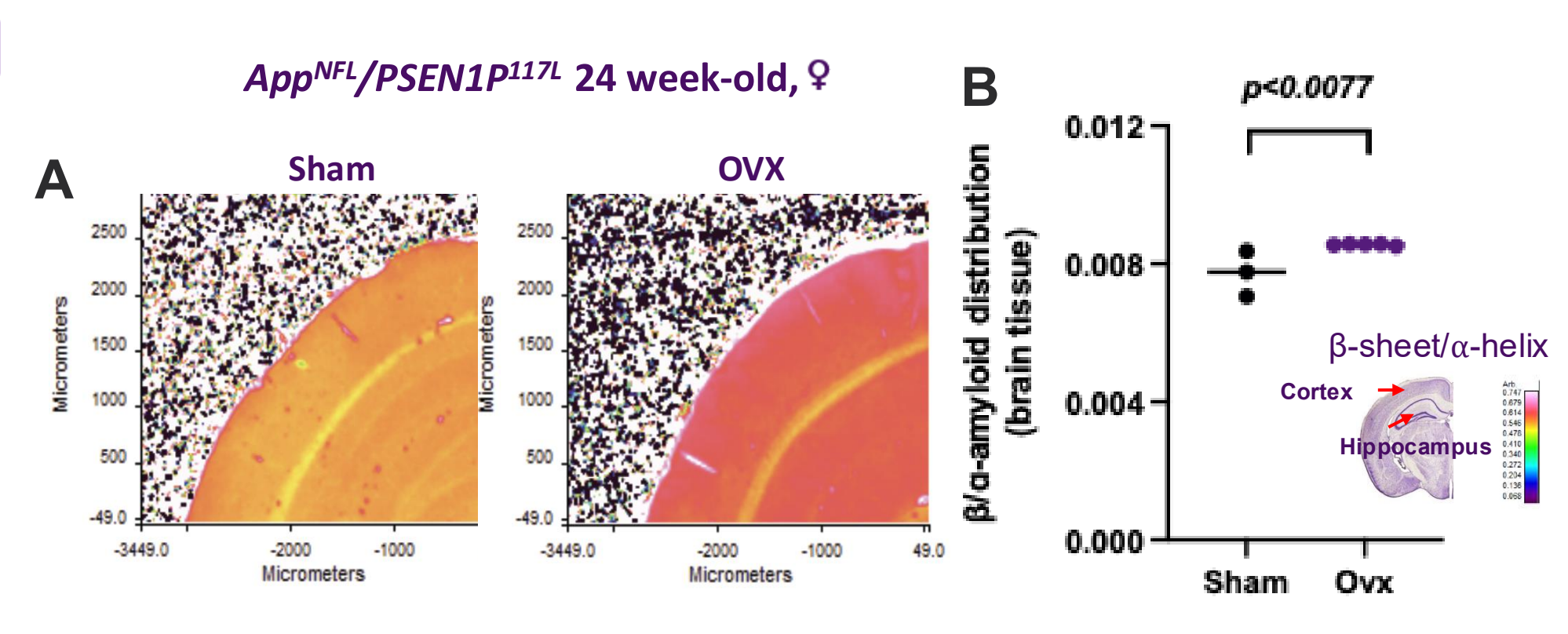
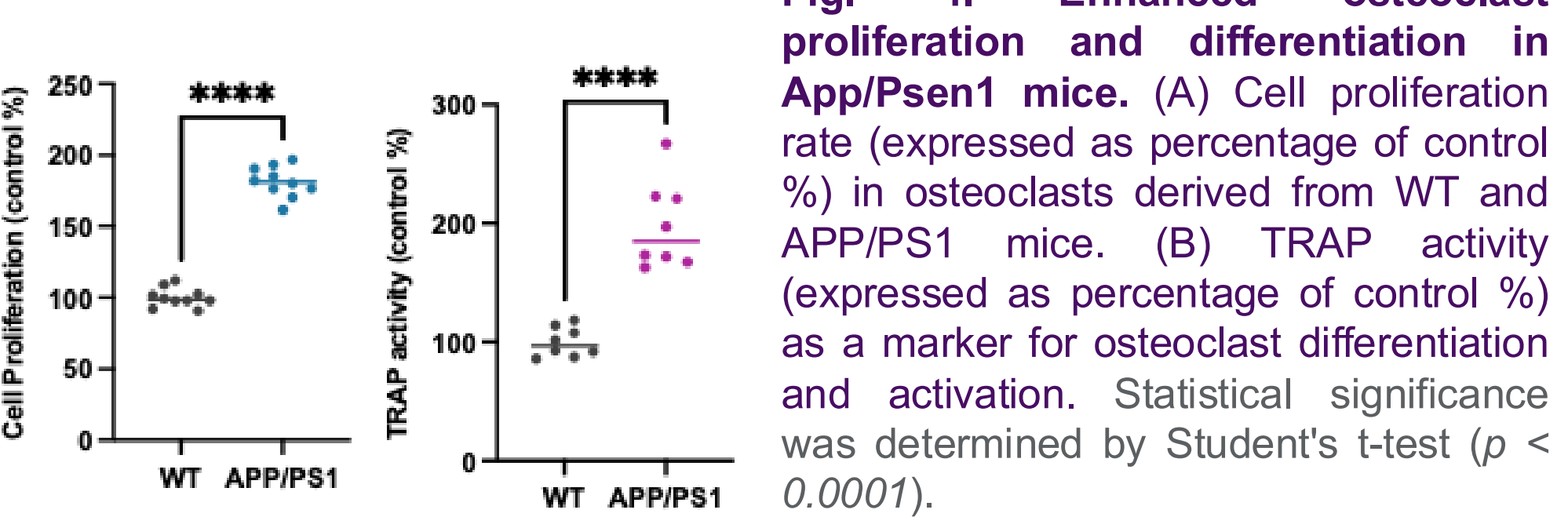


Fig. 3. FTIR imaing analysis of β-sheet structure alterations in the brain of Sham and Ovariectomized App/Psen1 mice. (A) Representative images of brain tissue section mapping (left and right panels) analyzed using FTIR imaging. (B) Quantitative analysis of β-sheet structure distribution across the experimental groups. Data are expressed as Mean ± SEM. Statistical differences were analyzed using Student's t-test.



Pyk2 inhibition enhances Aβ clearance & microglia–Aβ contact

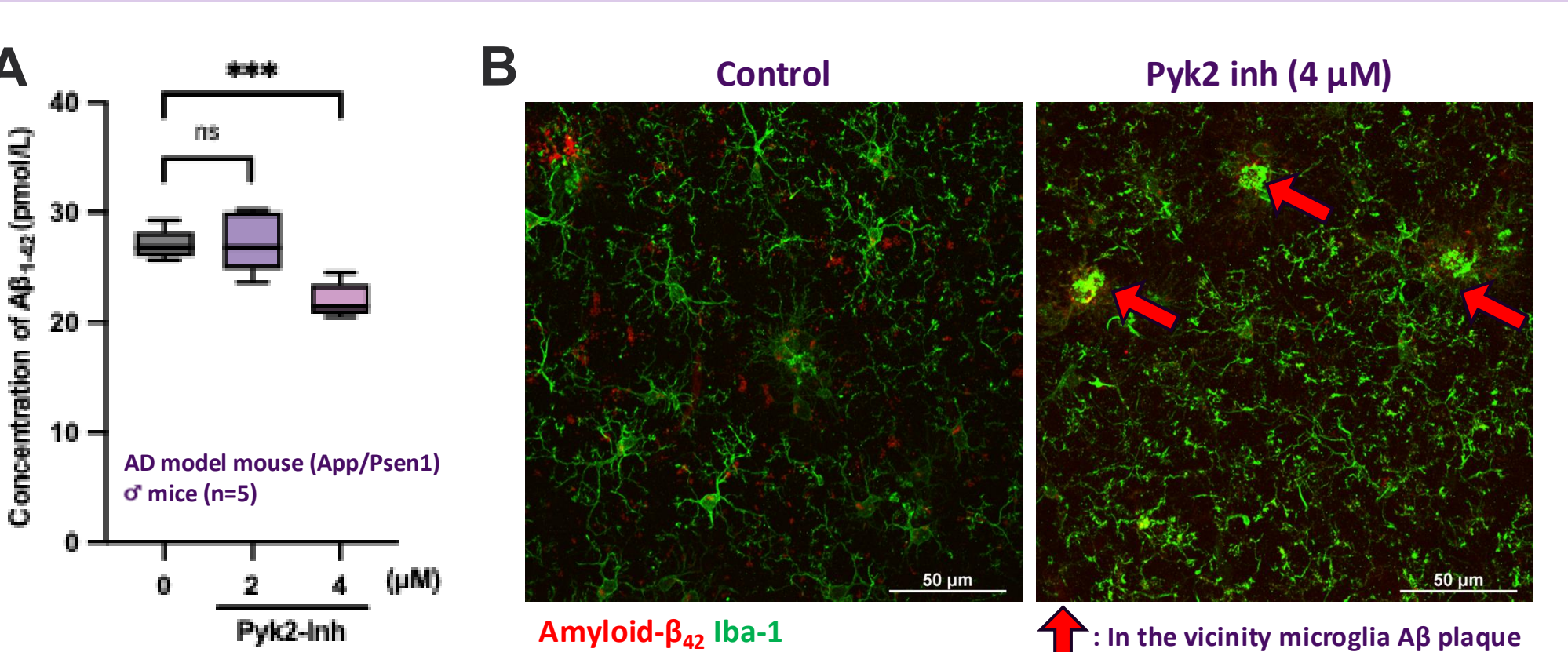


Figure 3. Impact of Pyk2 inhibitor (PF-431396) on Aβ Pathology and Microglial Recruitment. Inhibition of Pyk2 reduces systemic Amyloid-β42 levels in serum and modulates microglial phagocytosis in App/Psen1 mice. scale bar 50 μm. CON vs Pyk2 inh (4 μM). Aβ⁺ area 1.0% → 0.62%; Iba1/Aβ overlap 0.24% → 0.37%. (representative images)