

First FOXO1 PET imaging of brain senescence: A translational biomarker for therapeutic studies against AD and ADRD

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Introduction: Aging brain cells can enter cellular senescence, promoting chronic inflammation and neurodegeneration. Large-scale transcriptomic analyses, including the SenMayo gene set, identify FOXO1 as a conserved gene upregulated in senescent cells across multiple tissues and species, establishing its relevance to senescence (Fig. 1). Although senolytic therapies are being evaluated in Alzheimer's disease (AD) and other AD related dementias (ADRD), there is currently no noninvasive method to quantify senescence burden or monitor treatment efficacy in the living brain. Here, we tested whether FOXO1 PET imaging can quantify senescence-associated molecular activity in physiological aging, senescence-accelerated, and AD models.

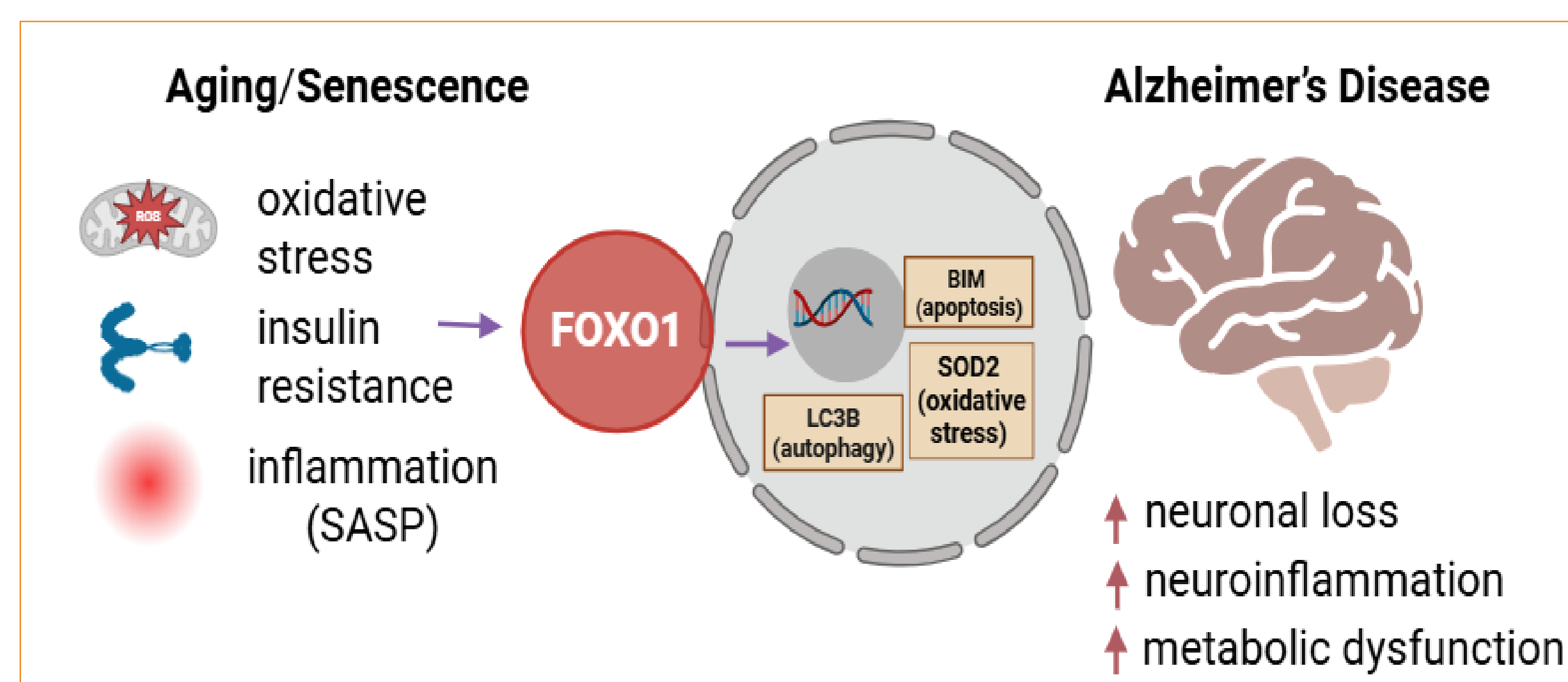


Fig.1 FOXO1: senescence driven pathway in AD

Methods: Using our [¹⁸F]FOXO1 targeted probe, uptake was measured in HeLa cells under baseline, FOXO1 knockdown (siRNA), and FOXO1 overexpression (plasmid) conditions. PET imaging was performed in male (a) young (2-4 mo) and aged (18-22 mo) C57BL/6 mice (n=8/group); (b) senescence-accelerated mice (SAMR1 vs SAMP8 at 3 and 12 mo); and (c) 5xFAD mice (n=8/group, 8-10 mo). Regional standardized uptake values were quantified in cortex, hippocampus, and whole brain. Autoradiography, and western blot assays were used for molecular validation.

Results:

1. In vitro assays

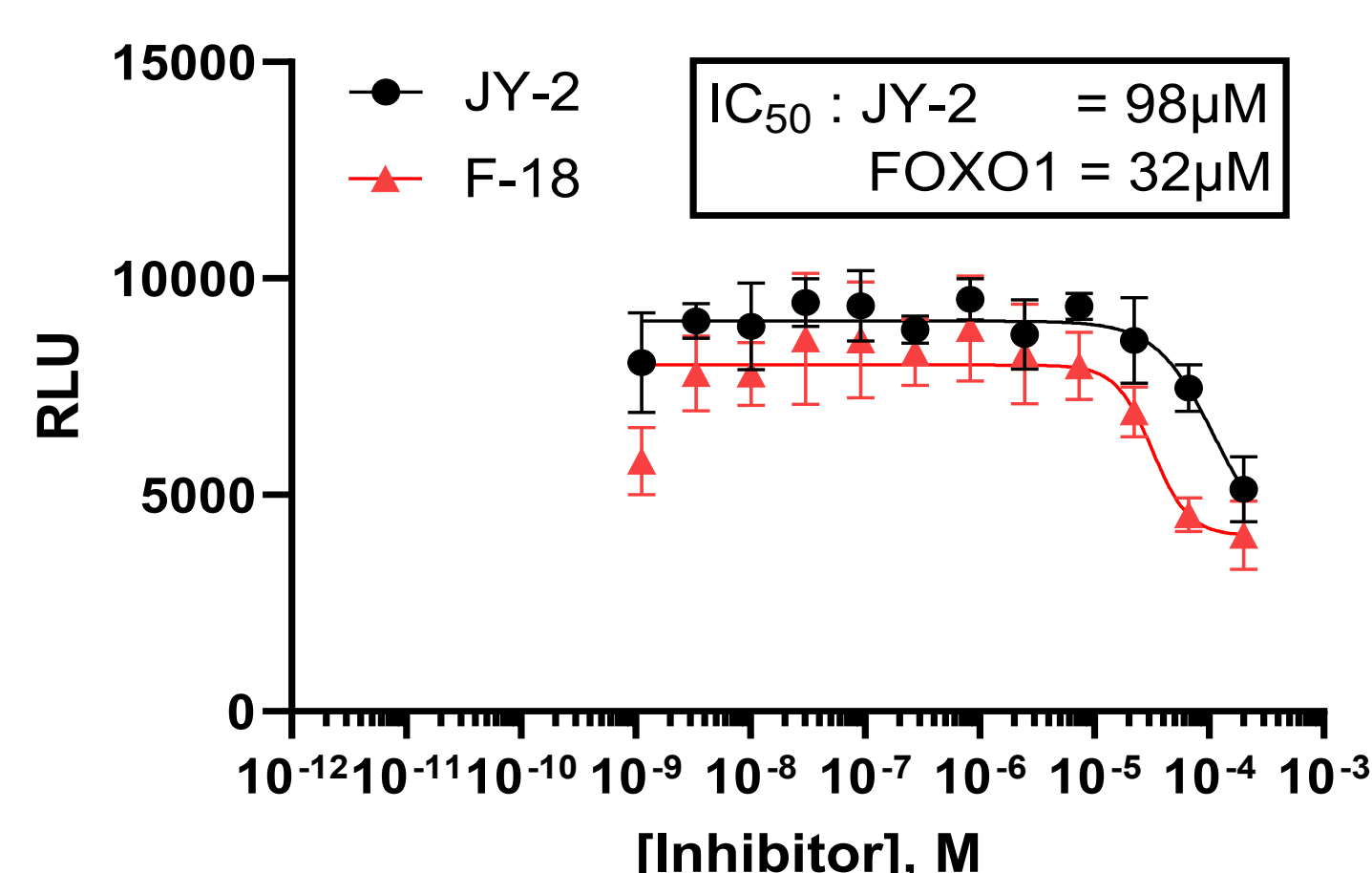


Fig.2 : U2OS FOXO Nuclear Translocation assay showing FOXO1 inhibition activity in cells treated with JY2 and FOXO1 ligand.

2. PET imaging validation

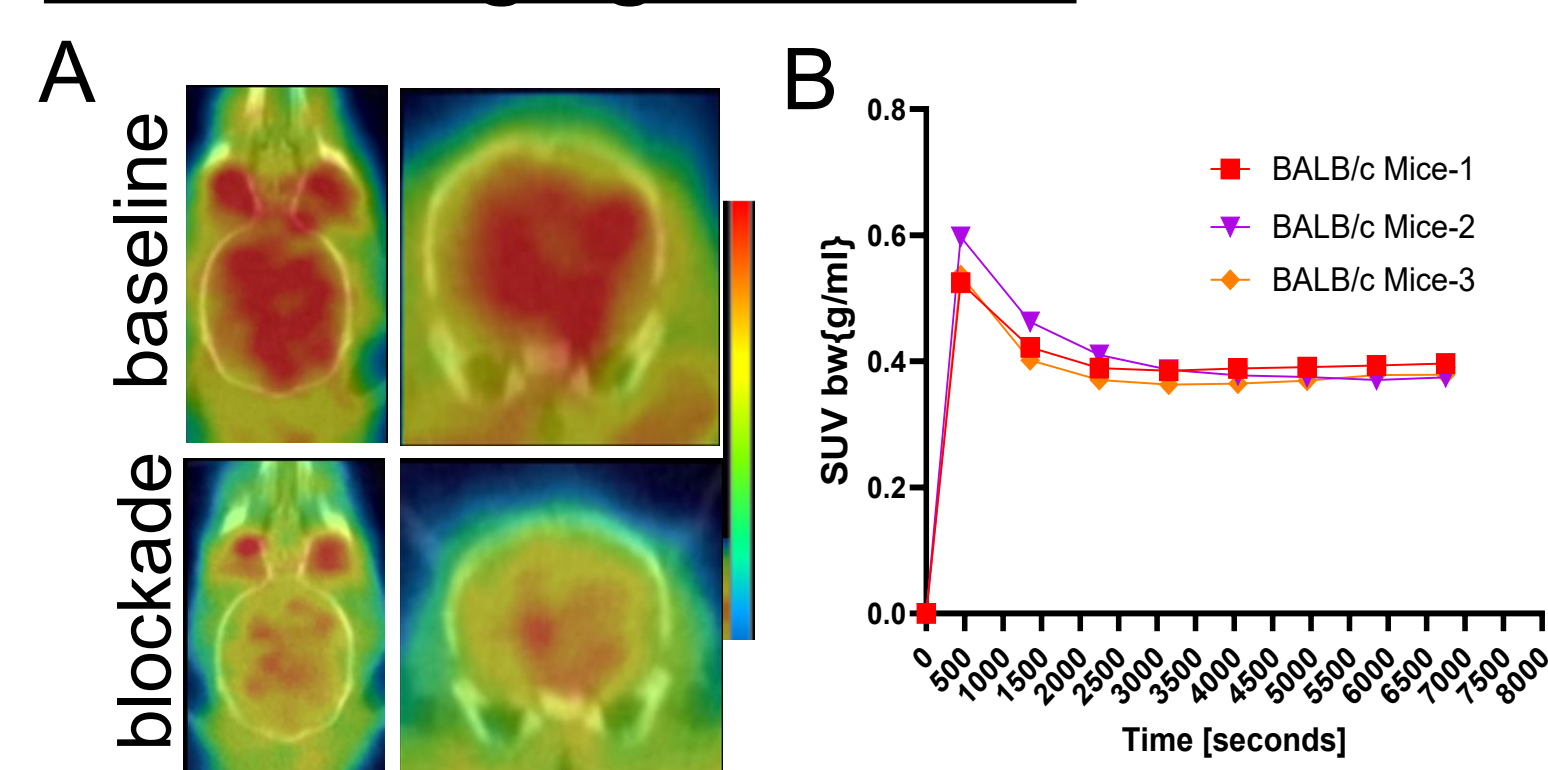
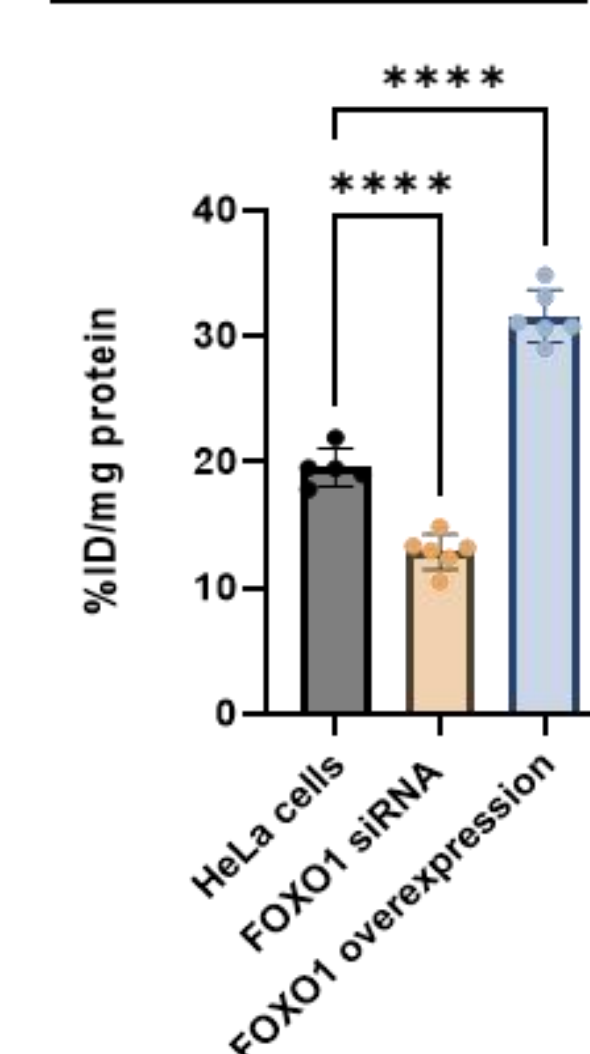


Fig.3 : (A) Representative axial and coronal mPET/CT images of [¹⁸F]FOXO1 in BALB/c mice with their post-JY2 blocked (B) time activity curves (n=3)

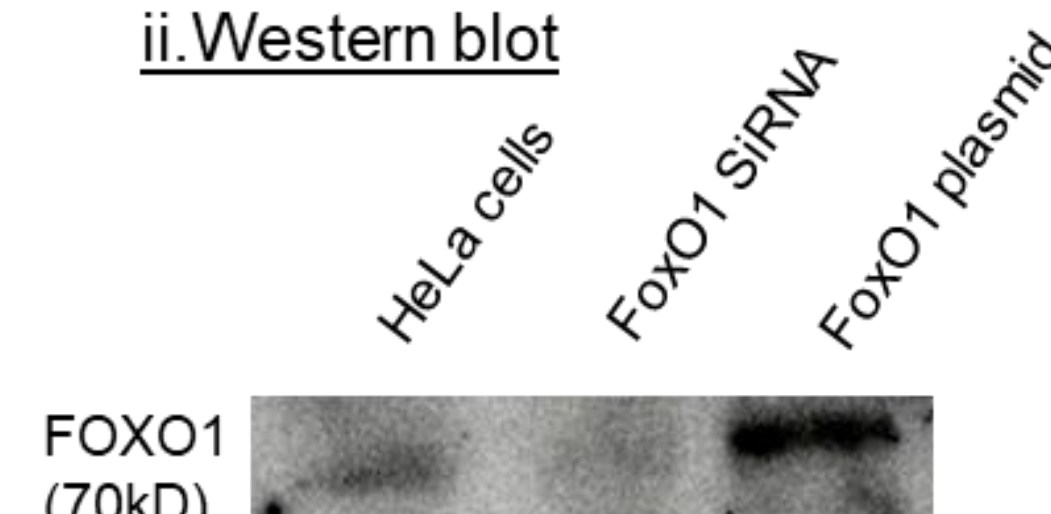
3. [¹⁸F]FOXO1 preclinical evaluation

A. Cell uptake

i. Gamma counting

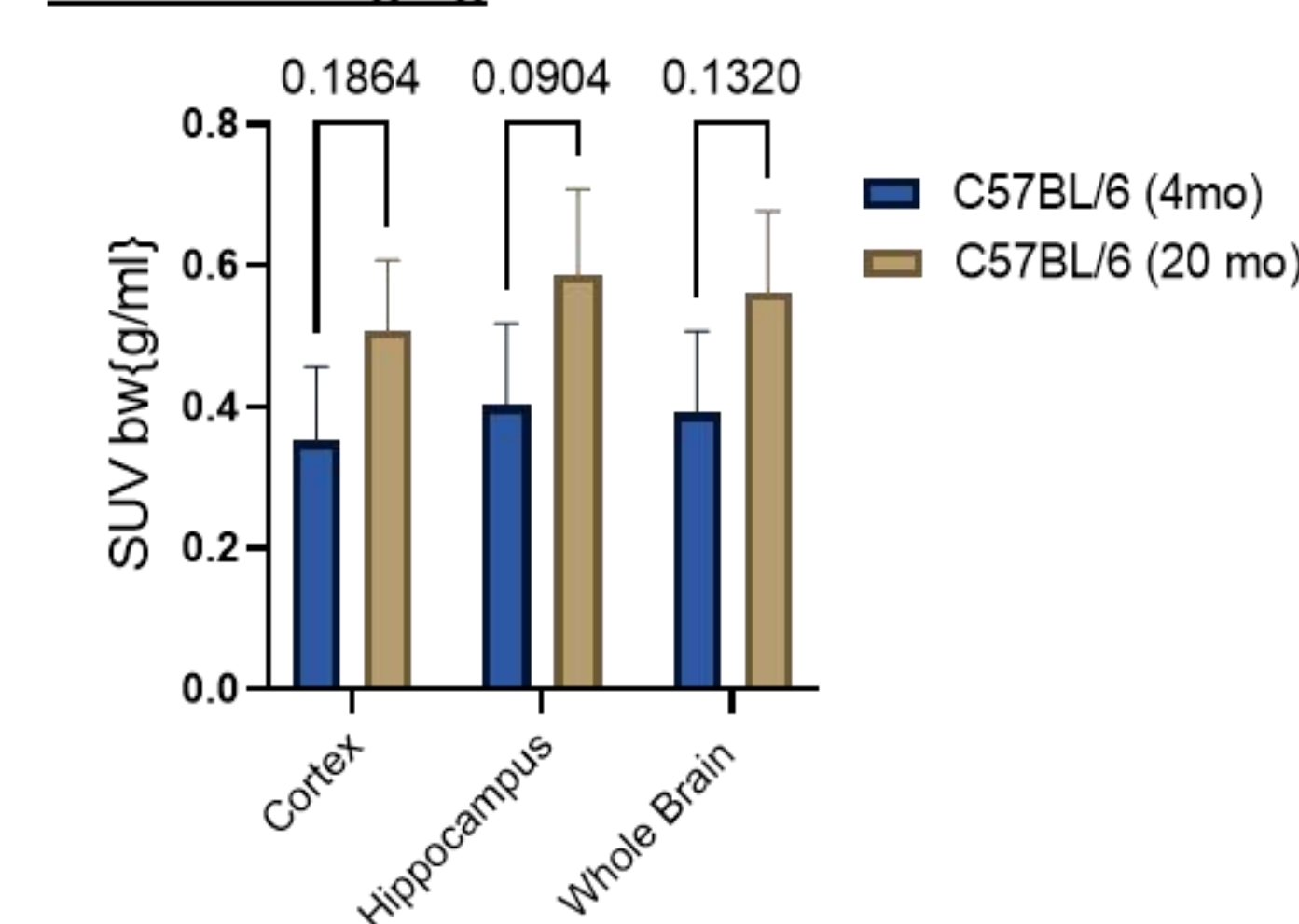


ii. Western blot

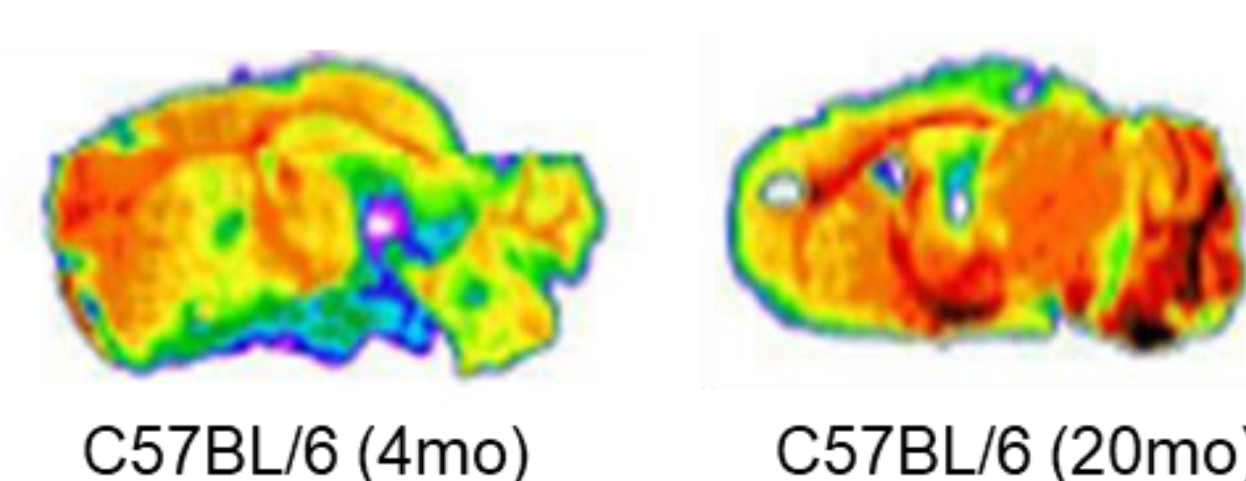


B. Young (2–4 mo) vs aged (18–22 mo) C57BL/6 mice

i. mPET imaging

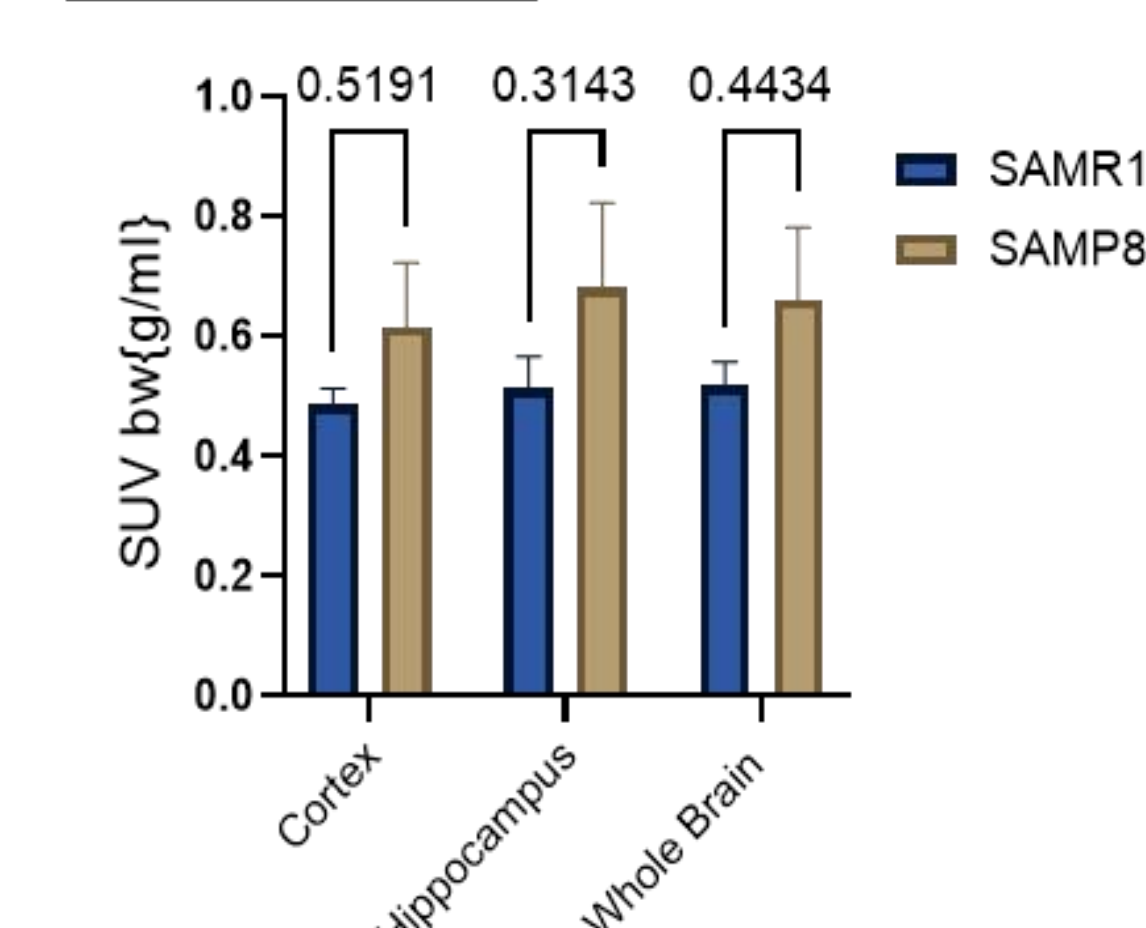


ii. In vitro autoradiography

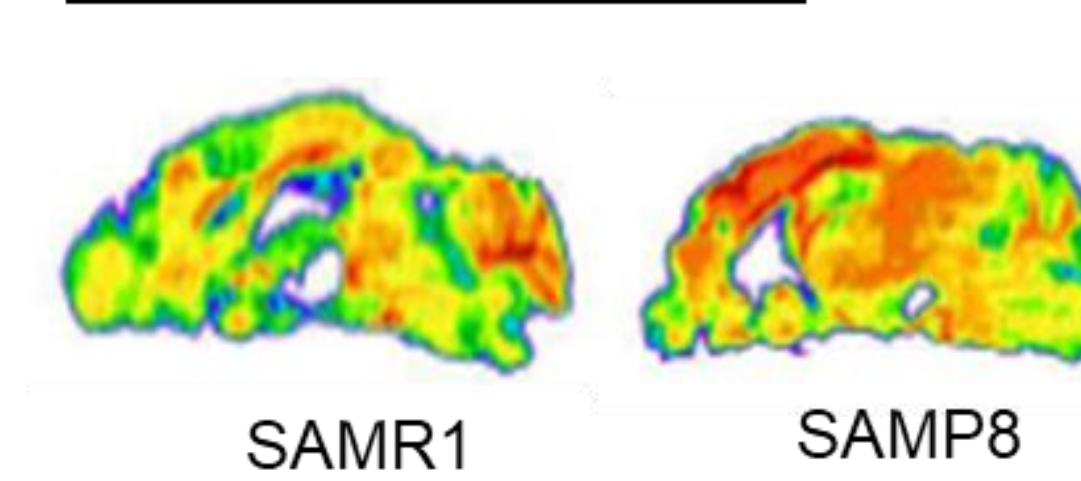


C. senescence accelerated mice (SAMR1 vs SAMP8)

i. mPET imaging

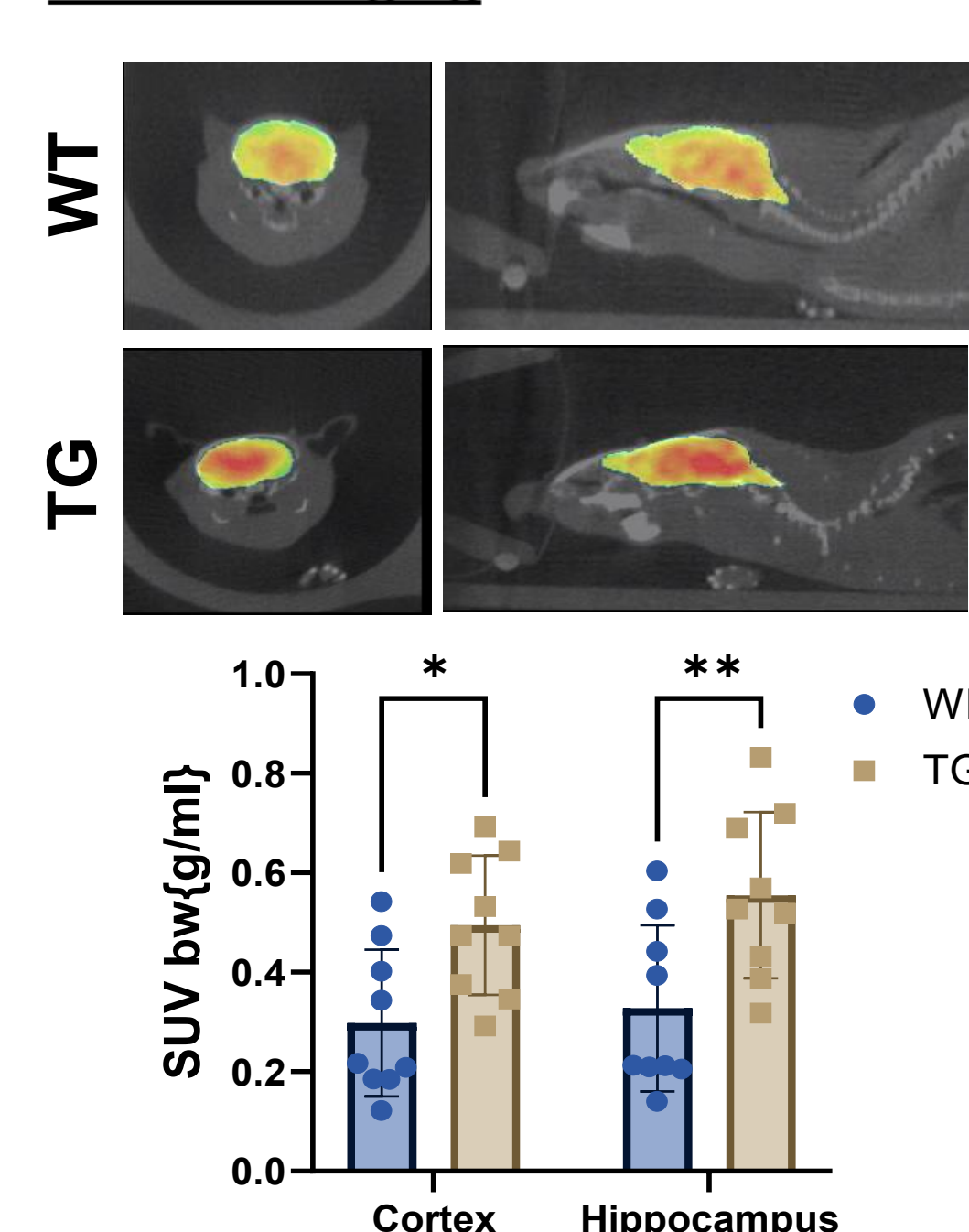


ii. In vitro autoradiography



D. AD mouse model (5xFAD vs wild)

i. mPET imaging



Conclusions:

- ✓ Developed the first brain-penetrant PET tracer targeting FOXO1
- ✓ Demonstrated high radiochemical yield, specificity, and *in vivo* target engagement
- ✓ High FOXO1 PET signal in 5xFAD AD mouse brains
- ✓ Next steps: correlate PET signal with senescence markers, and advance pharmacokinetic & metabolic studies

References: Solingapuram et al, p. Abstract 462, WMIS 2025; Liu L, et al., Oxid Med Cell Longev. 2022; Saul D et al; Nature Communications, 16;13(1):4827 (2022).

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