

Repurposing Idiopathic Pulmonary Fibrosis Drugs To Treat Vascular Alzheimer's Dementia: A Safe, Effective and Accessible Approach to Alzheimer's Treatment

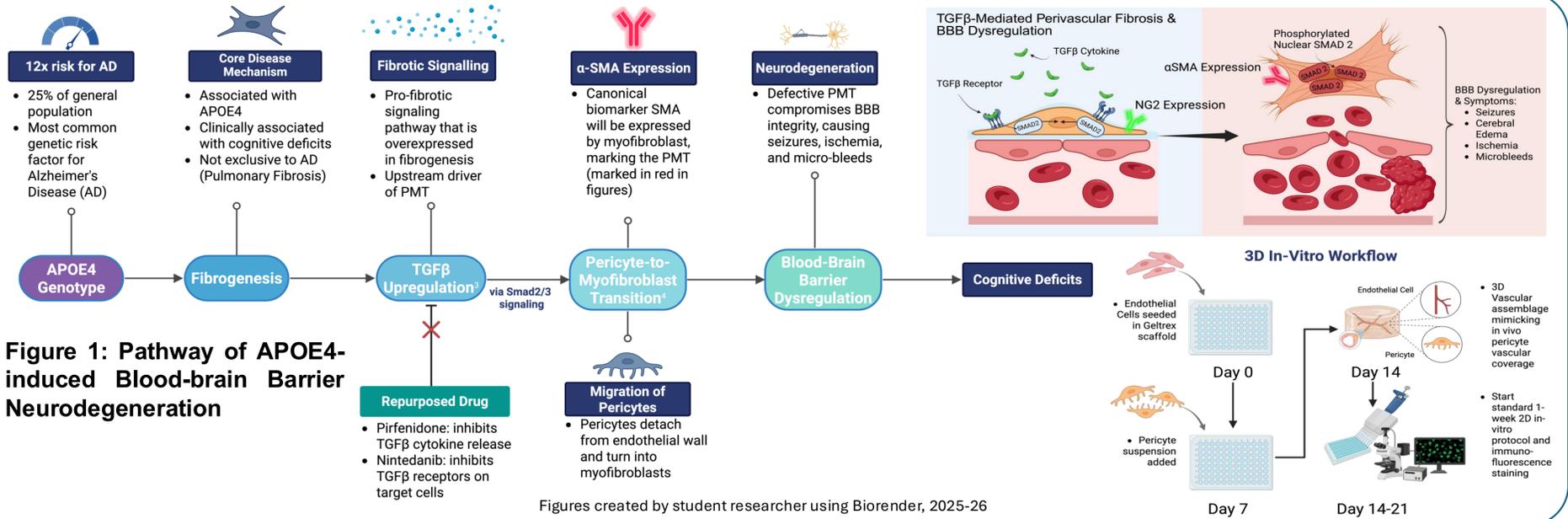


Figure 1: Pathway of APOE4-induced Blood-brain Barrier Neurodegeneration

Figures created by student researcher using Biorender, 2025-26

| Gene | Log2 Fold Change | P-value Adjusted | Annotation |
|--------|------------------|------------------|---|
| FBLN5 | 5.627431815 | 0.007224749 | Regulated by TGFβ signalling; involved in fibrosis and ECM remodelling (Kuang et al., 2006) |
| MAPK10 | 0.822401871 | 0.004255694 | MAPK Family is activated by TGFβ (Sapkota, 2013) |

Table 1. Key genes upregulated in APOE4 compared to APOE3 Genes of interest were selected from the results of the MAST analysis comparing gene expression in vascular cells with the APOE4/4 and APOE3/3 genotypes. Genes were selected based on the log-2 fold change (positive values indicate increased expression in APOE4/4 compared to APOE3/3) and the adjusted p-value, with priority being placed on genes with a large log-2 fold change and small p-value.

Figure created by student researcher using Excel and Rstudio 2025

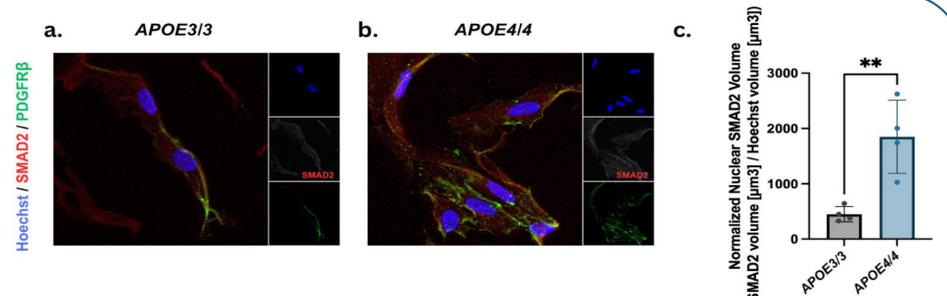


Figure 2. TGFβ signalling is upregulated in pericytes with the APOE4/4 genotype.

A-B) Immunofluorescent confocal microscopy images of APOE3/3 and APOE4/4 pericytes. Pericytes were stained for nuclear markers (Hoechst), SMAD2, and PDGFRβ, a canonical pericyte cell marker. C) Graphical comparison of nuclear SMAD2 in APOE3/3 and APOE4/4 pericytes. Two-tailed Student's t-test was performed and p = 0.0061. Error bars represent ±SD.

Figure created by student researcher using ImageJ, Prism 10, and Canva 2025

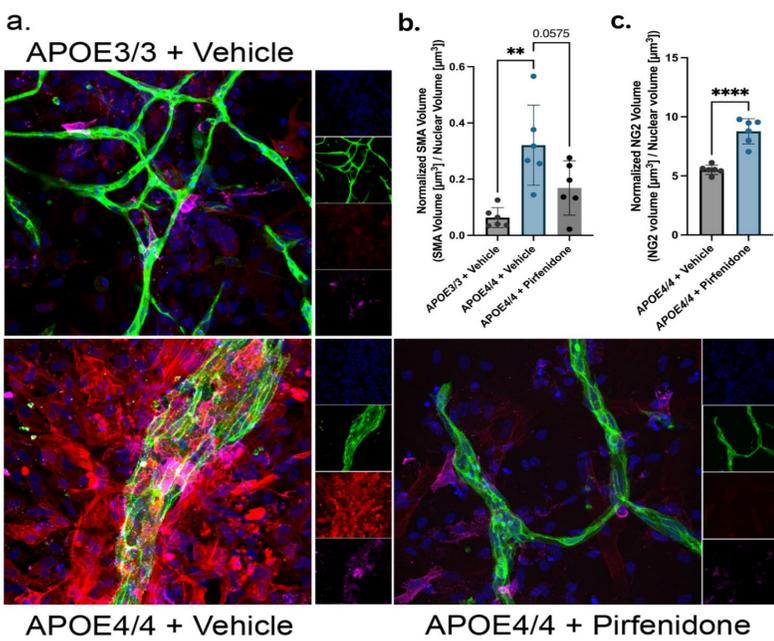


Figure 3. Pirfenidone rescues fibrotic phenotype in APOE4/4 3D endothelial-pericyte co-cultures. A) Pericytes stained for Hoechst nuclear marker, αSMA, PECAM endothelial cell marker, and NG2 pericyte cell marker. B) Graphical representation of mean SMA intensity that has been normalized against the average of the control group (mean volume intensity of experimental group/mean volume intensity of control group). A two-tailed two-way ANOVA with Tukey's multiple comparisons was used to determine the p-values. Figure created by the student researcher using Prism 10, Canva, and ImageJ 2025.

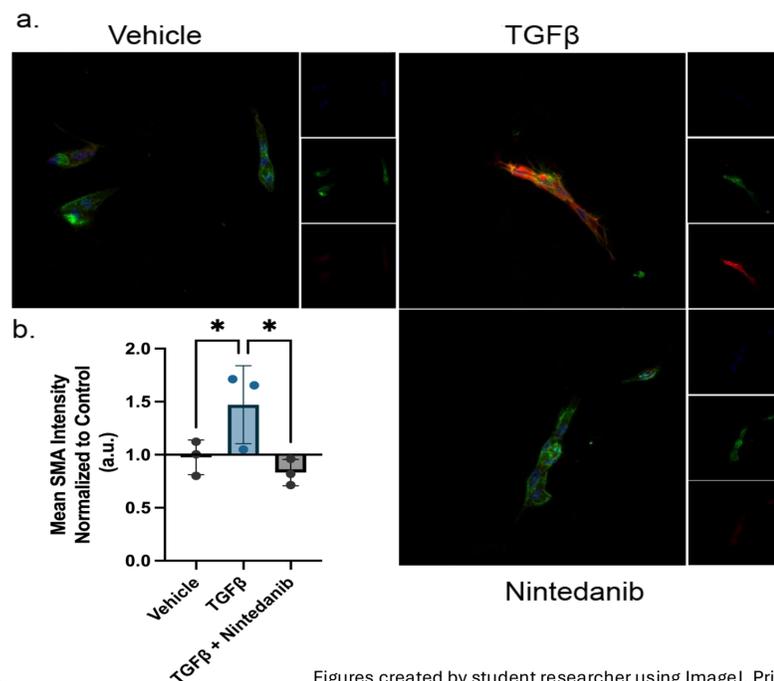


Figure 4. Nintedanib reduces fibrotic phenotypes in pericyte monoculture. A) Pericytes stained for Hoechst nuclear marker, αSMA, and NG2 pericyte cell marker. B) Graphical representation of mean SMA intensity that has been normalized against the average of the control group (mean volume intensity of experimental group/mean volume intensity of control group). A two-tailed two-way ANOVA with Tukey's multiple comparisons was used to determine the p-values. Figure created by the student researcher using Graphpad Prism, Canva, and ImageJ 2025.

Figures created by student researcher using ImageJ, Prism 10, and Canva 2025

Key Takeaways: Pirfenidone and Nintedanib drugs open up a new path for treating BBB-dysregulation driven AD

Nintedanib, an FDA approved drug for IPF, reduced SMA expression, a biomarker of fibrosis and BBB dysregulation, suggesting that it could be a viable option for treating BBB dysregulation in the context of APOE4 genotype

Pirfenidone, an FDA approved drug for IPF, not only reduced SMA expression in APOE4 endothelial-pericyte co-cultures, suggesting that pirfenidone can rescue APOE4-induced BBB dysregulation in the context of AD

Success of repositioned FDA-approved drugs meaningful because they are less costly (8.4 M vs 1.3B) and approved sooner compared to de novo drugs, which is essential given that low household income consistently ranks as a top 3 leading cause of AD both among APOE4 carriers and non carriers

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Leon Wang