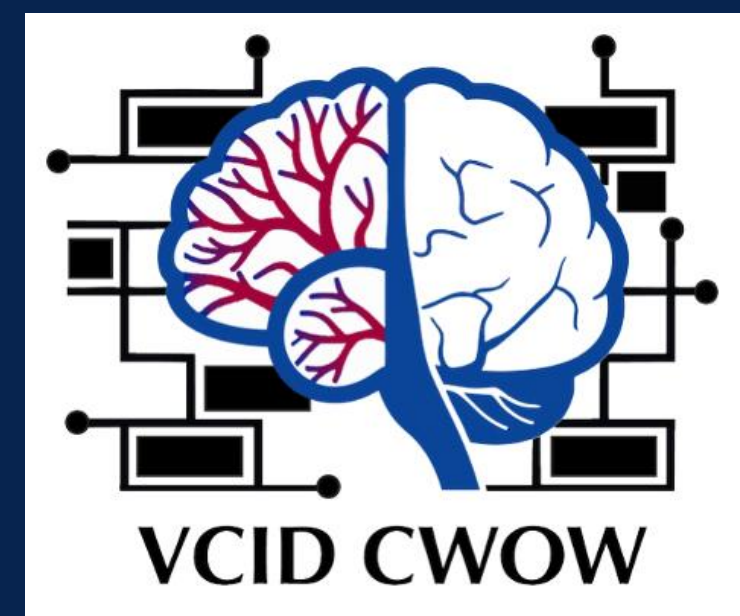




Goal

White matter vascular lesions (WMVLs) are a major contributor to cognitive impairment and dementia, yet are often conceptualized dichotomously as either diffuse “small vessel disease” or focal ischemic injury. Emerging evidence suggests that WMVLs represent a biological spectrum ranging from early molecular and cellular dysfunction to overt ischemic white matter infarction. Endothelial–glial communication is central to neurovascular unit integrity, but specific cellular and molecular interactions involved in coordinating white matter repair after vascular injury remain incompletely understood. Interleukin inflammatory signaling between endothelia and microglia is proposed as a critical pathway in WMVLs. The **UCLA VIBRANT VCID CWOW** is focused on defining endothelial–glial communication in the context of WMVLs.

Endothelia vTRAP profiling

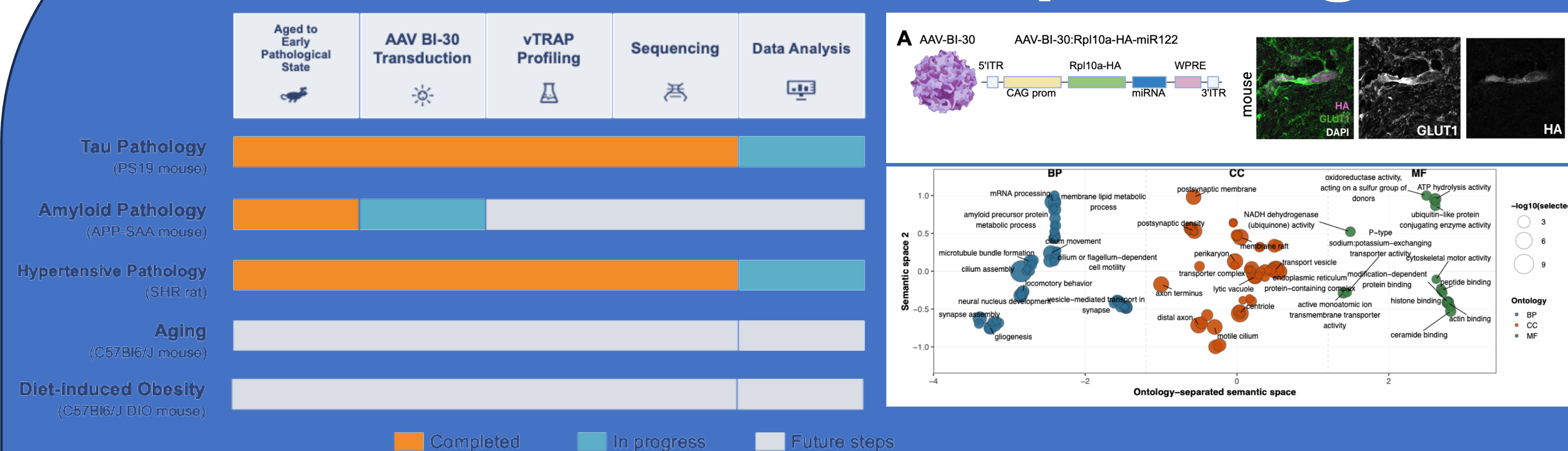


Figure 2. Endothelial profiling across prodromal AD/ADRD conditions. Schematic diagram of AD/ADRD model profiling using viral translating ribosome affinity profiling with AAV BI-30:Rp10a-HA. Viral endothelial RiboTAG labeling enriches for endothelial ribosome HA labeling. HA immunoprecipitation enables transcriptome profiling of AD/ADRD conditions. The GO profile of SHRP endothelia enriches for gliogenesis, intercellular communication, and mRNA processing.

Endothelial-Glial Signaling in WMVLs

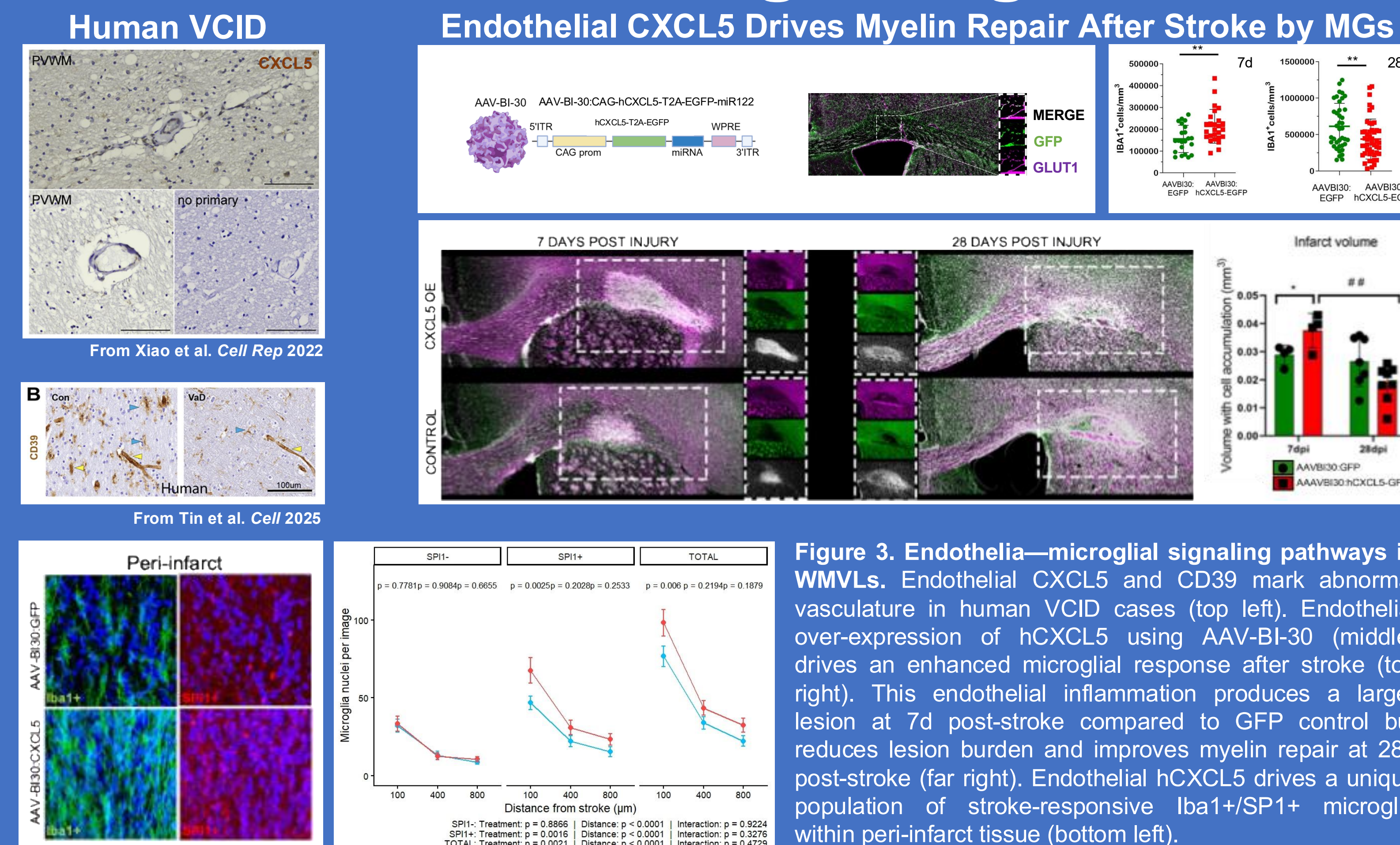


Figure 3. Endothelial–microglial signaling pathways in WMVLs. Endothelial CXCL5 and CD39 mark abnormal vasculature in human VCID cases (top left). Endothelial over-expression of hCXCL5 using AAV-BI-30 (middle) drives an enhanced microglial response after stroke (top right). This endothelial inflammation produces a larger lesion at 7d post-stroke compared to GFP control but reduces lesion burden and improves myelin repair at 28d post-stroke (far right). Endothelial hCXCL5 drives a unique population of stroke-responsive Iba1+SP1+ microglia within peri-infarct tissue (bottom left).

Novel Tg Rat Model of Mixed Dementia

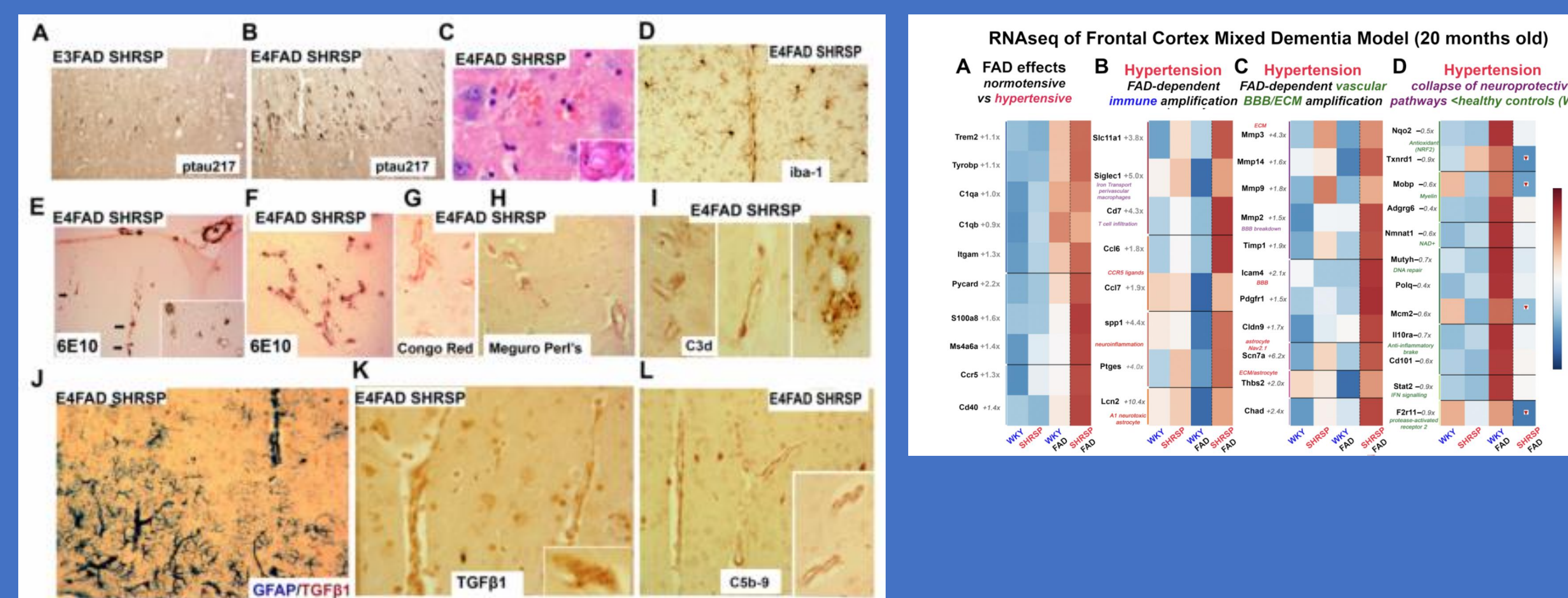


Figure 4. A novel transgenic rat model of mixed vascular dementia. SHRSP rats were crossed with rats carrying humanized E4 and the FAD transgene resulting in widespread vascular amyloid, tau deposition, complement deposition, and glial reactivity. Bulk RNA-seq of the frontal cortex highlights the interaction between vascular risk factors including hypertension and amyloid deposition with enrichment of immune signaling and ECM modulation in the presence of amyloid. The UCLA VIBRANT CWOW is using this novel transgenic rat model to validate concordant AD/ADRD endothelial intercellular signaling pathways and to develop MRI biomarkers of mixed vascular dementia.

Human Pathologic Studies

To confirm endothelial–glial communication pathways relevant to WMVLs in human brain, we partnered with the Banner Sun Health System to identify selected cases of AD, VCID, and mixed pathology. Comparative analyses between frontal vs. temporal lobes will discriminate pathways unique to VCID from AD using sn-seq and confirmatory pathology (LFB, synaptic density, BBB leak).

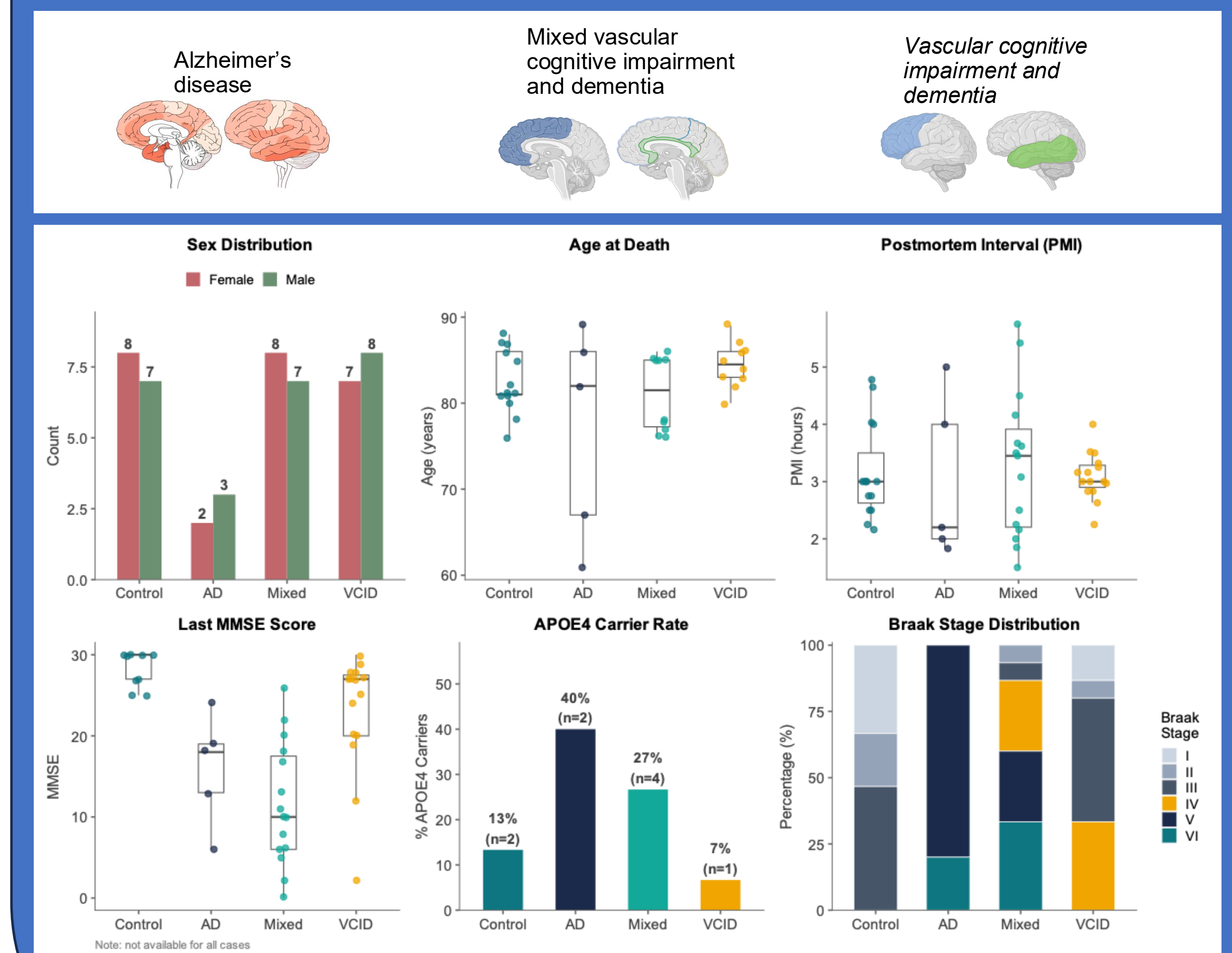


Figure 5. Human pathology confirmation in the UCLA VIBRANT CWOW. Regional comparison by underlying clinical diagnosis. Clinicopathologic characteristics of case selection includes control (n=15), AD (n=5), mixed (n=15), and VCID (n=15) with comparable dex, age, PMI and cognitive impairment with ApoE rates and Braak Stage pathology.

Experimental Framework

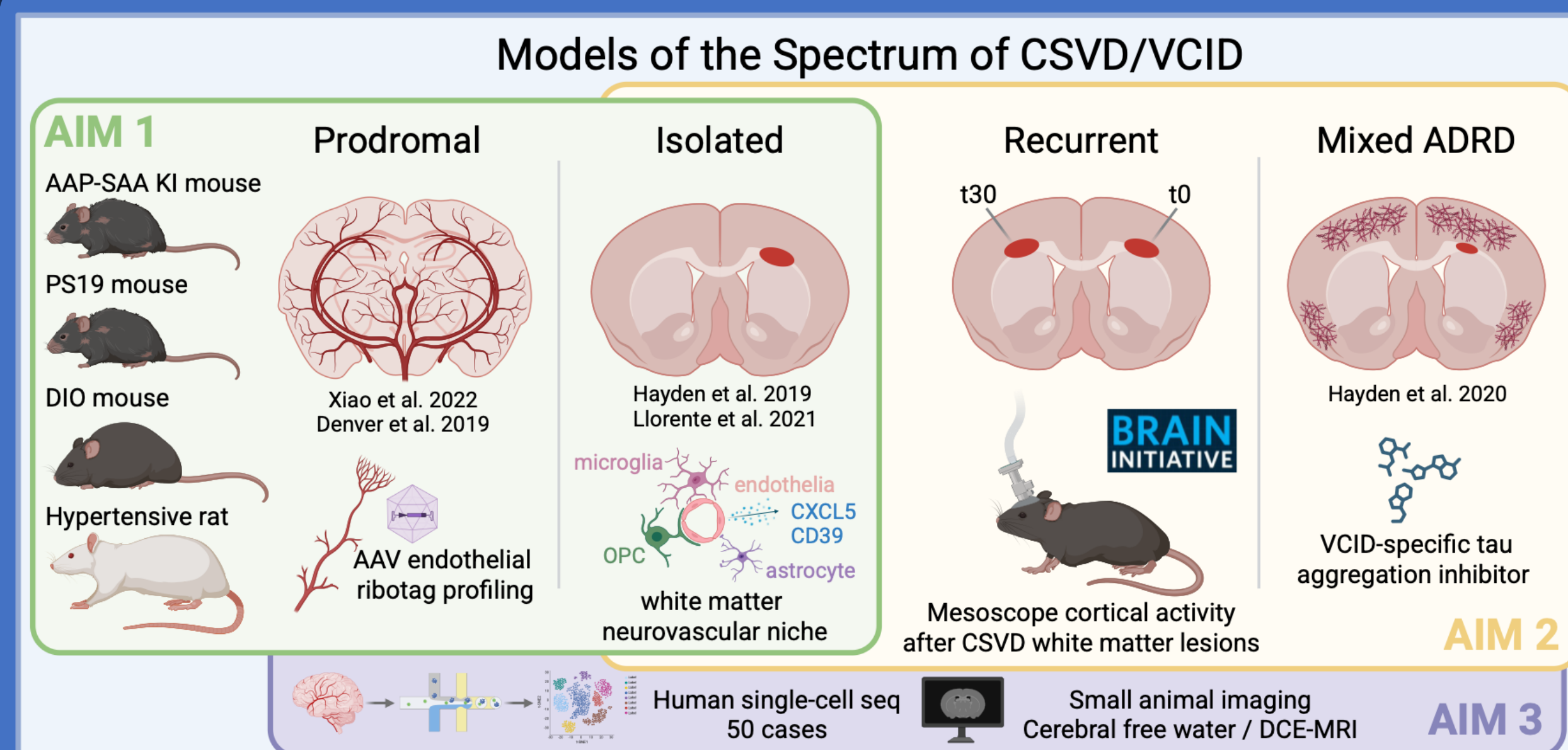


Figure 1. We examined endothelial–microglial intercellular signaling in experimental models of white matter ischemic injury and complementary human tissue. Transcriptomic, regional, and immunohistochemical approaches were used to characterize endothelial activation states, microglial responses, and signaling pathways associated with tissue injury and repair. Temporal analyses were performed to distinguish acute injury responses from reparative phases following ischemic white matter damage.

Conclusions/Next Steps

- WMVLs exist along a spectrum from molecular dysfunction to ischemic lesion formation
- The endothelium as an active signaling hub in white matter resilience
- Endothelial–microglial intercellular signaling as a critical regulator of white matter repair following vascular injury
- Targeting endothelial–glial communication may represent a novel therapeutic strategy for vascular cognitive impairment and dementia

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