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Cell-type specific effects of murine Lecanemab in a knock-in mouse model of Alzheimer's disease

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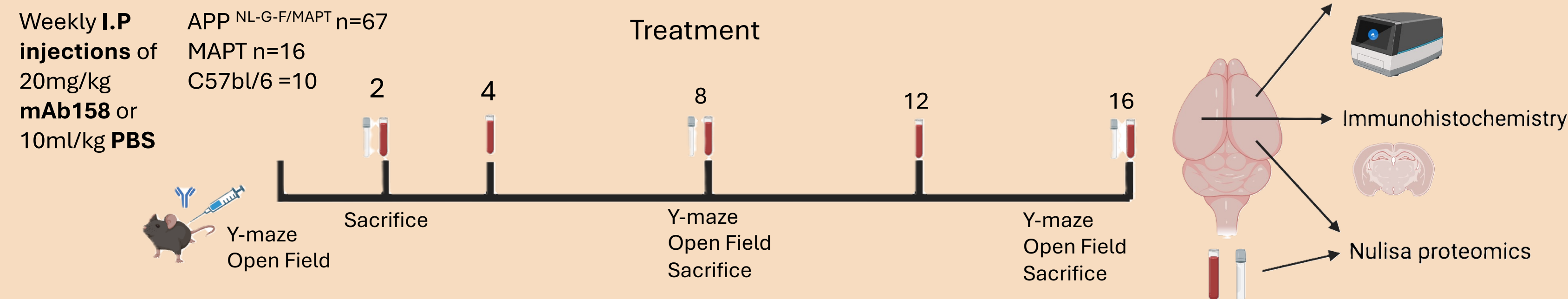


Introduction

Immunotherapy against amyloid- β for Alzheimer's disease (AD) has been successful and is now in clinical use in several countries. However, the cell-type specific changes induced by these antibodies and how these changes evolve over time has yet to be elucidated. An increased understanding of the biological effects of these treatments can both support new tools for treatment monitoring, and aid in the development of new and improved immunotherapies for AD in the future.

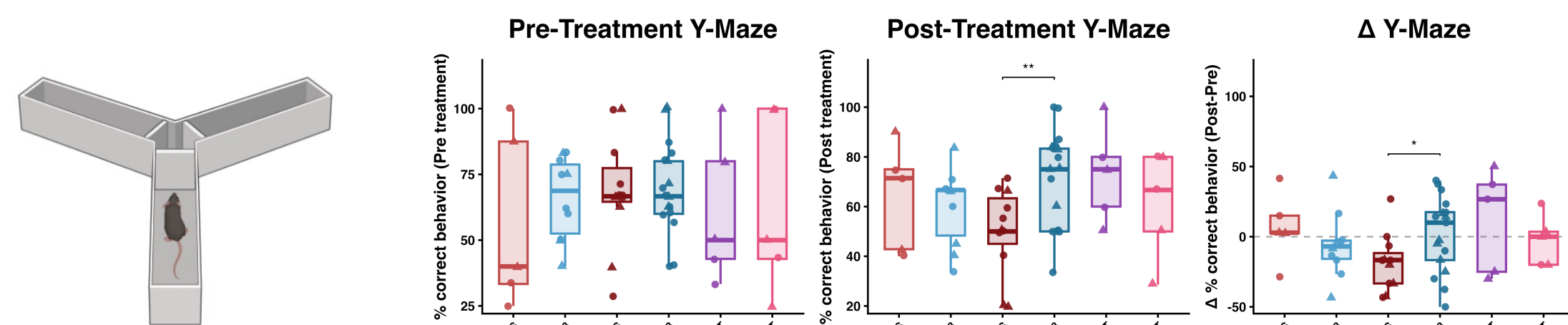
Experimental design

Here, we have treated APP^{NL-G-F/MAPT} knock in mice with the murine version of Lecanemab (mAb158) or PBS control for 2, 8 and 16 weeks. Immunohistochemistry and single-nuclei sequencing are used to analyse pathological and cell-type specific changes. NULISA-proteomics was performed on brain, CSF and plasma and is currently being analysed.

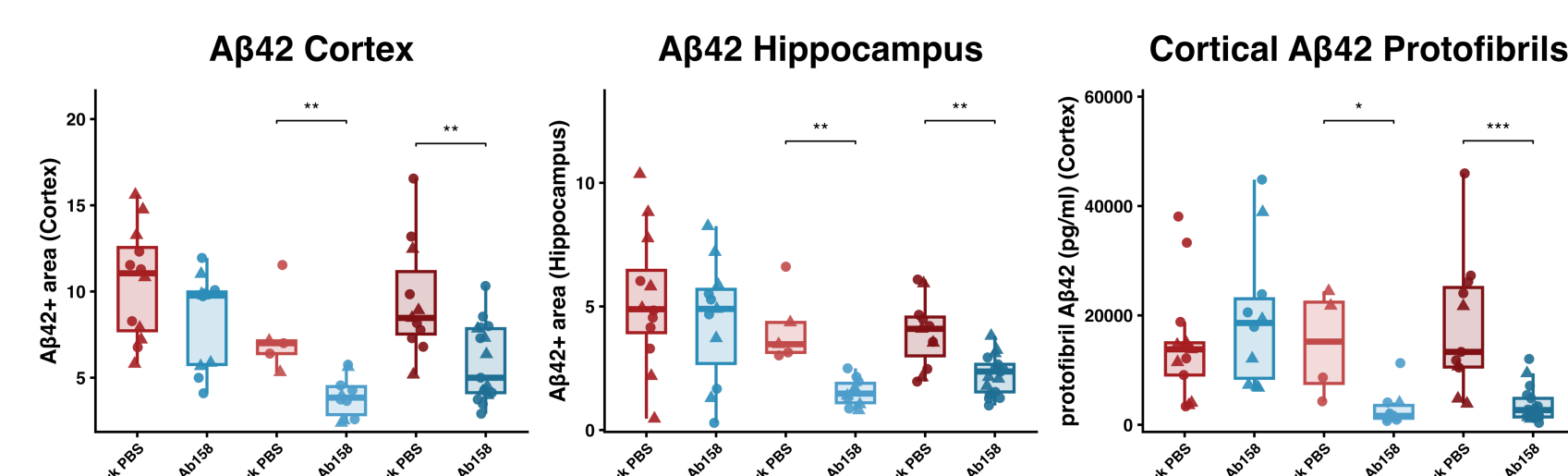
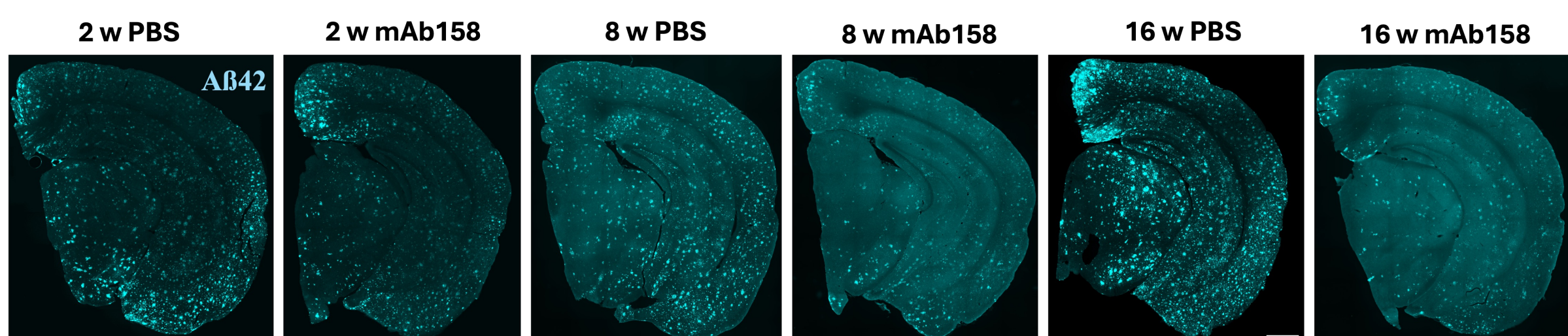


Results

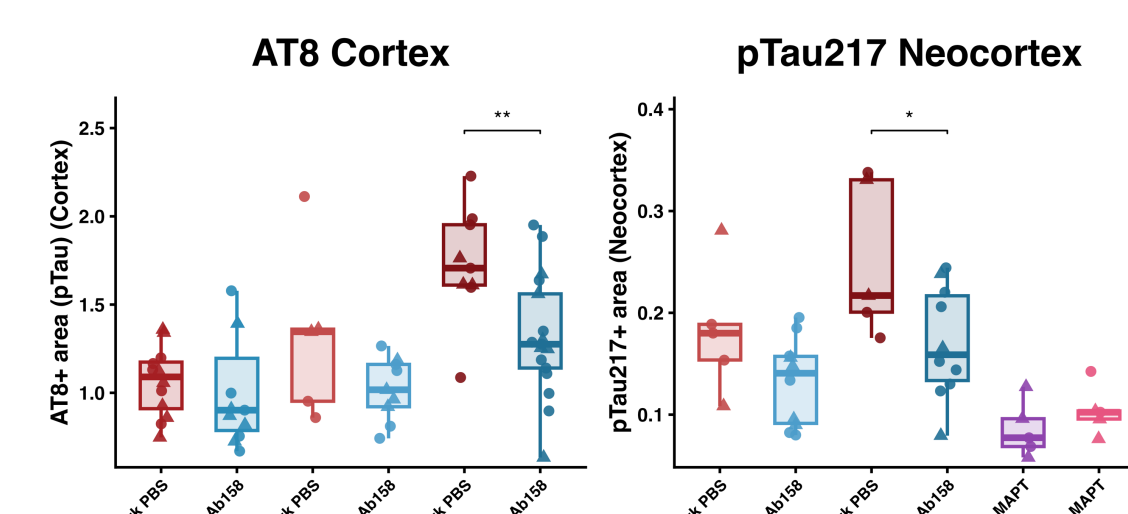
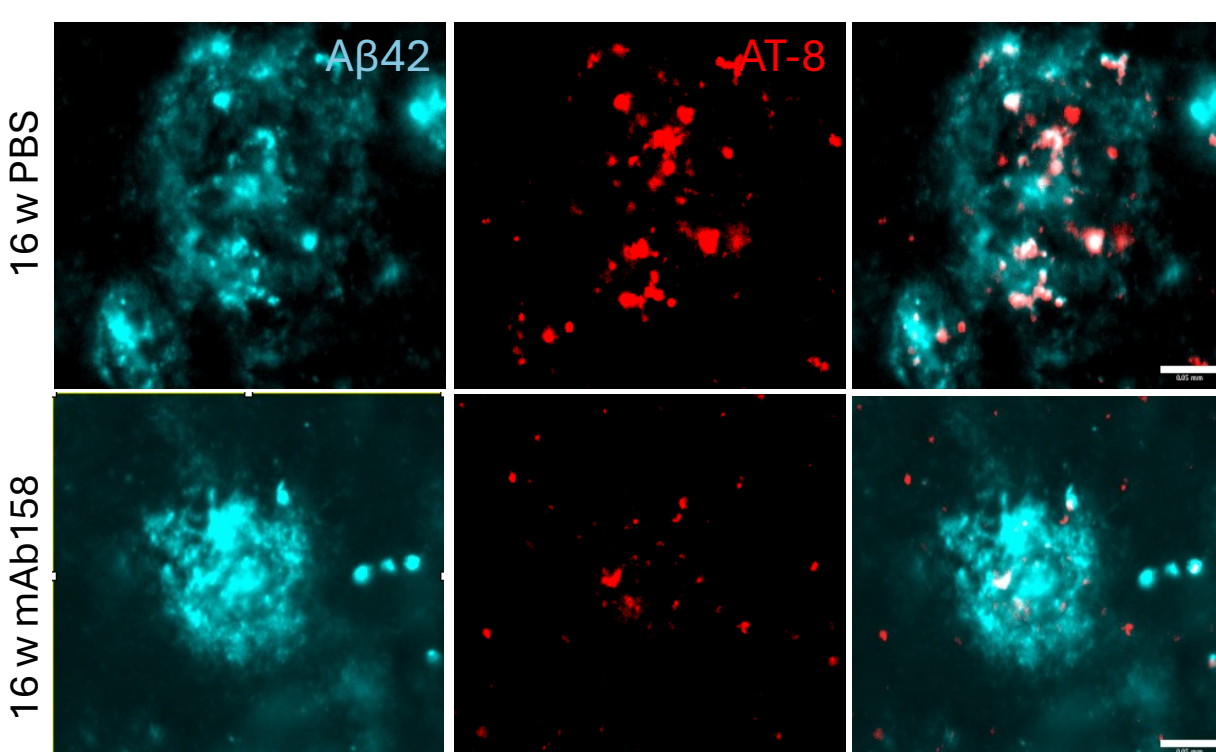
- Y-maze was performed before and after murine Lecanemab treatment
- There was no difference between the groups at the start of treatment
- After 16 weeks, the Lecanemab group stabilized but the PBS group declined



Lecanemab similarly reduces brain A β including protofibrils after 8 and 16 weeks

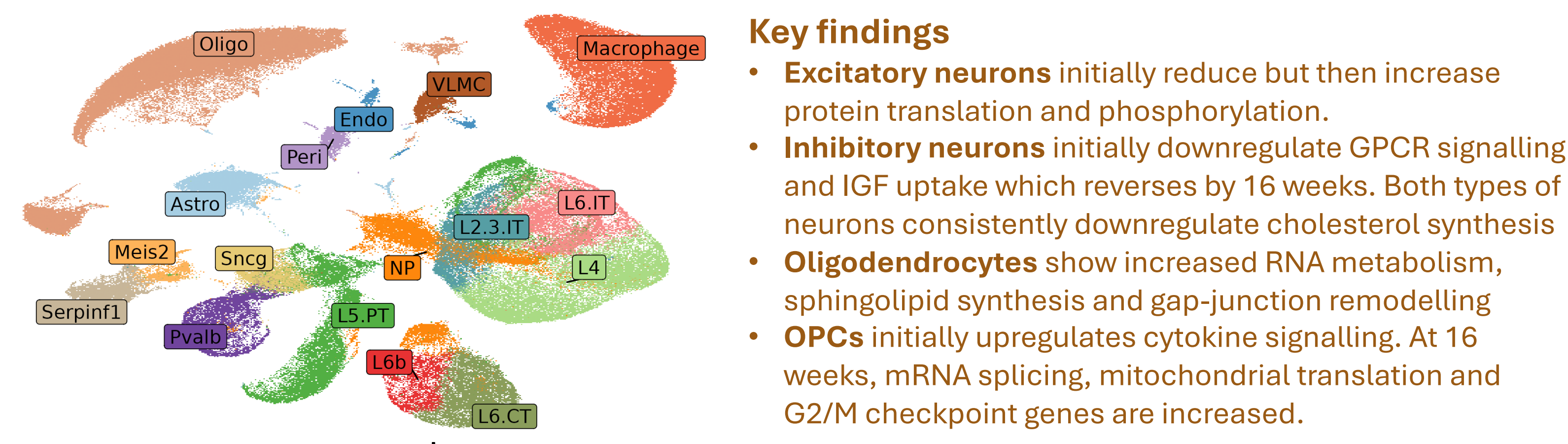


Lecanemab reduces brain p-tau, primarily in dystrophic neurites and around plaques, after 16 weeks but not 8 weeks of treatment



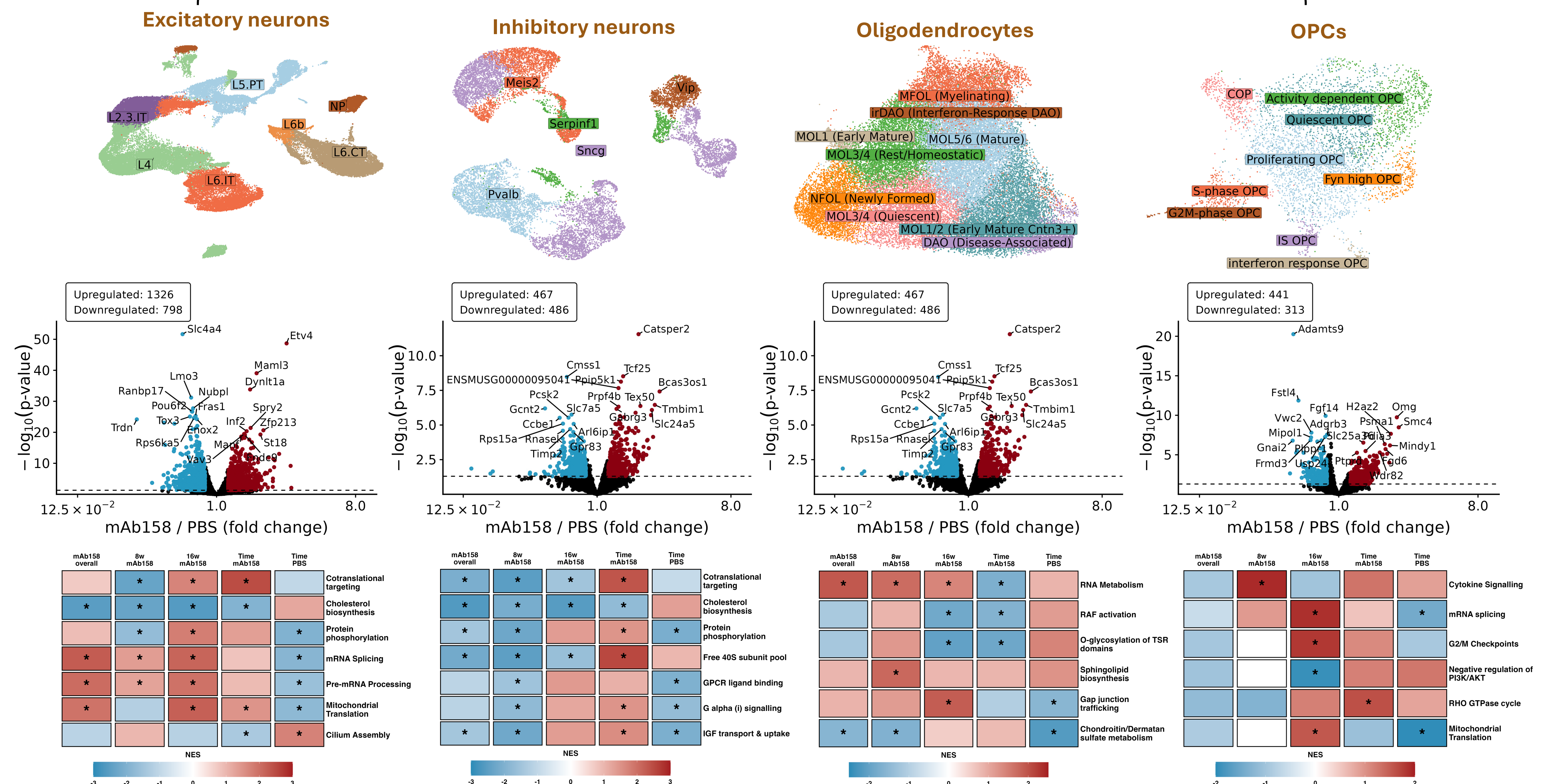
Single-nuclei sequencing reveals extensive transcriptional changes after murine Lecanemab treatment

- Single nuclei sequencing was performed on the cortex of 22 mice after 8 or 16 weeks of Lecanemab or PBS treatment
- Dataset consists of ~190k nuclei from neurons, oligodendrocytes, OPCs, microglia, astrocytes, pericytes, endothelial cells and VLMCs
- This poster focuses on neurons, oligodendrocytes and OPCs
- DEG and GSEA analysis summarizes key changed genes and pathways after lecanemab treatment



Key findings

- Excitatory neurons** initially reduce but then increase protein translation and phosphorylation.
- Inhibitory neurons** initially downregulate GPCR signalling and IGF uptake which reverses by 16 weeks. Both types of neurons consistently downregulate cholesterol synthesis
- Oligodendrocytes** show increased RNA metabolism, sphingolipid synthesis and gap-junction remodelling
- OPCs** initially upregulates cytokine signalling. At 16 weeks, mRNA splicing, mitochondrial translation and G2/M checkpoint genes are increased.



Conclusions and future directions

- Treatment with murine Lecanemab reduces A β pathology after 8 weeks, whereas p-tau reduction requires 16 weeks
- Short-term working memory is stabilized after 16 but not 8 weeks of Lecanemab treatment
- Neurons initially downregulate protein translation, which reverses by 16 weeks. Cholesterol synthesis is consistently downregulated.
- Oligodendrocytes upregulate RNA metabolism, gap junction remodelling and sphingolipid synthesis
- OPCs initially upregulate cytokine signalling, whereas at 16 weeks pathways associated with increased proliferation are increased.
- To verify that lecanemab is shifting the transcriptome towards a healthier state we are sequencing our healthy MAPT mice
- We are currently analysing NULISA proteomic data from brain, plasma and CSF

Funding



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