

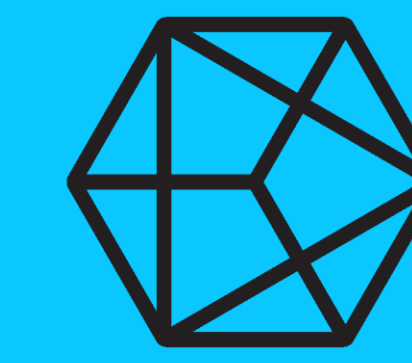
Investigating the role of microglial senescence in Lewy Body Dementia

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Introduction and Background

Cellular senescence is a stress-induced, irreversible cell cycle arrest characterised by upregulation of p16, p21 and γ H2AX. α -Syn aggregates have been shown to directly induce senescence across multiple brain cell types^{1,2}.

As the resident immune cells of the CNS, **microglia** maintain brain homeostasis but adopt pro-inflammatory states in neurodegeneration^{3,4}. **Senescent microglia are elevated in PD**, triggered by α -Syn accumulation in mouse models (Figure 1)².

Figure 1: Decreased Lamin B1 and increased p21 expression in IBA1+ cells after α -Syn PFFs treatment in mouse cortex².

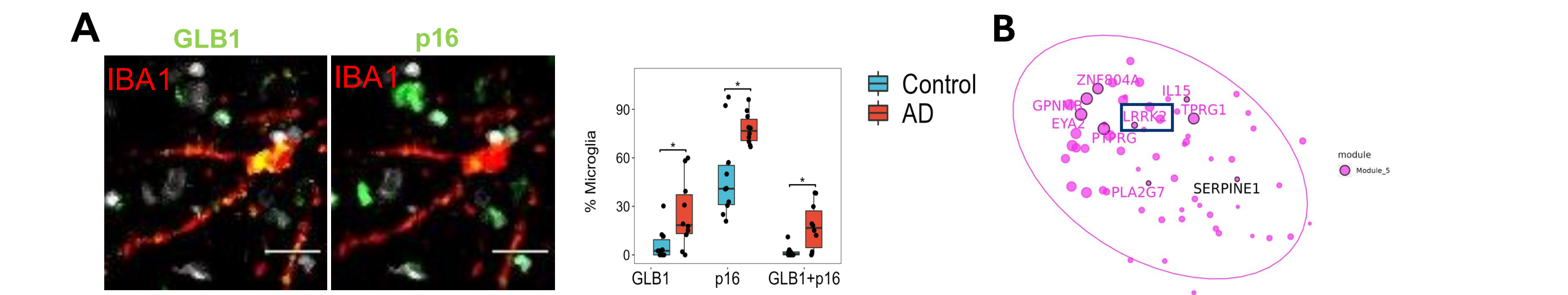


Figure 2: A. Increased number of microglia expressing senescent markers, GLB1 and p16 observed in postmortem cortical brain tissue of diagnosed Alzheimer's disease (AD) compared to non-diseased controls. B. Co-expression of LRRK2 with senescence-associated genes in microglia⁴.

Research Plan – Aims and Methods

1. Test whether senescence gene expression is increased in LBD cases compared to non-disease Control (NDC) using meta-analysis of single-nuclei RNA sequencing data.
2. Test whether increased microglia expressing senescence markers are increased in LBD cases compared to non-disease Control (NDC) using **Imaging Mass Cytometry (IMC)** spatial proteomics.
3. Test if the senescent microglia burden is associated with the levels of α -Syn aggregates using **Imaging Mass Cytometry (IMC)** spatial proteomics.

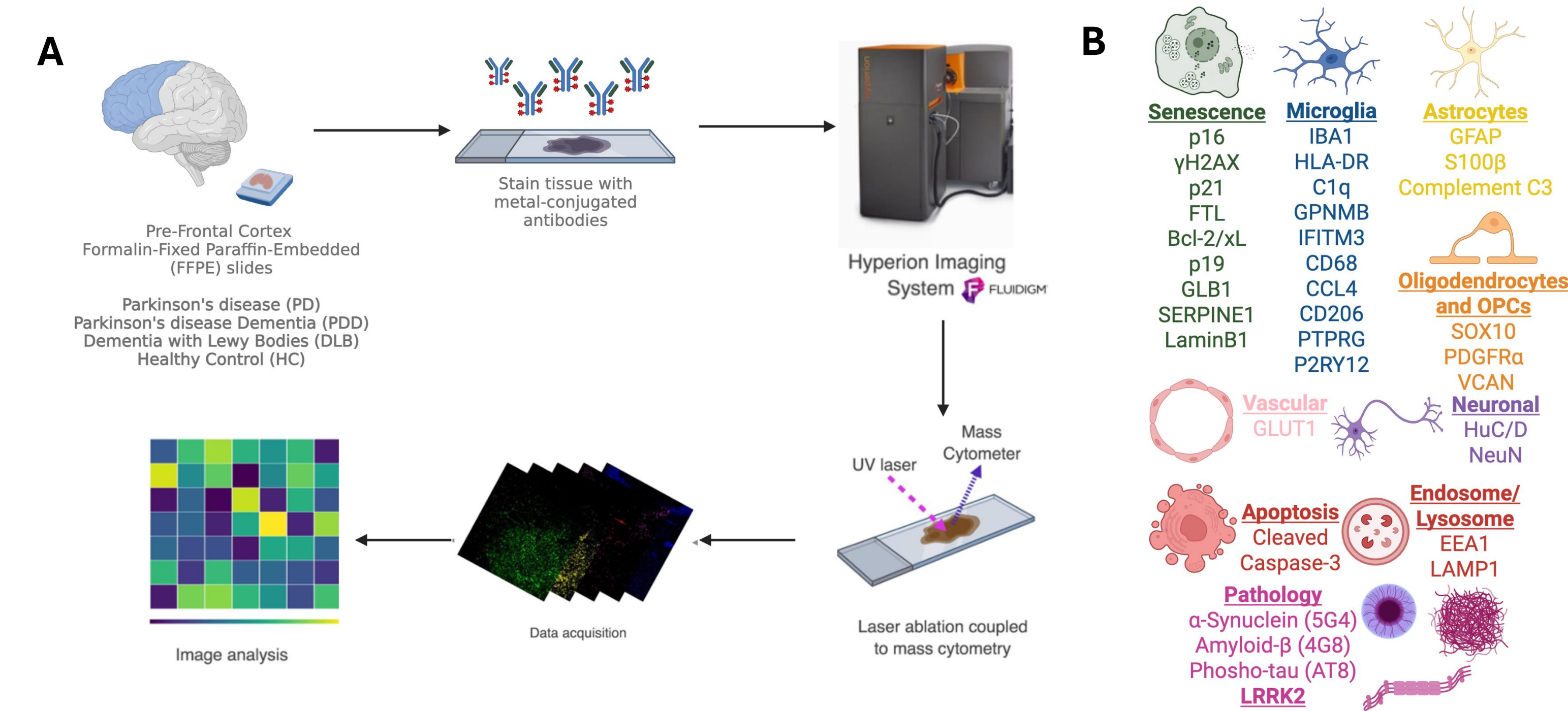


Figure 3: A) IMC workflow of staining, acquisition and analysis of postmortem pre-frontal cortex FFPE slides from PD, PDD, DLB, and controls (n = 15/patient cohort). B) IMC panel candidate markers (created with BioRender)

Results

snRNAseq Meta-analysis

We performed a meta-analysis using published single-nucleus RNA sequencing (snRNAseq) datasets from PD cases using the “canonical senescence pathway (CSP)” gene set in microglia. Our analysis showed **significant upregulation** of this pathway in microglia in PD compared to controls in these datasets.

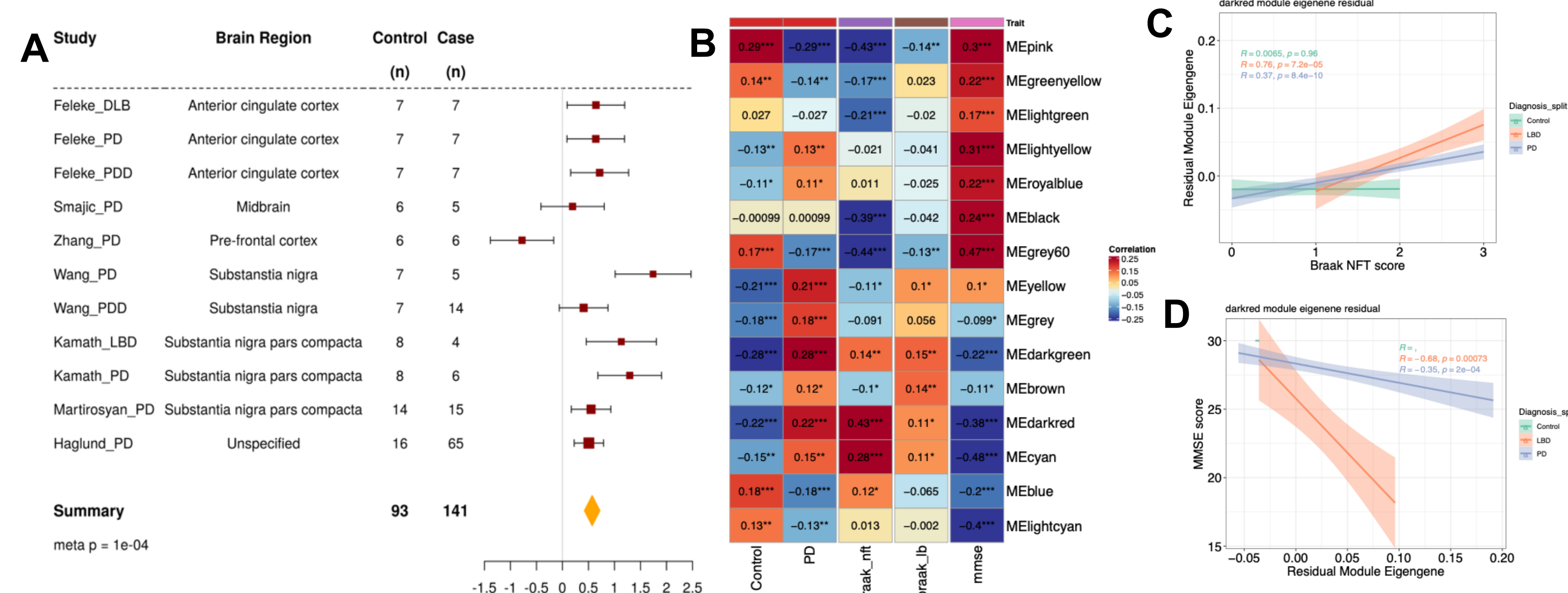
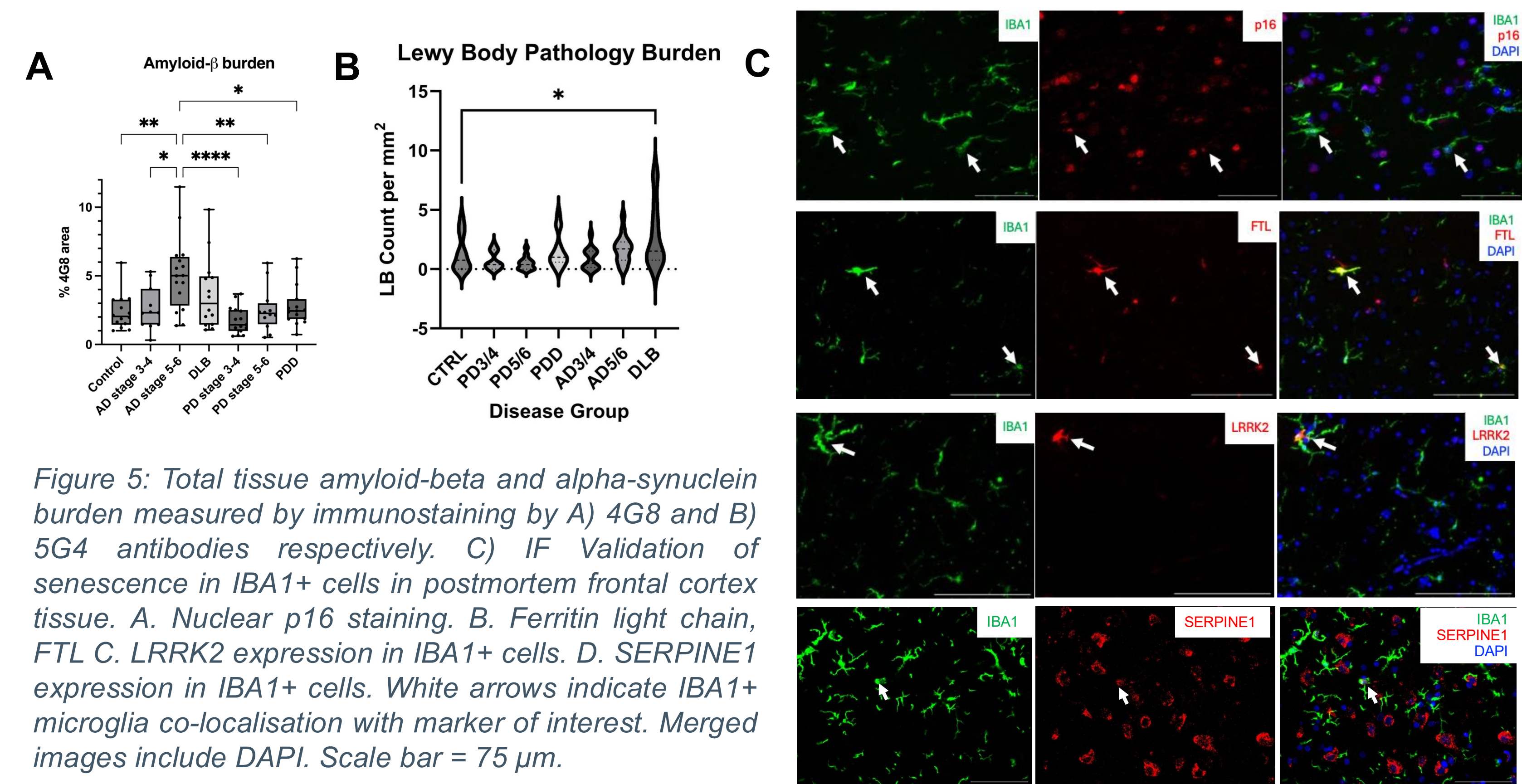


Figure 4: A) Meta-analysis using single-nuclei RNA sequencing data of postmortem brains shows increased senescence gene-set expression in microglia from PD, Parkinson's disease dementia (PDD) and Dementia with Lewy Bodies (DLB) compared to that of healthy controls. (10/11, p-value = 1e-04). B) Weighted gene co-expression network analysis (WGCNA) identified an LRRK2-containing module (darkred). Module-trait Pearson correlation is shown via heatmap. (C-D) The residual module eigengene for darkred module (after correcting for age, sex and APOE4 status) is shown C) against Braak NFT score, D) MMSE score.

Immunofluorescence (IF) – Antibody Optimisation



References

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