



# Oligodendrocyte Remodeling Across Human Alzheimer's Disease and Humanized Mouse Models of AD

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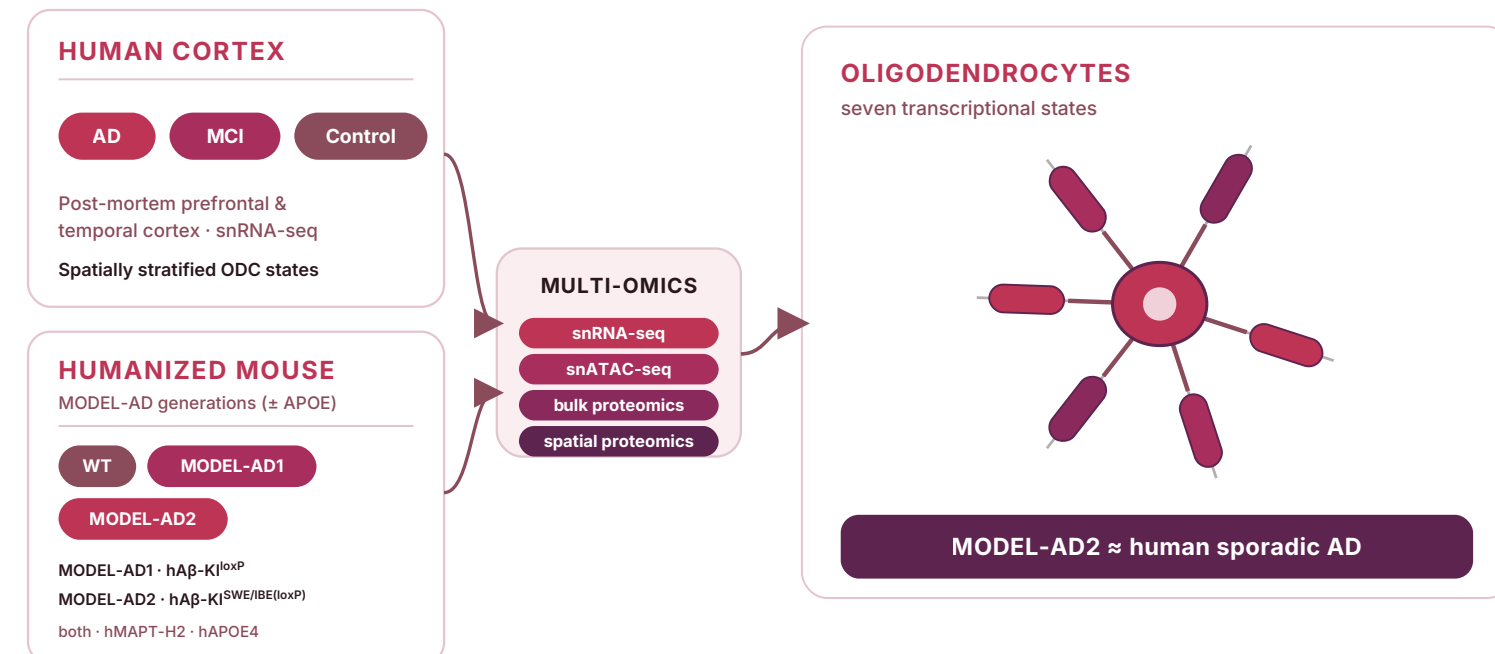
<sup>1</sup>Neurobiology and Behavior · <sup>2</sup>Developmental and Cell Biology · University of California, Irvine, CA, USA



## TAKE-HOME

Next-generation MODEL-AD2 humanized mice reproduce the oligodendrocyte transcriptional program of human sporadic AD — the concordance first-generation models miss — pinpointing oligodendrocytes as a conserved, translatable therapeutic axis.

## Graphical Overview



Human AD / MCI / Control plus humanized **MODEL-AD1** and **MODEL-AD2** mice (± APOE) feed one multi-omics pipeline, converging on a seven-state oligodendrocyte atlas.

## Abstract

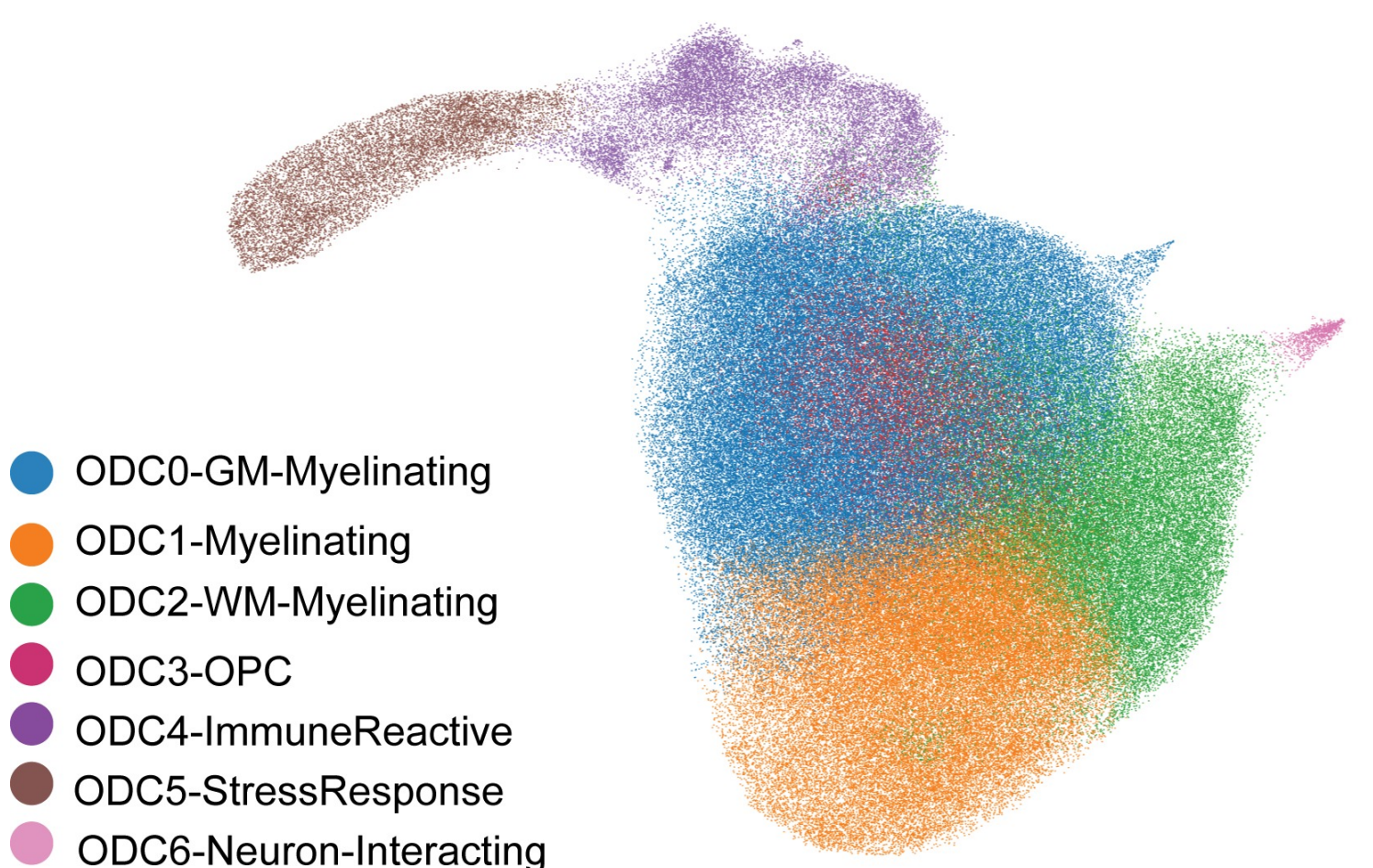
**Background.** Human AD cortex shows profound, spatially stratified oligodendrocyte perturbation across grey and white matter — altered myelination, lipid and stress-response pathways.

**Methods.** Two humanized MODEL-AD generations — **MODEL-AD1** (hAβ-K<sup>loxP</sup>) and **MODEL-AD2** (hAβ-K<sup>SWE/IBE(loxP)</sup>), both on hMAPT-H2 and hAPOE4 — profiled by snRNA + ATAC, bulk proteomics and spatial proteogenomics.

**Results.** Progressive ODC dysfunction; APOE4 shifts amyloid to vasculature; cross-species comparison reveals conserved lipid / endo-lysosomal / OPC programs and grey-white divergence.

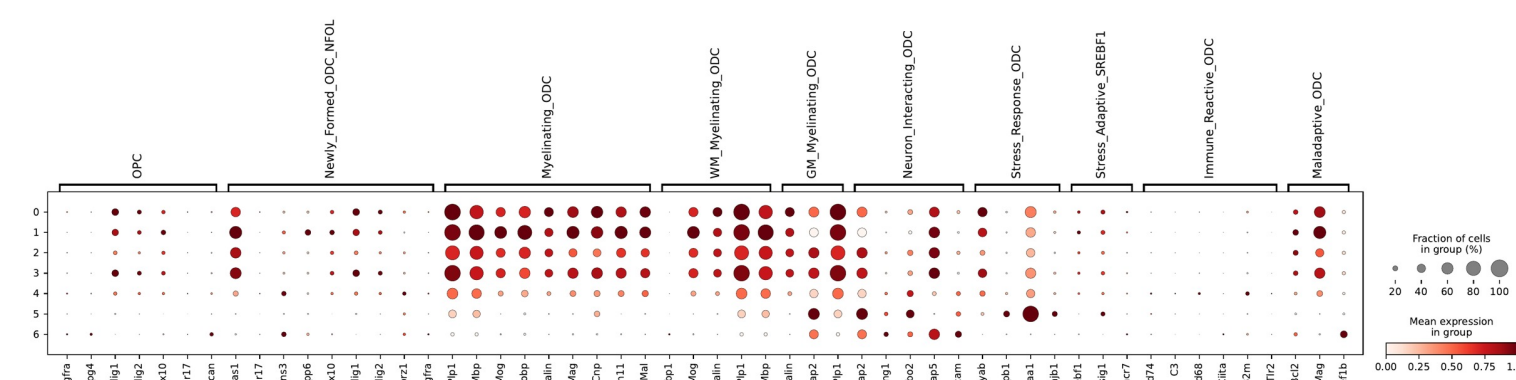
**Conclusion.** A cross-species framework to test therapies that enhance oligodendrocyte resilience and myelin maintenance.

## Oligodendrocyte Atlas



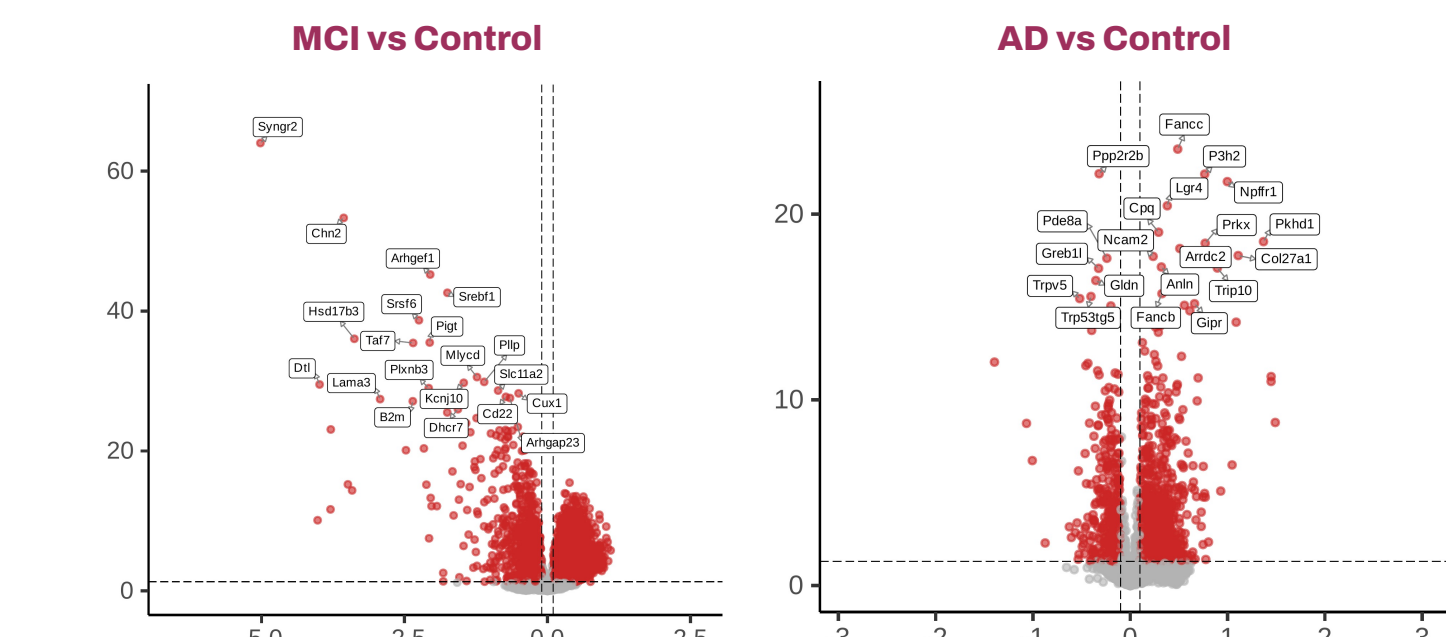
Integrated snRNA-seq UMAP — seven oligodendrocyte states (GM/WM myelinating, OPC, immune-reactive, stress-response, neuron-interacting).

## Oligodendrocyte Functional States



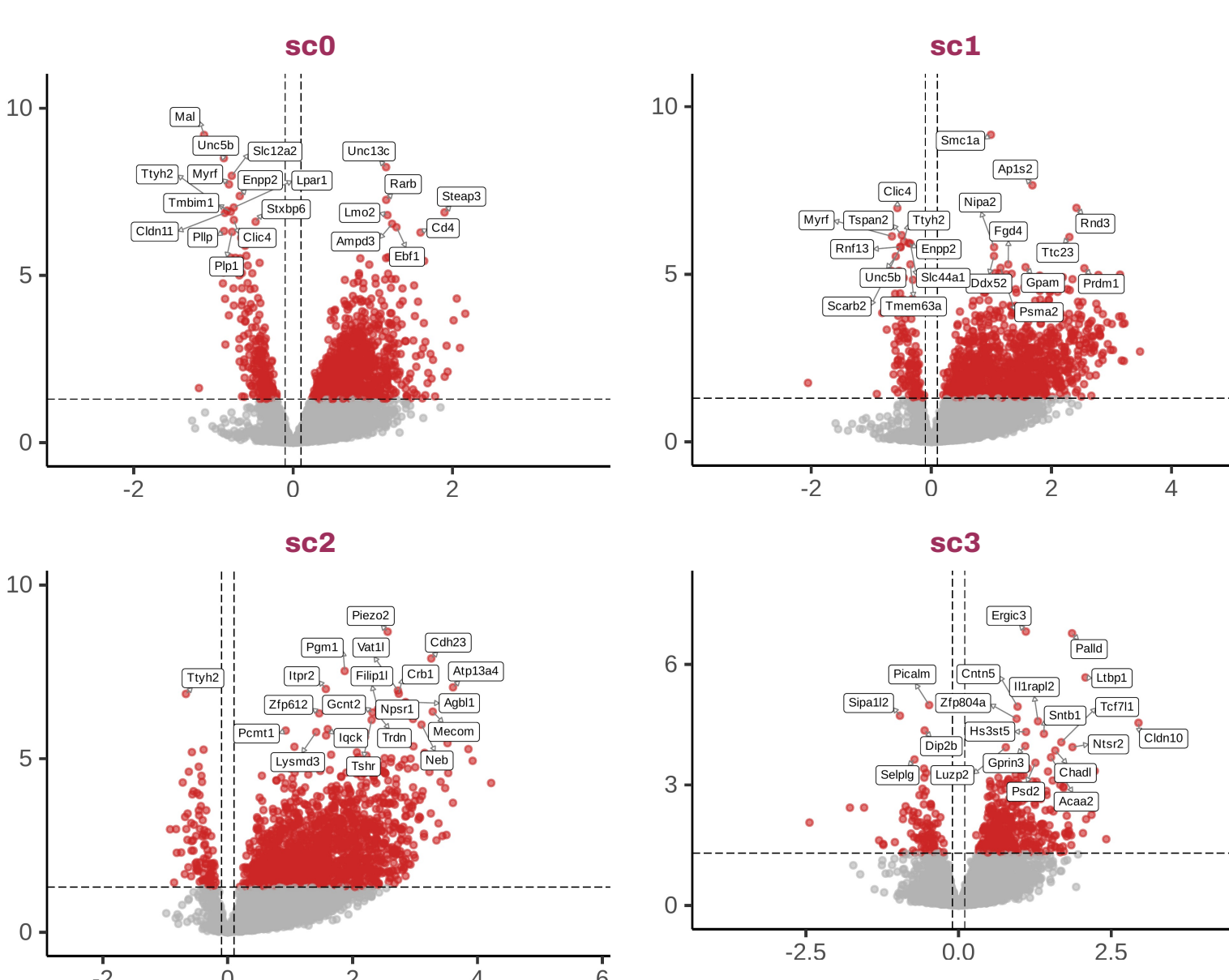
Marker programs define each state: OPC → newly-formed → myelinating (GM / WM) → neuron-interacting → stress-response → maladaptive.

## Human ODC — Disease Progression



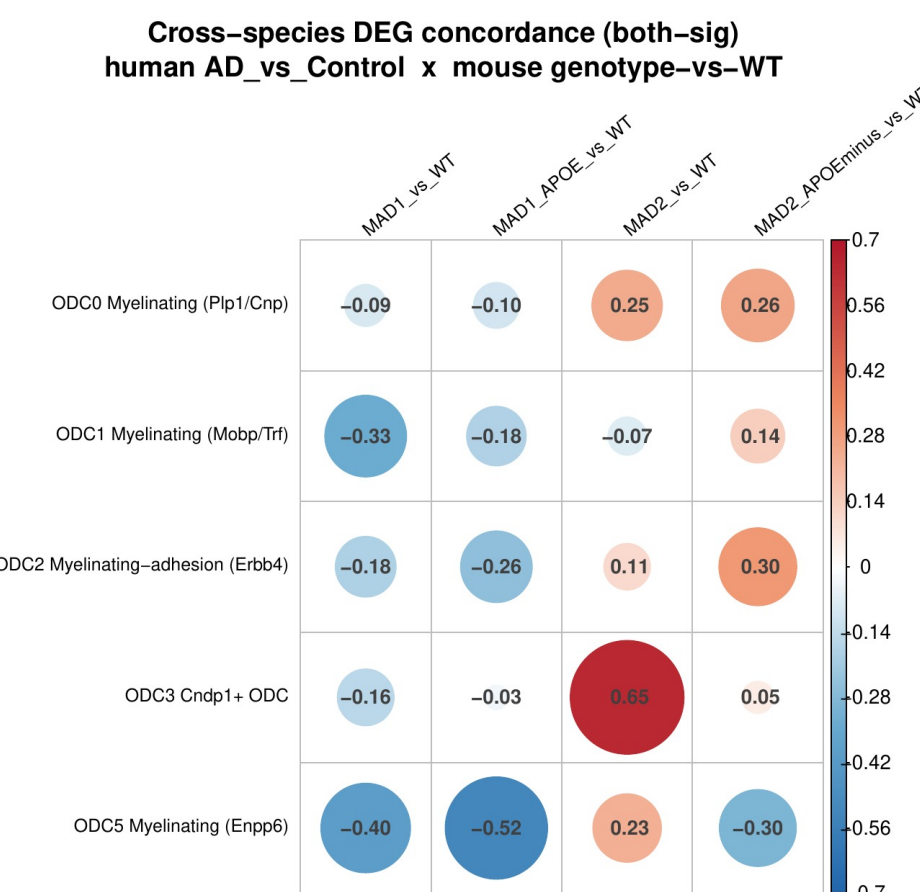
Oligodendrocyte DE across stages: changes appear by MCI and intensify in AD (807↑ / 369↓, 1,176 significant).

## MODEL-AD2 vs MODEL-AD1 — ODC Clusters



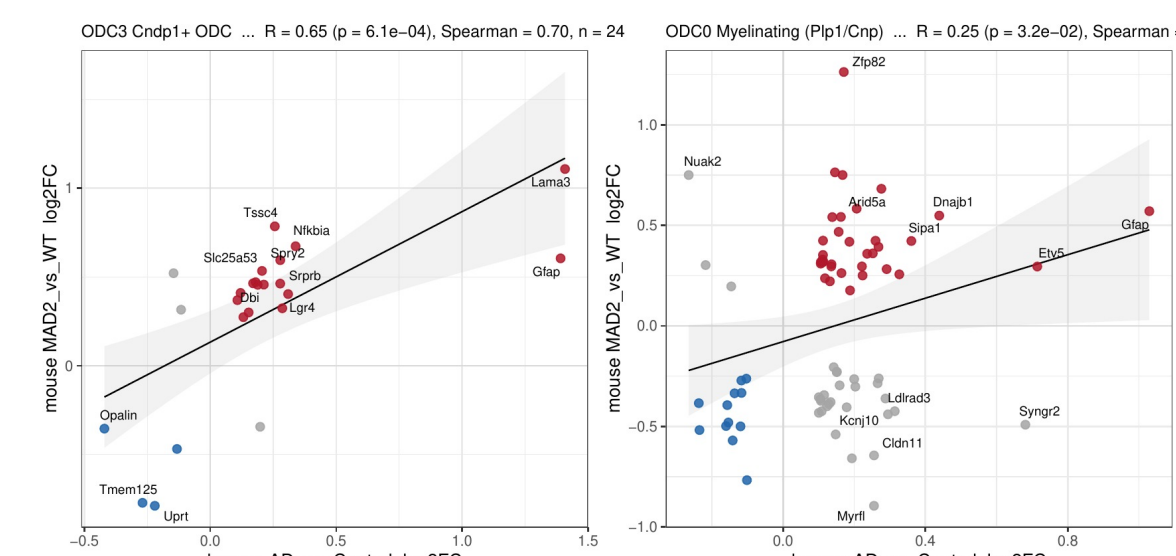
Direct genotype contrast across oligodendrocyte clusters (sc0-sc3): MODEL-AD2 **diverges extensively** from the first-generation model — hundreds-thousands of DEGs per cluster.

## Cross-Species Concordance



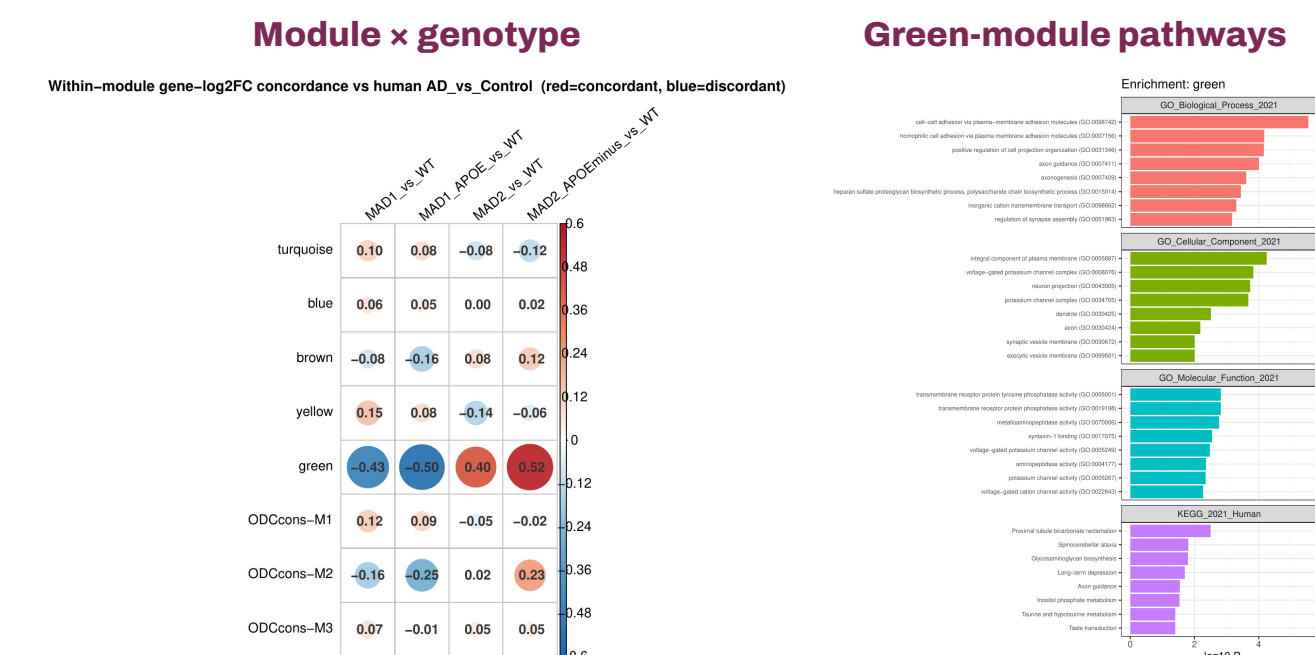
Per-subtype correlation of human-AD vs mouse fold-changes. **MODEL-AD2 is concordant** (ODC3 Cndp1+ **R = +0.65**, red); **MODEL-AD1 is discordant** (blue). The central result.

## Focal Gene Concordance



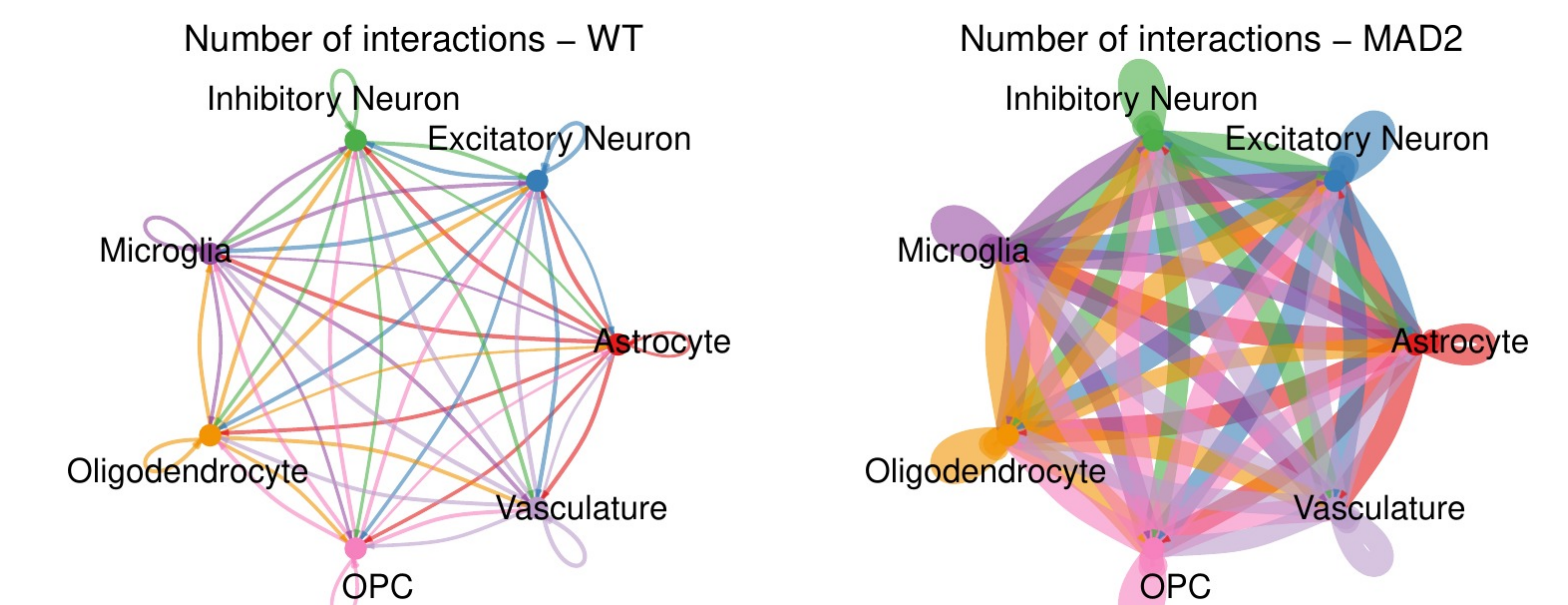
ODC3 (Cndp1+): human-AD and MODEL-AD2 fold-changes track tightly — **R = 0.65**, Spearman  $\rho = 0.70$  (n = 24 shared DEGs).

## Co-Expression (hdWGCNA)



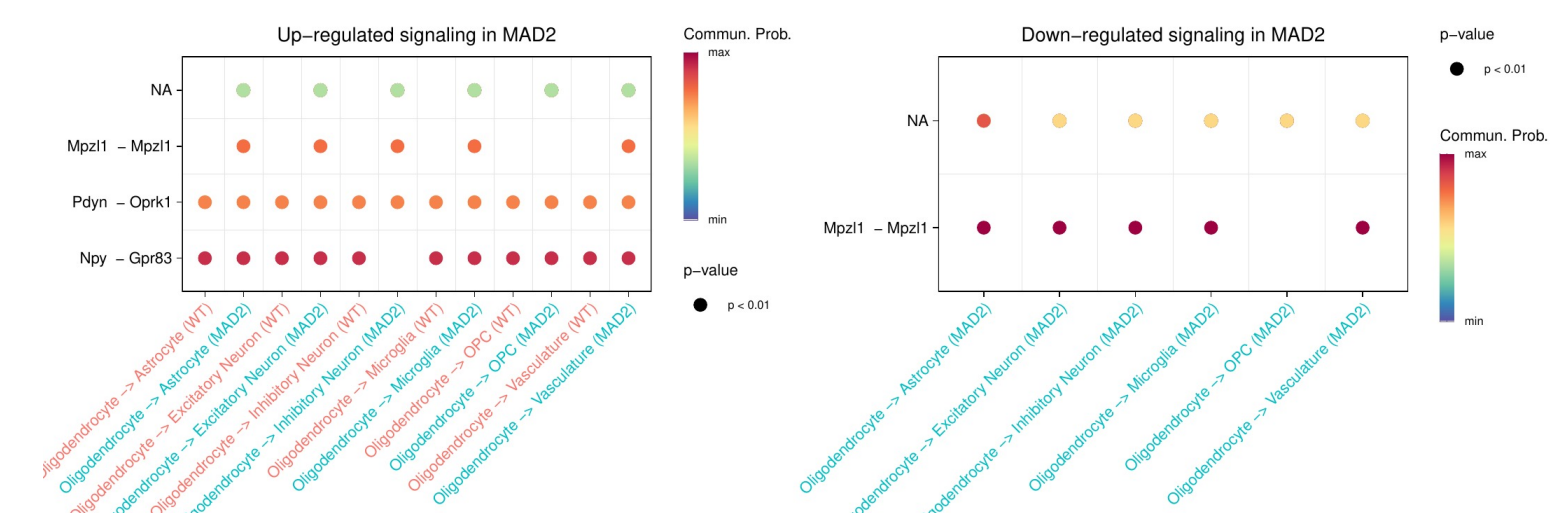
Green ODC module (adhesion / axon-guidance / myelination): **concordant in MODEL-AD2** (+0.40 / +0.52), **discordant in MODEL-AD1** (-0.43 / -0.50).

## CellChat — Network Rewiring



Cell-cell signaling, **MODEL-AD2 vs WT**, across seven cell types: total interactions rise sharply and oligodendrocytes become a central hub.

## Oligodendrocytes as Signaling Hubs



ODC → all differential signaling, **MODEL-AD2 vs WT**: up-regulated **Npy-Gpr83**, **Pdyn-Oprk1**, **Mpz11** to astrocytes, neurons, microglia, OPCs and vasculature.

## Synthesis & Implication

Four independent layers converge on one conclusion:

- DE** Oligodendrocytes are broadly remodeled in human AD.
- Concordance** MODEL-AD2 mirrors that signature; MODEL-AD1 does not.
- Co-expression** Green ODC network agrees: concordant in MODEL-AD2, not MODEL-AD1.
- CellChat** In MODEL-AD2, oligodendrocytes become active signaling hubs.

⇒ MODEL-AD2 faithfully models human-AD oligodendrocyte biology — nominating **oligodendrocyte resilience & myelin maintenance** as a translatable therapeutic axis.

## A TRANSLABLE THERAPEUTIC PATH



## POSTER WALKTHROUGH

**1** Human AD remodels oligodendrocytes (atlas + DE) → **2** MODEL-AD2 mirrors it, MODEL-AD1 does not (concordance + hdWGCNA) → **3** oligodendrocytes become signaling hubs (CellChat) → **4** a translatable model for myelin-protective therapy

Reads left-to-right as the spoken 60-second narration of the poster.

## Acknowledgements

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