



天津市环湖医院
Tianjin Huanhu Hospital

Perivascular Macrophages As A Crucial Endogenous Pathway For Mitigating Amyloid- β Burden And Its Response To Lecanemab Treatment In AD Mice

Chen Wen¹, Junyi Wang¹, Qiongqiong Niu¹, Shuai Liu¹, Hao Wu¹, Pan Wang¹, Yong Ji¹.

¹Department of Neurology, Huanhu Hospital Affiliated to Tianjin Medical University

Background

- Perivascular macrophages (PVMs) are crucial for A β clearance and neurovascular health. This study investigates PVMs distribution, their impact on neurovascular interface integrity, and their role in Lecanemab treatment within Alzheimer's disease (AD) models.

Methods

- PVMs distribution in WT and APP/PS1 mice were assessed across different age groups via intracisternal injection of fluorescent tracers into the cerebellomedullary cistern. To investigate functional roles, clodronate liposomes were administered to deplete PVMs in brain. PVMs identity was authenticated by CD163 immunofluorescence, with robust co-localization confirming high labeling specificity and accurate cellular identification. Cognitive performance was evaluated using the eight-arm radial maze (RAM), and BBB permeability via Evans blue extravasation. Tight junction protein expression and A β deposition were analyzed using immunofluorescence, western blotting, and ELISA. Additionally, to explore how PVMs mediate Lecanemab's therapeutic effects, the antibody was injected via tail vein to AD mice, followed by systematic evaluation of blood-brain barrier integrity and cognitive function.

Results

- AD mice exhibited increased PVMs numbers compared to WT ($P=0.03$), with an age-dependent rise from 4 to 8 months ($P=0.01$) (Figure 1A-D).
- PVMs depletion in AD mice exacerbated cognitive decline ($P<0.05$) (Figure 2A-D) and increased BBB permeability, evidenced by enhanced Evans blue extravasation ($P=0.03$) and downregulated tight junction proteins (ZO-1, Claudin-5, and Occludin; $P=0.03$) (Figure 3A-I).

- Furthermore, PVMs depletion aggravated A β pathology, significantly increasing mean fluorescence intensity of A β plaques ($P=0.02$) and overall A β levels ($P=0.01$) (Figure 3K-Q). Notably, Lecanemab treatment in AD mice increased PVMs number ($P<0.05$), slowed cognitive decline ($P<0.05$), and upregulated tight junction protein expression ($P<0.05$) (Figure 1E & Figure 2E-H & Figure 3J).

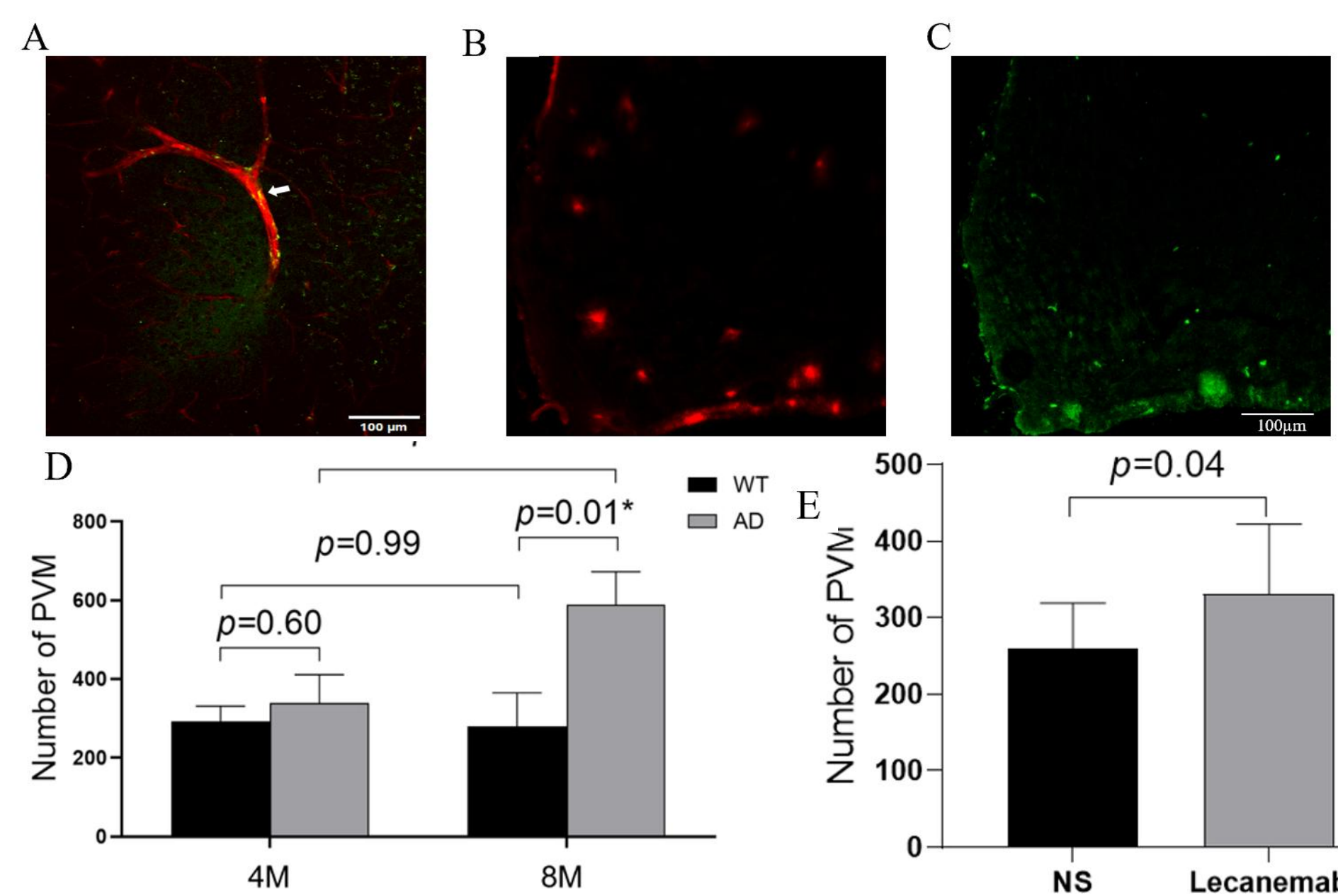


Figure 1. PVMs distribution.

A. PVMs are widely distributed along the blood vessels. Green: Fluoro-Emerald, Red: Evans Blue; Scale bar: 100 μ m. B-C. The PVM marked with Fluoro-Ruby (B) was co-stained with CD163 (D). Red: Fluoro-Ruby; Green: CD163; Scale bar: 100 μ m. D. Distribution of PVMs for different months WT and AD model mice. E. The number of PVMs in AD model mice treated with Lecanemab versus placebo.

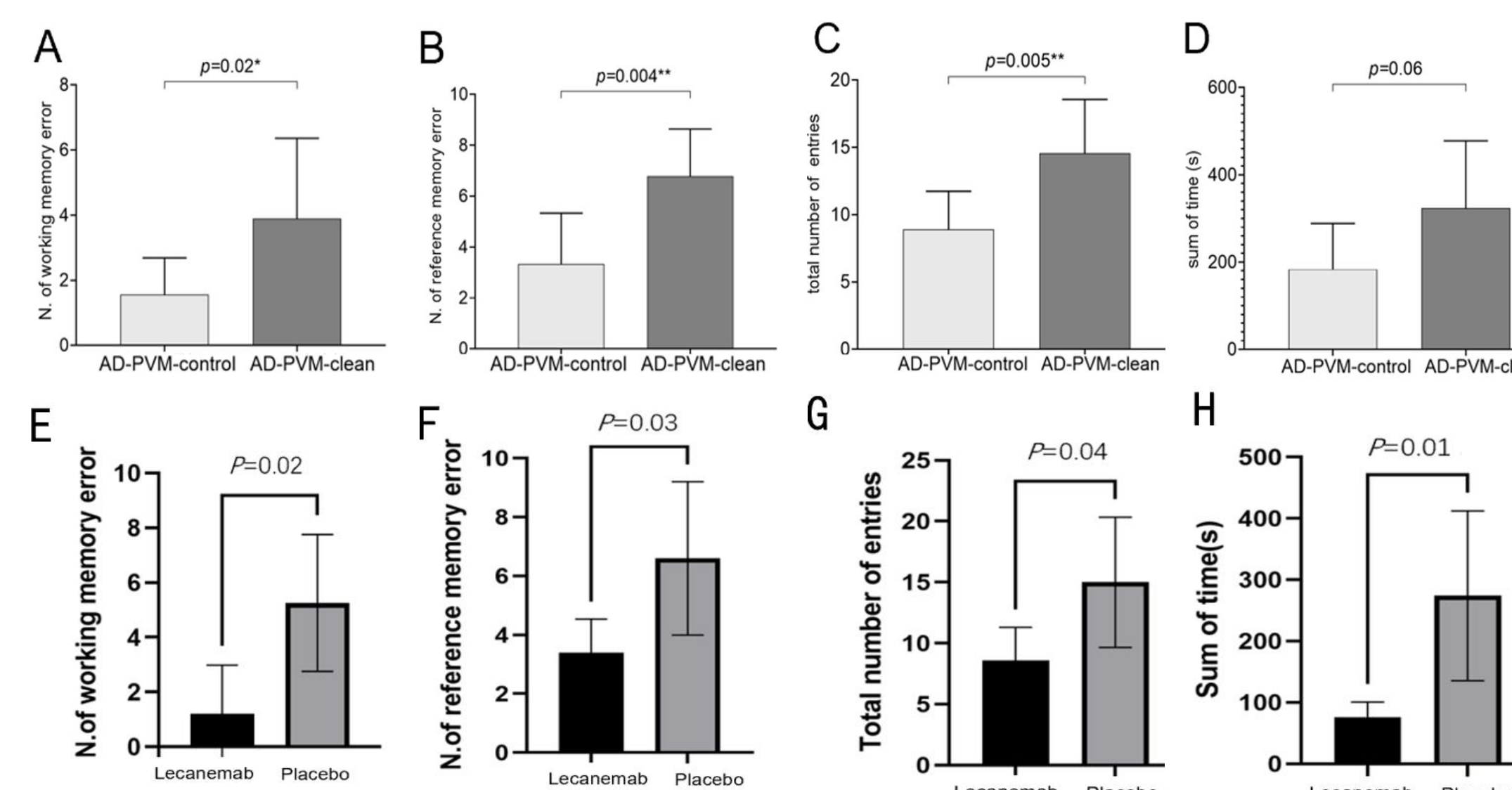


Figure 2. Eight-arm radial maze test results.

A-D: Eight-arm radial maze test results of AD model mice. E-H: Eight-arm radial maze test results of AD model mice treated with Lecanemab versus placebo.

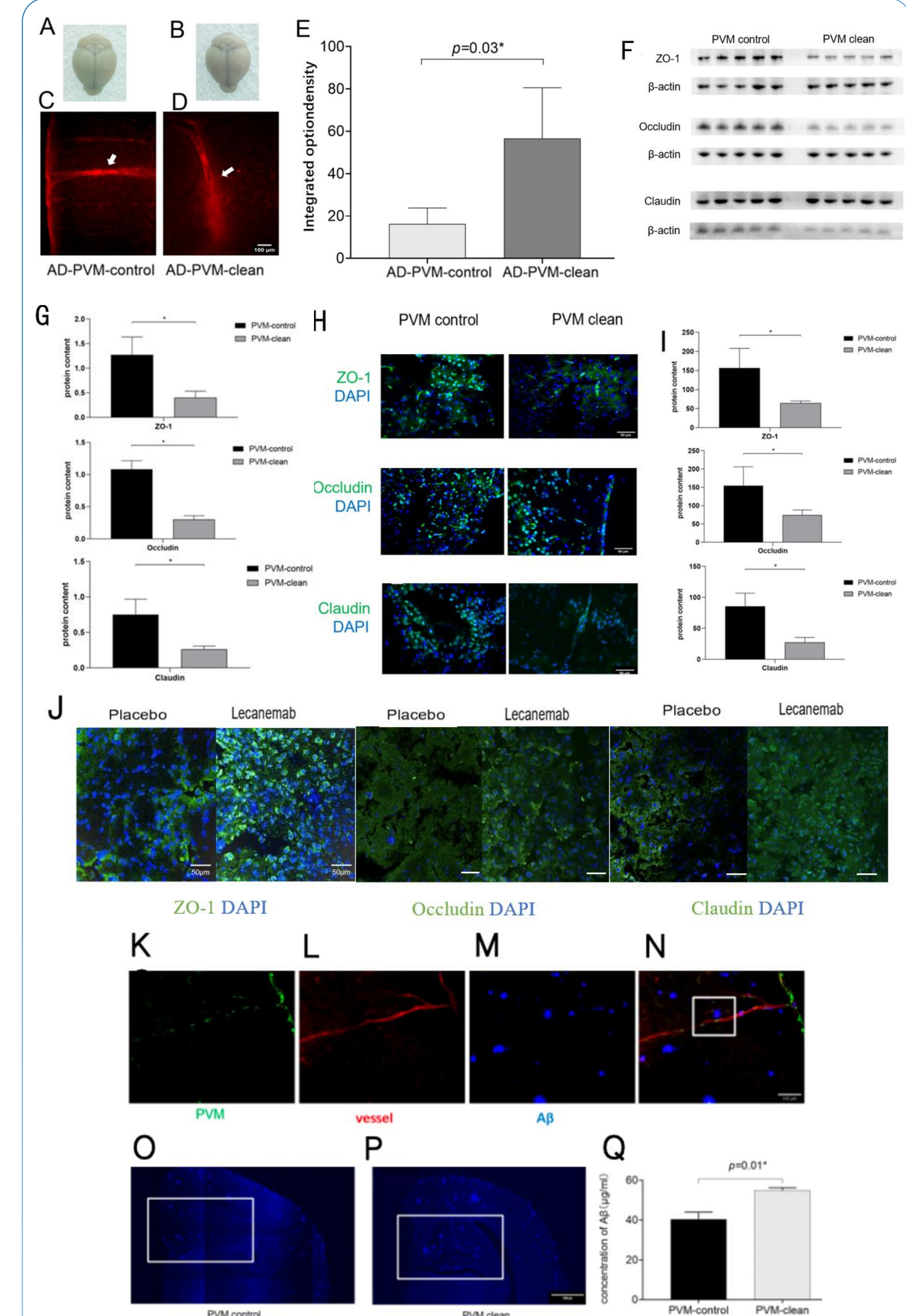


Figure 3. Analysis of BBB permeability and A β deposition.

A-D, Evans blue leakage in the PVM-clean group and PVM-control group; E, Evans blue leakage fluorescence intensity analysis. (Red: Evans blue; Scale bar: 100 μ m). F, WB results of tight junction proteins in the PVM-clean group and PVM-control group; G, Intensity analysis. (Green: ZO-1/Occludin/Claudin; Blue: DAPI; Scale bar: 50 μ m.) H, Distribution of tight junction proteins in the PVM-clean group and PVM-control group; I, Fluorescence intensity analysis. (Green: ZO-1/Occludin/Claudin; Blue: DAPI; Scale bar: 50 μ m.) J, Distribution of tight junction proteins in AD model mice treated with Lecanemab versus placebo. (Green: ZO-1/Occludin/Claudin; Blue: DAPI; Scale bar: 50 μ m.)

Results

- PVMs serve as a critical endogenous protective pathway in AD, where their recruitment mitigates A β burden and preserves BBB integrity via tight junction protein regulation. The increasing of PVMs following Lecanemab treatment likely reflects a resolution of this compensatory response as the A β burden is alleviated. Regarding the ARIA issue currently observed in Lecanemab, PVMs is expected to become a new therapeutic target.