



DONG-A ST

A Novel GPX4 Positive Allosteric Modulator Ameliorates Cognitive Impairment by Inhibiting Ferroptosis and Neuroinflammation

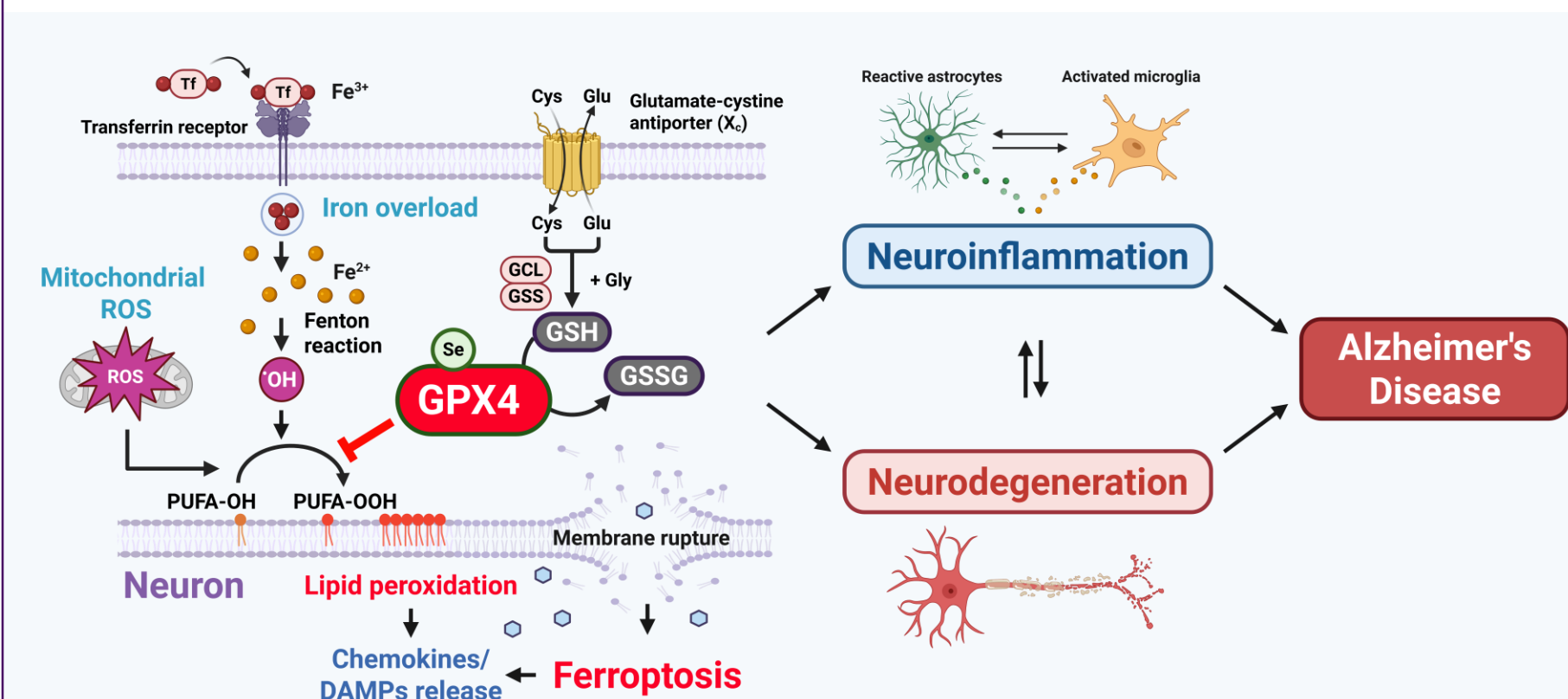
Seo-Yun Yang, Jihyun Park, Jeongmi Lee, Byunghyun Park, Yonghyun Joo, JaeWook Yoo, Sangbin Jeon, Yoonjung Kim, HyeonSeok Jung, JiHoon Choi, SeungHyun Song, Jieun Lee, HyunSoo Ha, Daewon Cha, Sunho Choi, Jungwoo Kim, HanEol Kim, Eunjin Kim, DaeYoung Lee, Mi-Kyung Kim. Dong-A ST, Yongin-si, Republic of Korea

[Poster #13101] Request for Presentation Materials: GPX4 positive allosteric modulator

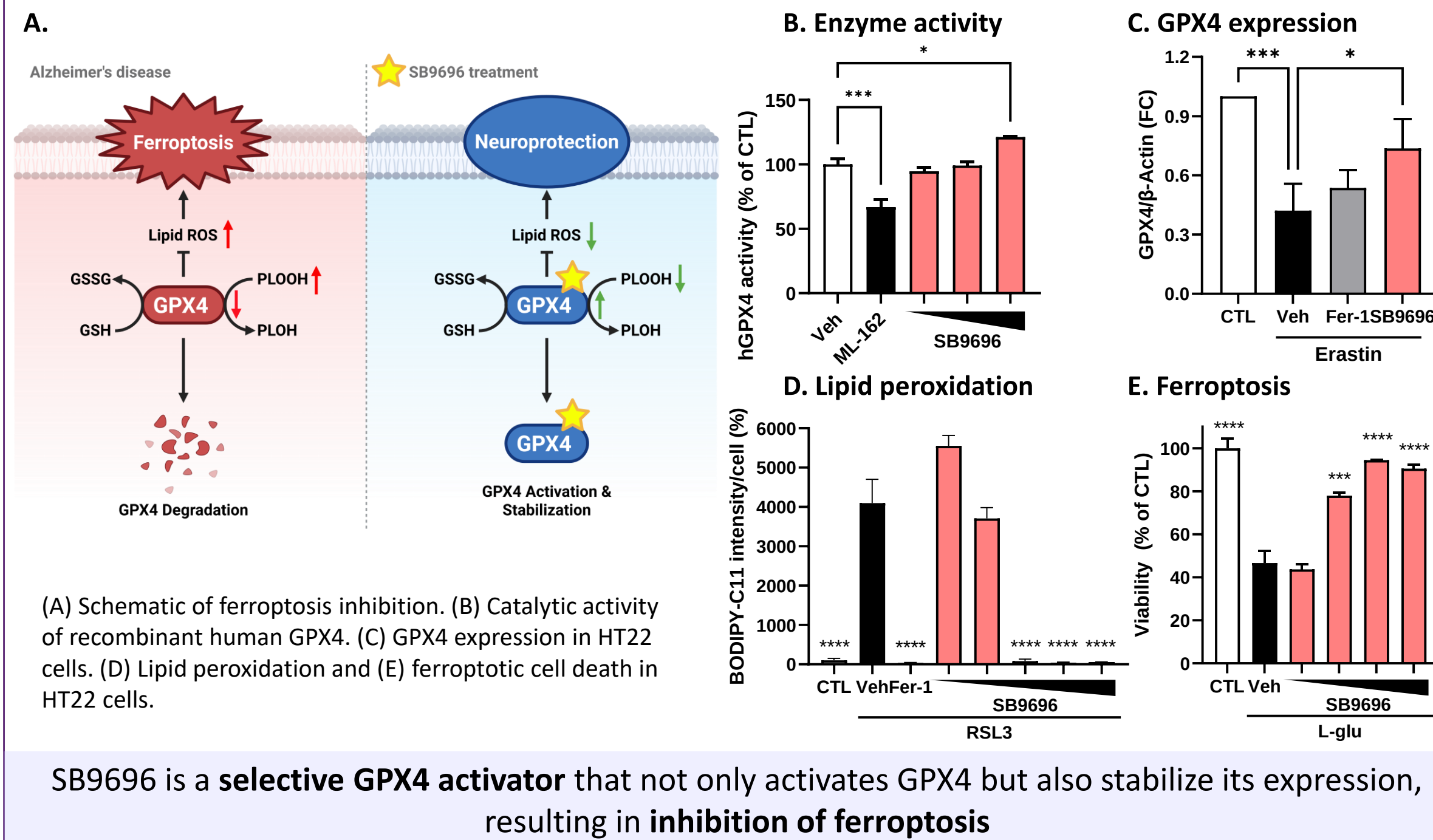


Introduction

Ferroptosis is an iron-dependent form of regulated cell death driven by lipid peroxidation, which plays a pivotal role in neurodegeneration and neuroinflammation. Glutathione peroxidase 4 (GPX4), a key antioxidant enzyme that directly reduces toxic lipid peroxides, is a master regulator of ferroptosis. Dysregulation of GPX4 drives the progression of neurodegenerative diseases such as Alzheimer's disease (AD). In this study, we investigated the therapeutic potential of SB9696—a novel, first-in-class small molecule GPX4 positive allosteric modulator—as a disease-modifying therapy for AD.

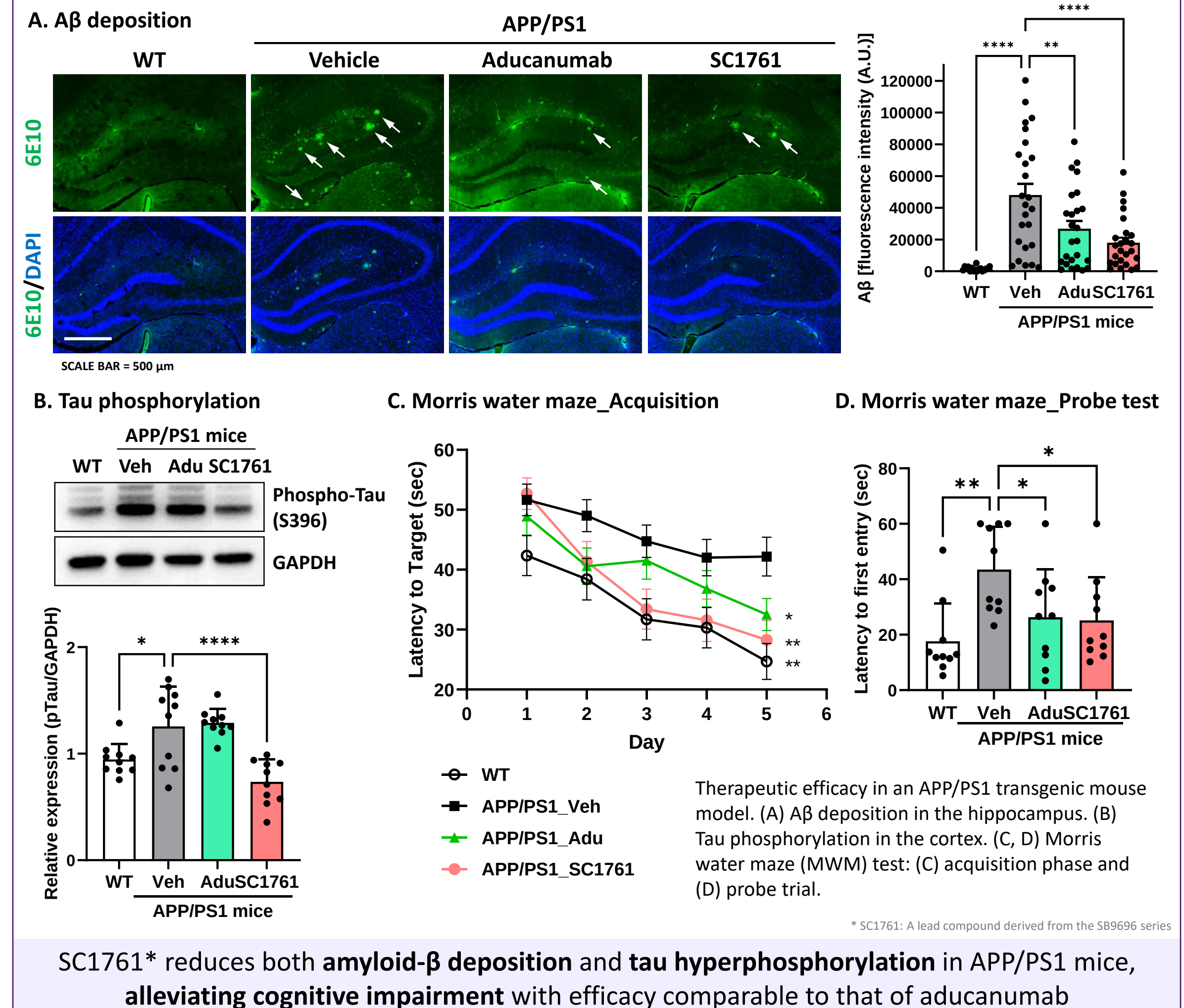


Potent & Selective Ferroptosis Inhibition in Neuronal Cells



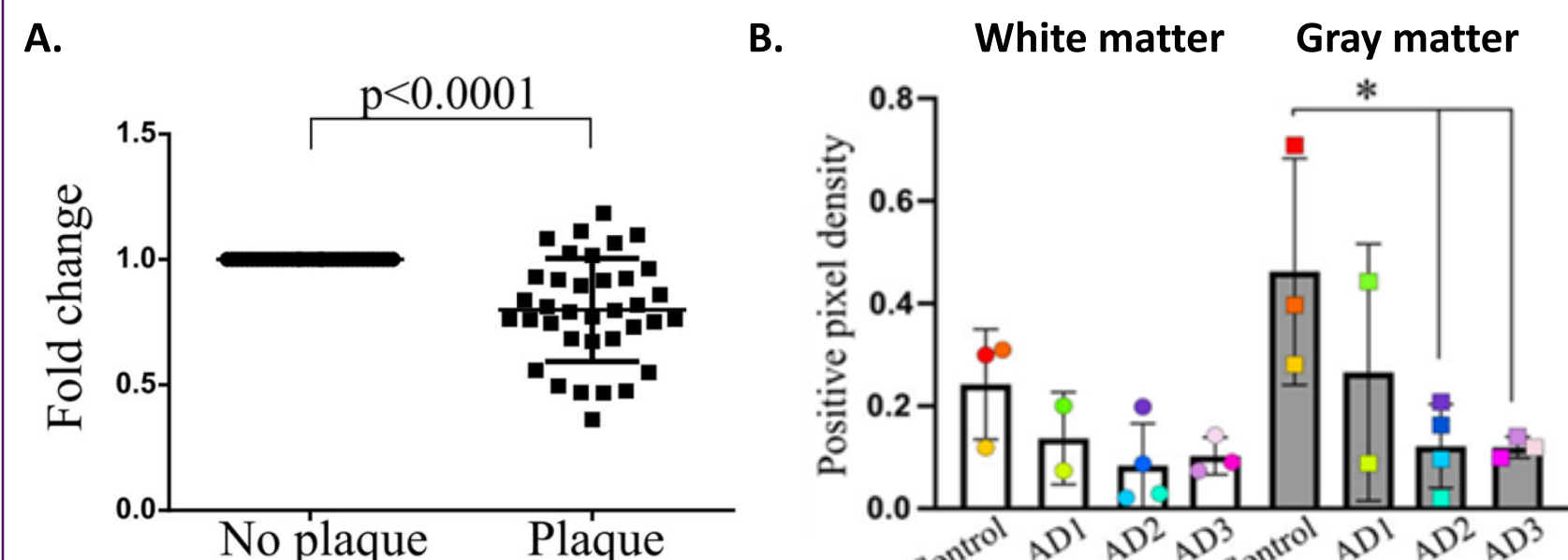
Robust Pathological & Behavioural Improvement

In vivo AD Model (APP/PS1 TG mice)



GPX4 as a Therapeutic Target for AD

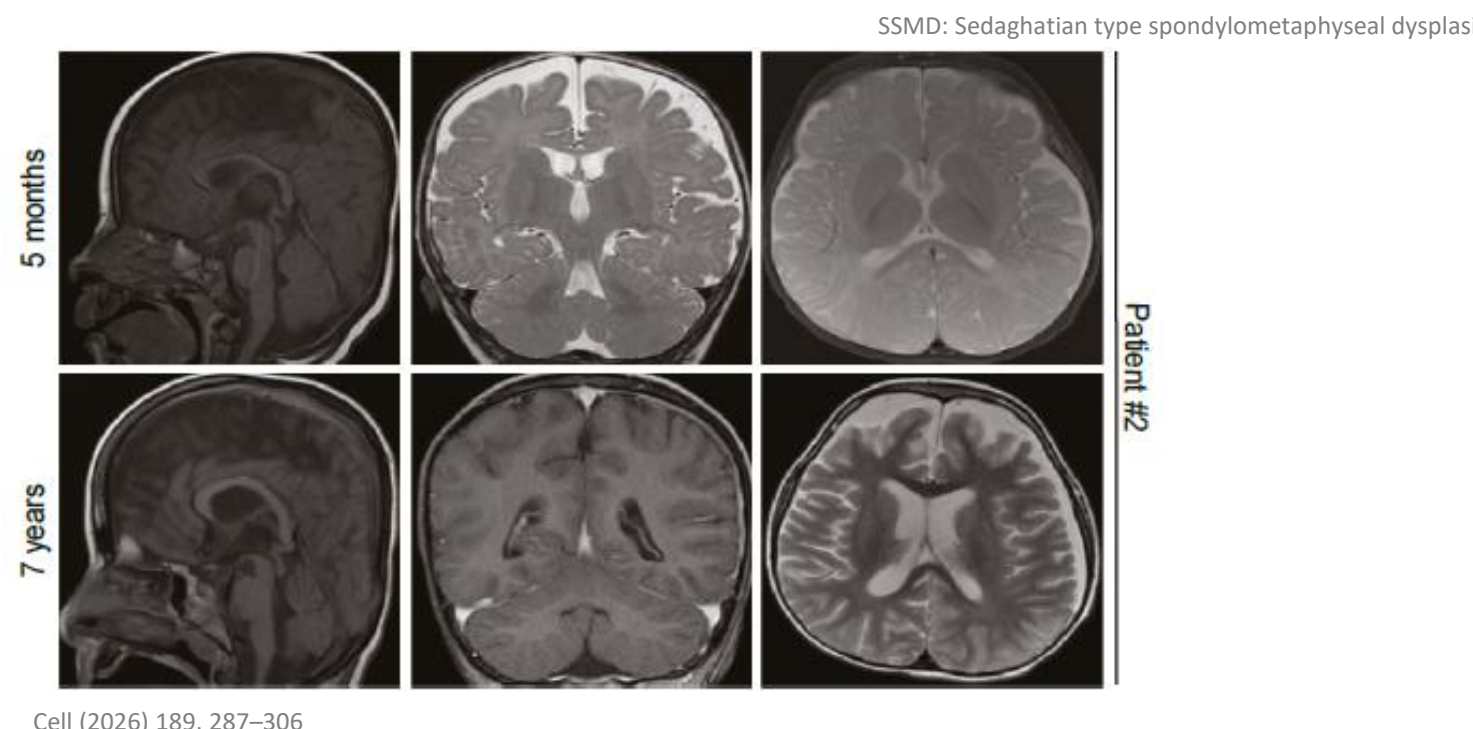
GPX4 expression in AD patients



GPX4 expression in the brains of AD patients. (A) Overall expression levels in the Aβ plaque area. (B) Expression in white versus gray matter, stratified by the severity of AD pathology.

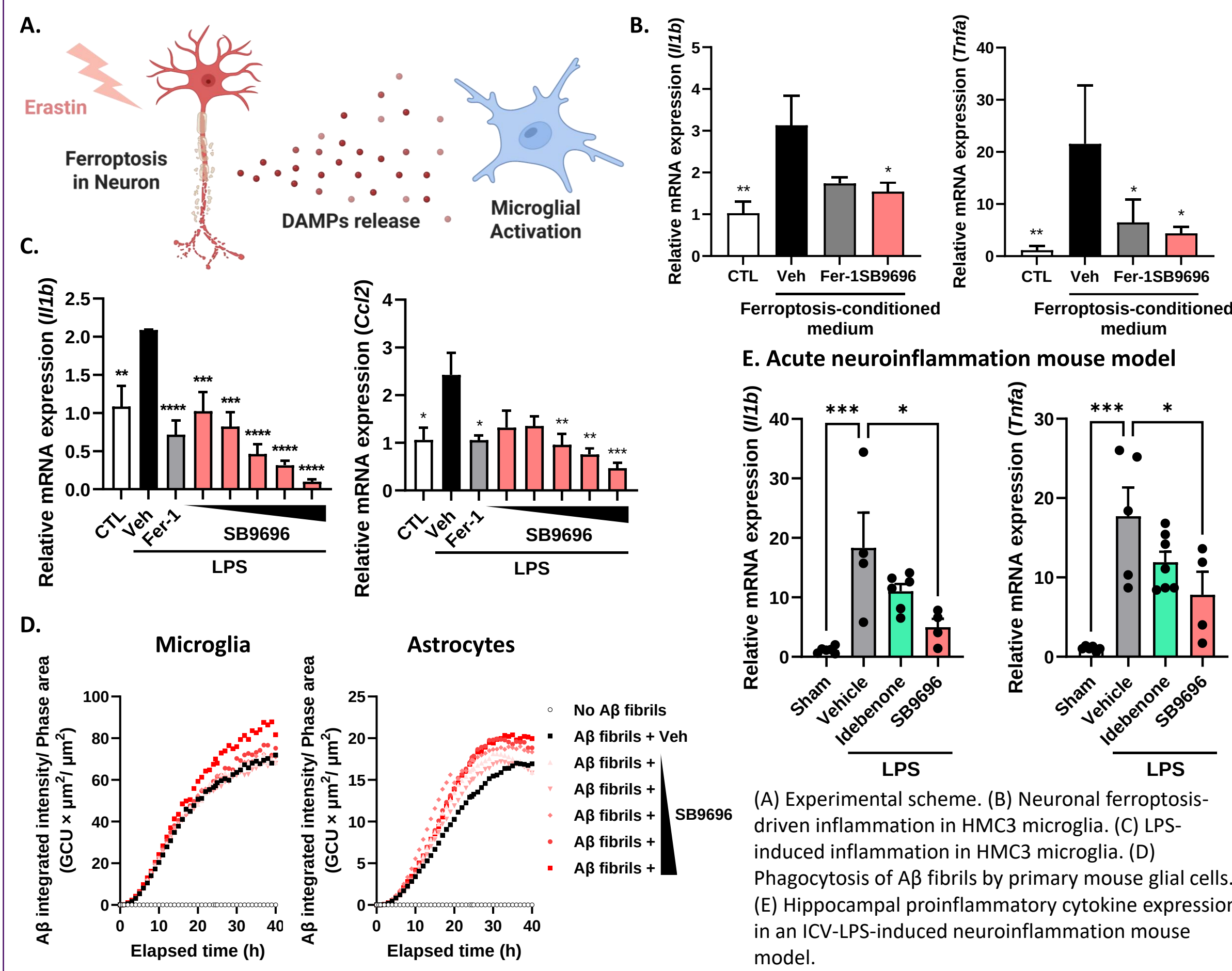
GPX4 level is lower in the Aβ plaque area and negatively correlates with the severity of AD pathology, especially within the gray matter

GPX4 mutation in SSMD patients



The patient-associated GPX4 R152H mutation reveals Alzheimer's-like pathology, positioning ferroptosis as a key driver for AD

Significant Inhibition of Neuroinflammation in Microglial Cells



SB9696 effectively blocks microglial activation and enhances glial phagocytosis, thereby suppressing neuroinflammation in the hippocampus

Conclusion

01. Orally bioavailable, BBB-penetrant small molecule
02. Potent and selective ferroptosis inhibition
03. Dual inhibition of neurodegeneration and neuroinflammation

- **Multifaceted Efficacy:** Mitigates cognitive decline by blocking neuronal ferroptosis, suppressing neuroinflammation, and enhancing glial clearance of Aβ
- **Next-Generation Strategy:** Offers a promising therapeutic breakthrough for AD beyond current amyloid-targeted therapies
- **Future Milestones:** Currently in late lead optimization, targeting preclinical candidate nomination in Q4 2026

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