

Type 2 Innate Lymphoid Cells Confer Neuroprotection Against Alzheimer's Disease Pathology

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Background

Type 2 innate lymphoid cells (ILC2s) are tissue-resident immune cells that play essential roles in type 2 immune responses by secreting cytokines such as interleukin (IL)-5 and IL-13. In the central nervous system (CNS), ILC2s localize to the meninges and choroid plexus (CP). Alzheimer's disease (AD) is characterized by progressive cognitive decline, extracellular amyloid- β (A β) plaque accumulation, hyperphosphorylated tau tangles, and sustained neuroinflammation. Given their immunoregulatory roles, we examined the role of ILC2s in an AD mouse model and in an A β - and tau-induced neuronal toxicity using differentiated SH-SY5Y cells.

Methods

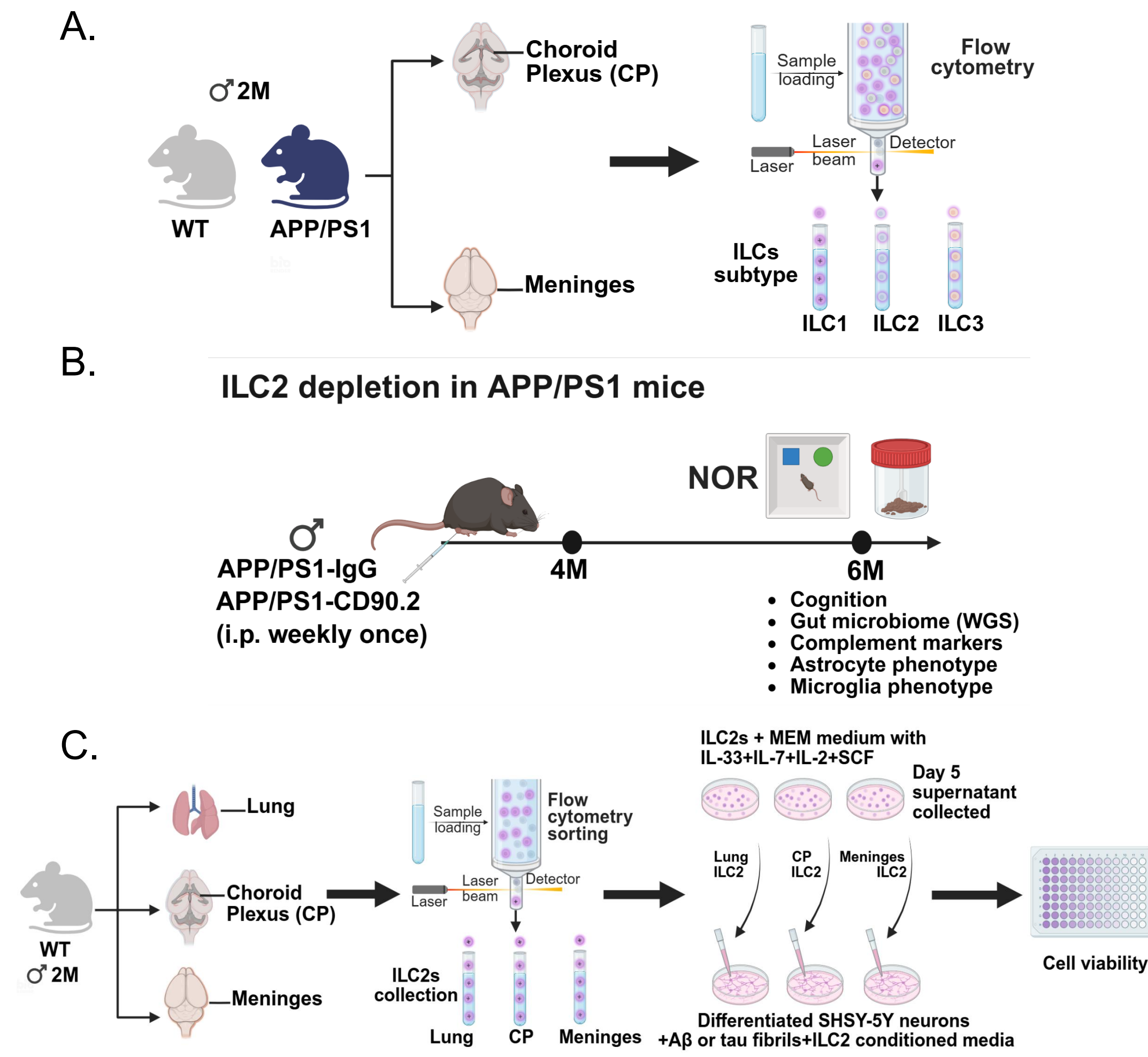
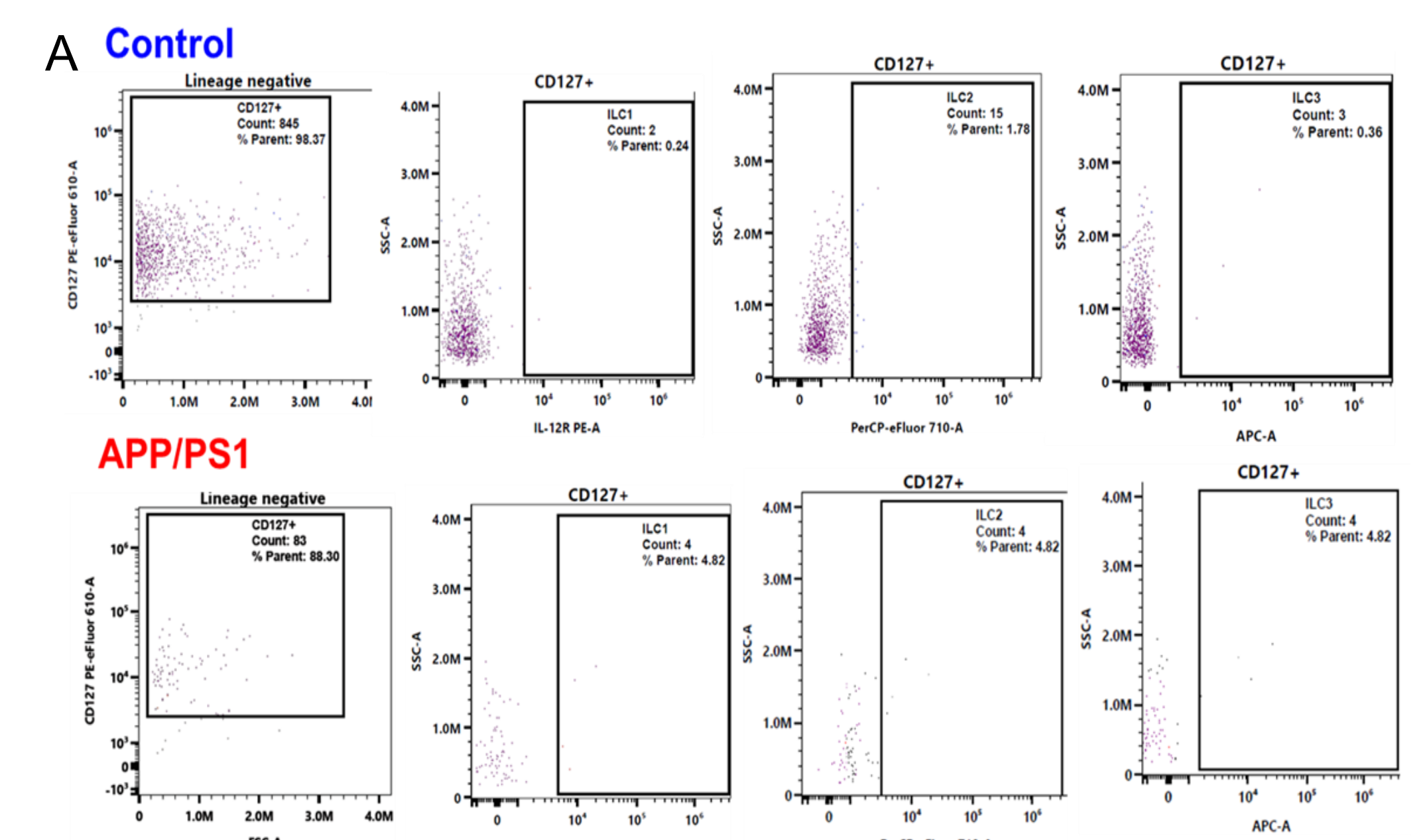


Figure 1. (A) Study design for in vivo ILC2 sorting, (B) ILC2 depletion and (C) in vitro neuroprotection assays.

Results



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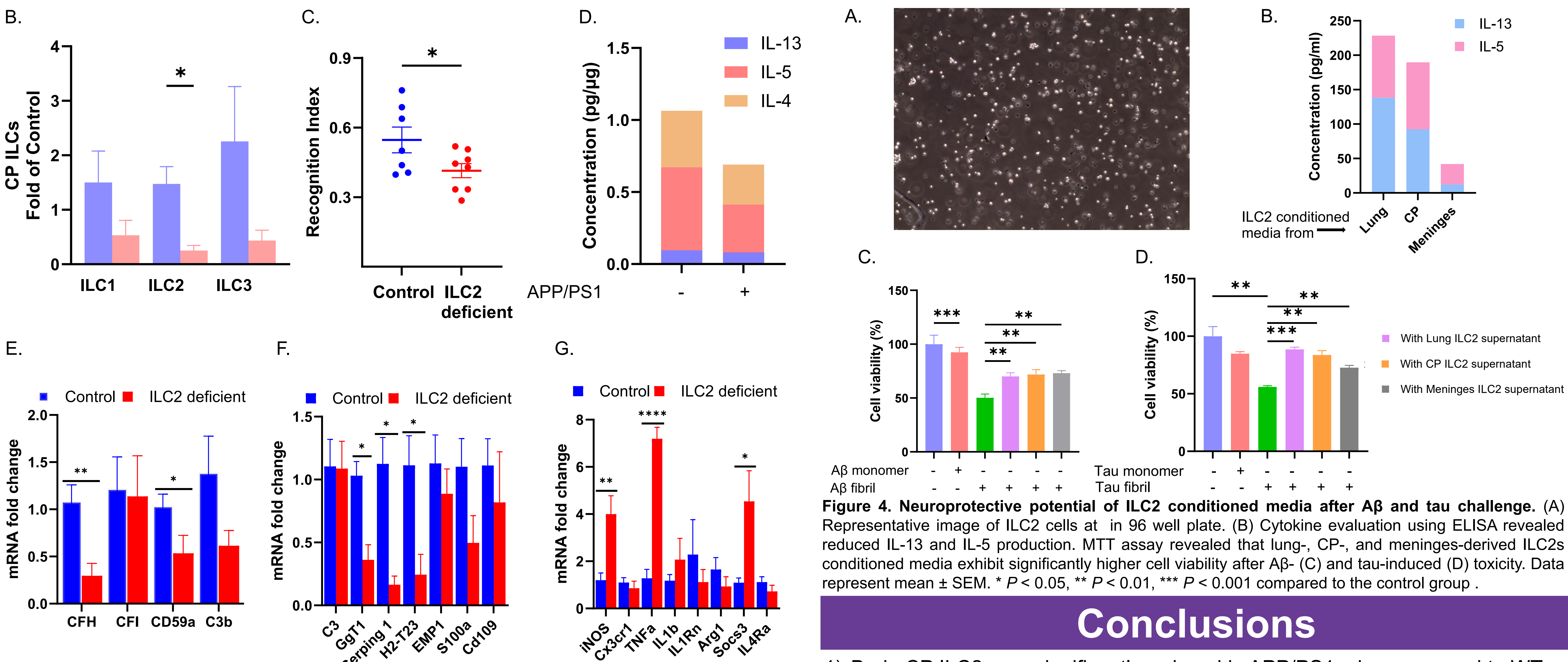


Figure 2. Flow cytometry, behavior, cytokine and regulatory marker analyses in WT and APP/PS1 mice. (A) Gating strategy showing lineage⁻CD127⁺ cells, and identification of ILC1s (IL-12R⁺), ILC2s (GATA-3⁺) and ILC3s (ROR γ ⁺). (B) Quantification shows significantly reduced ILC2 in CP of APP/PS1 mice. (C) Novel object recognition test demonstrates impairment in cognition after ILC2 deficiency in APP/PS1 mice. (D) Reduced IL-5 and IL-4 production after ILC2 deficiency in APP/PS1 brain cortex. Bar graphs show mRNA expression of complement regulators (E), pro-inflammatory and anti-inflammatory mediators in astrocytes (F) and microglia (G). Data represent mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$ compared to the control group.

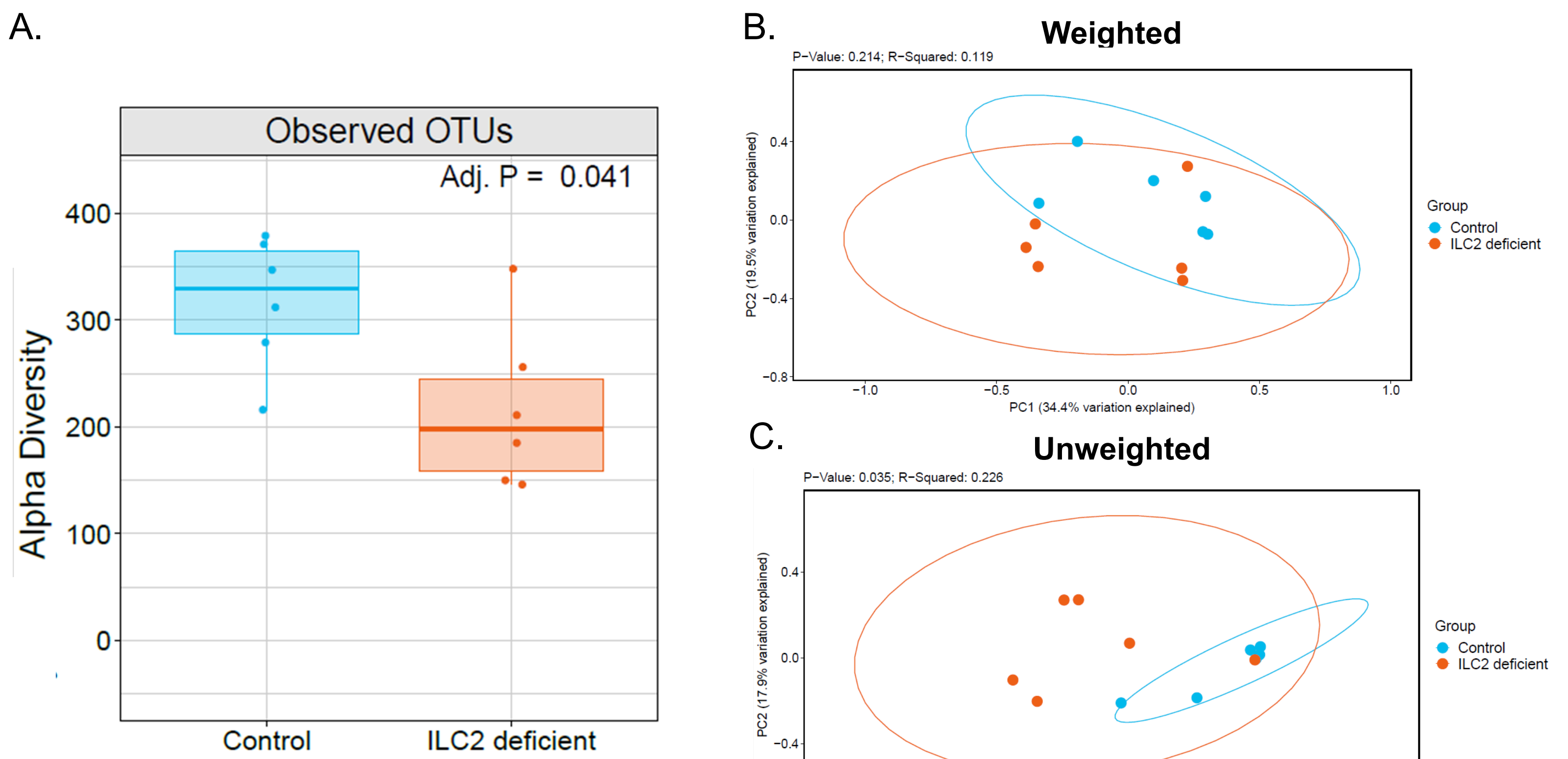


Figure 4. Neuroprotective potential of ILC2 conditioned media after A β and tau challenge. (A) Representative image of ILC2 cells at 96 well plate. (B) Cytokine evaluation using ELISA revealed reduced IL-13 and IL-5 production. MTT assay revealed that lung-, CP-, and meninges-derived ILC2s conditioned media exhibit significantly higher cell viability after A β - (C) and tau-induced (D) toxicity. Data represent mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared to the control group.

Conclusions

- 1) Brain CP ILC2s are significantly reduced in APP/PS1 mice compared to WT.
- 2) ILC2 depletion in APP/PS1 mice impaired memory performance, in the novel object recognition task, & reduced cortical levels of IL-4, IL-5, and IL-13.
- 3) ILC2 loss disrupts immune homeostasis, reducing complement regulators and increasing pro-inflammatory genes.
- 4) WGS sequencing reveled significant microbial diversity in ILC2 deficient mice compared with WT.
- 5) Lung- and CP-derived ILC2s expand in culture and produce higher cytokine levels.
- 6) Conditioned media from activated ILC2s increased SH-SY5Y neuron viability under A β & tau challenge.
- 7) These findings provide insights into exploring ILC2s as a potential therapeutic targets for modulating neuroinflammation and promoting CNS repair in AD.

Future Scope

- 1) In vivo studies to validate the therapeutic potential of ILC2s in an AD mouse model.
- 2) Define the brain-gut-lung axis regulating neuroprotection and evaluate ILC2-associated pathways as potential therapeutic targets in AD.

Acknowledgment