

Multi-omics Profiling of Aducanumab-induced Changes in Brain, CSF, and Plasma of 5XFAD Mice Highlights Mechanistic Benefits And Risks

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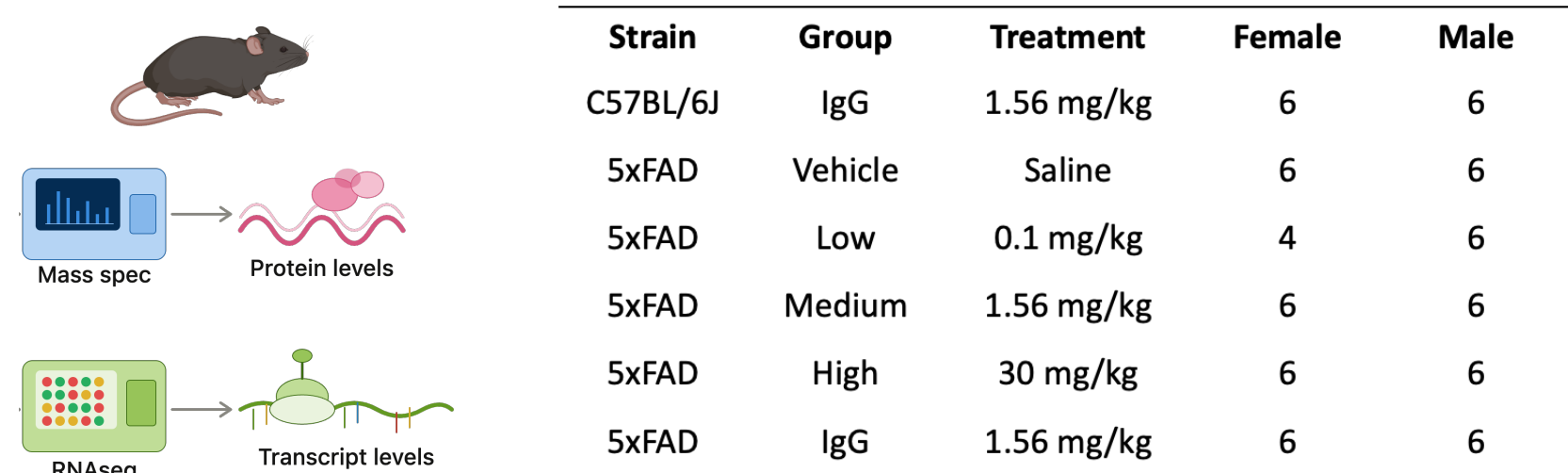
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OBJECTIVE

The emergence of anti-amyloid therapies has heightened interest in their broader pharmacodynamic effects within the brain and peripheral biomarker profiles. Mechanistic studies using multi-omics approaches are essential to dissect treatment effects at the molecular level. Improving the predictive validity of preclinical Alzheimer's disease (AD) models is critical for evaluating therapeutic safety and efficacy, including sex-specific responses. Furthermore, understanding the brain molecular landscape after amyloid clearance remains a priority, as disease progression and cognitive decline persist despite plaque reduction. In the present study, we examined molecular signatures associated with amyloid lowering by aducanumab and explore their translational implications.

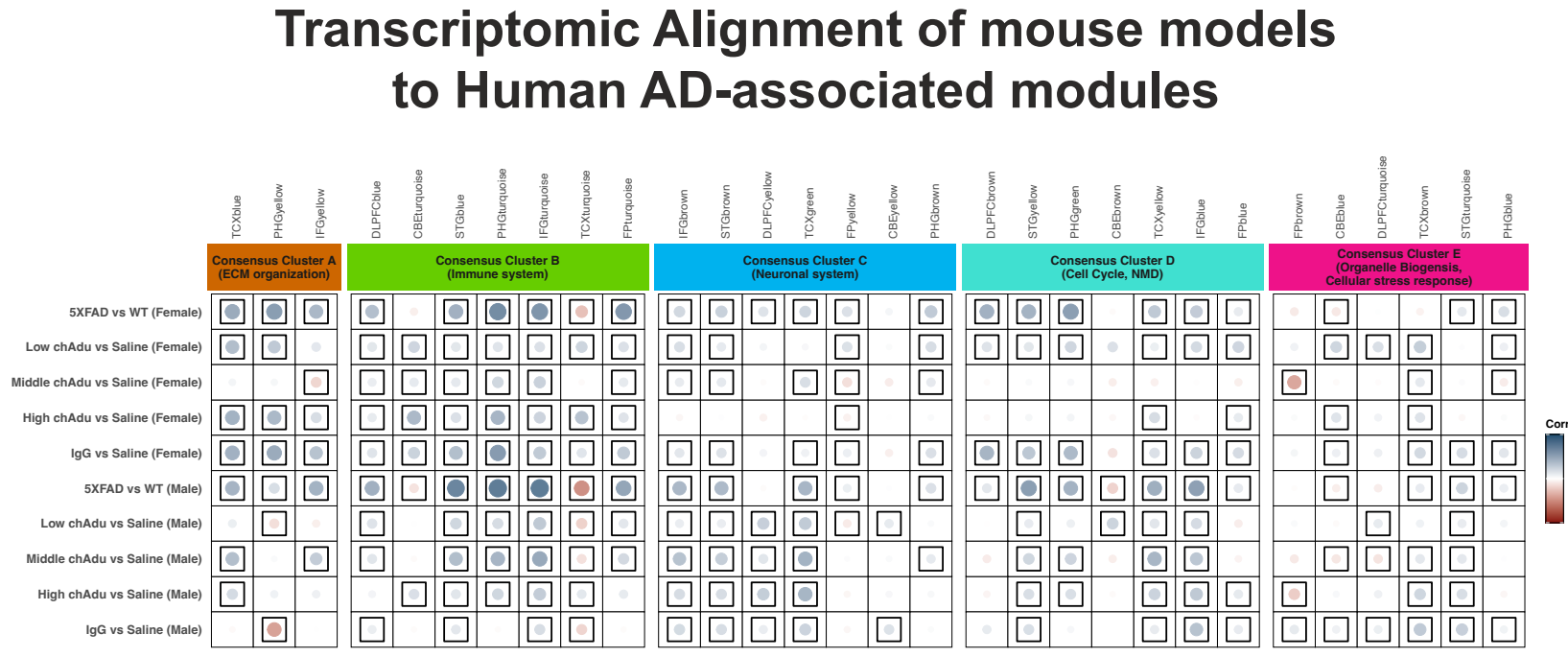
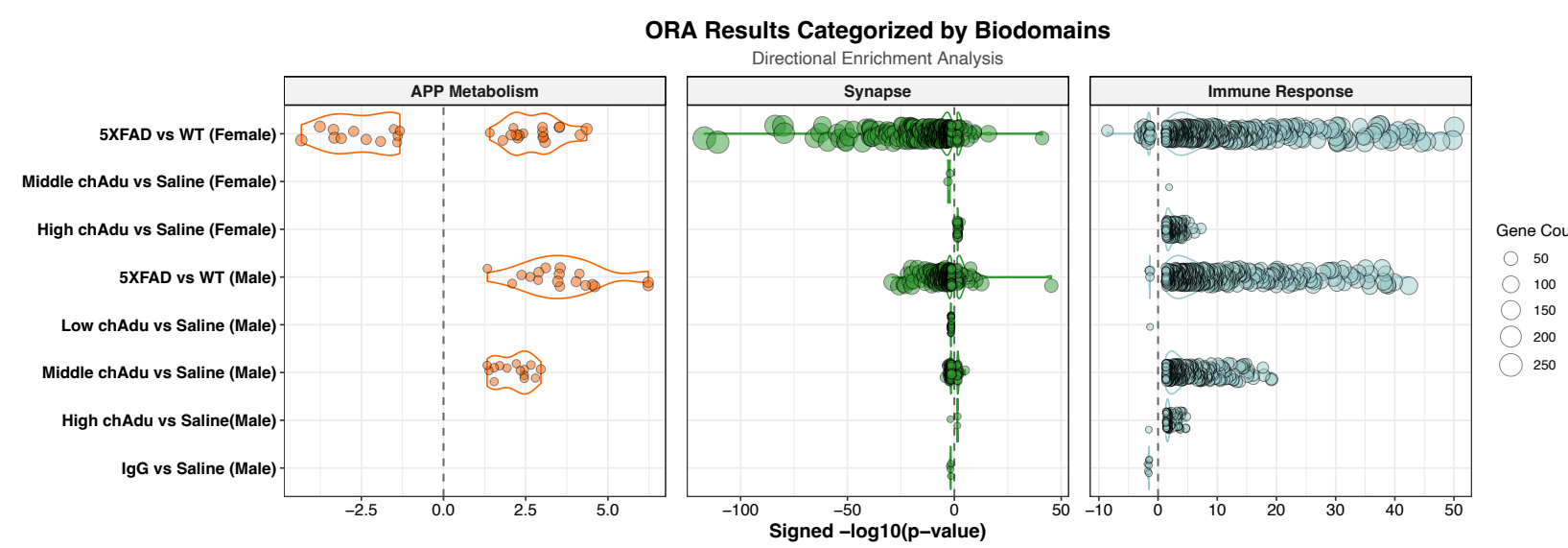
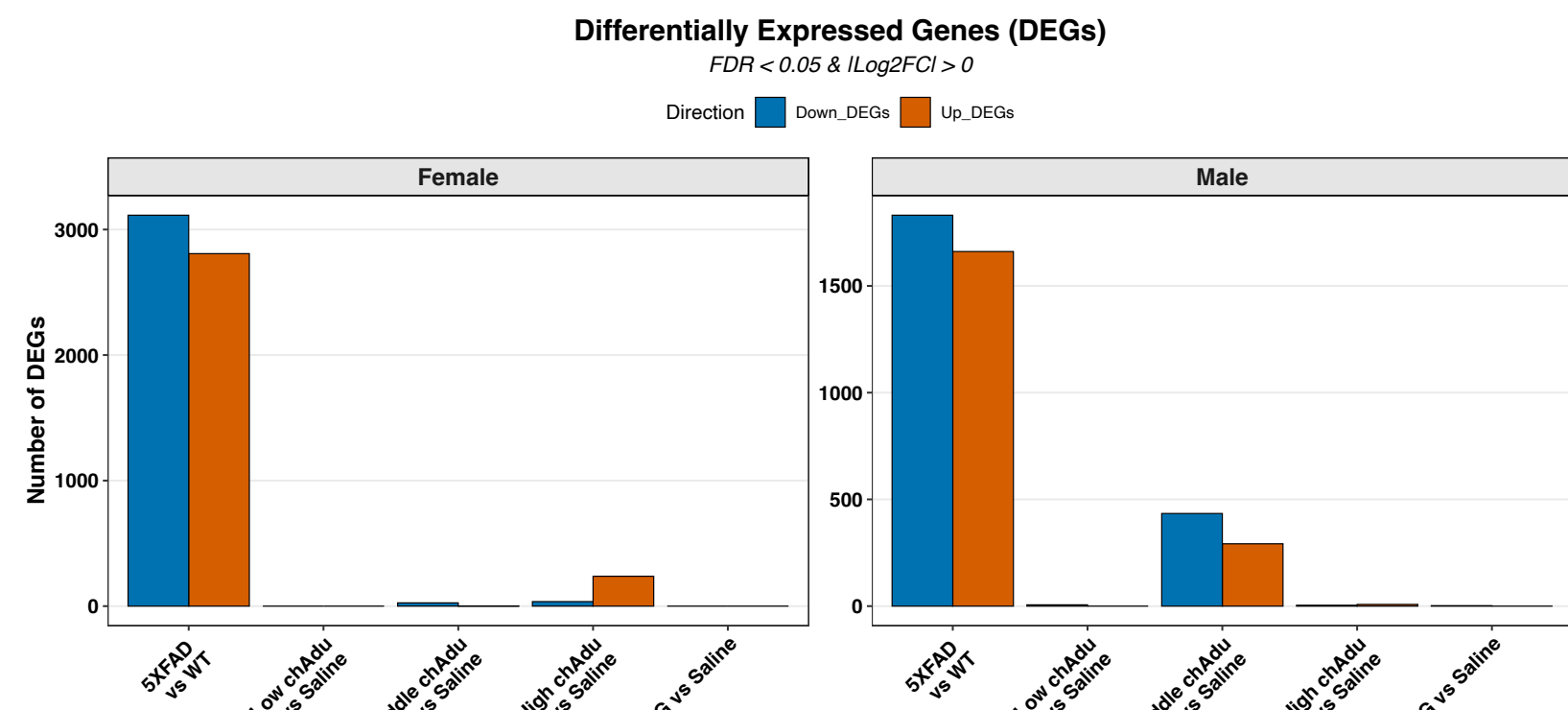
METHODOLOGY

Male and Female 5XFAD mice were treated weekly with murinized aducanumab (chAdu) beginning at 8 months of age and compared to sex-matched murine treated with saline and IgG2ak isotype (IgG) controls. Post-treatment, transcriptomic (bulk RNA-seq) and proteomics analyses (with TMT mass spectrometry, DIA mass spectrometry and Alamar NULISA) were performed on homogenized brain tissue, cerebrospinal fluid, and plasma to assess molecular pathways associated with chAdu and IgG exposure following 17-week treatment.



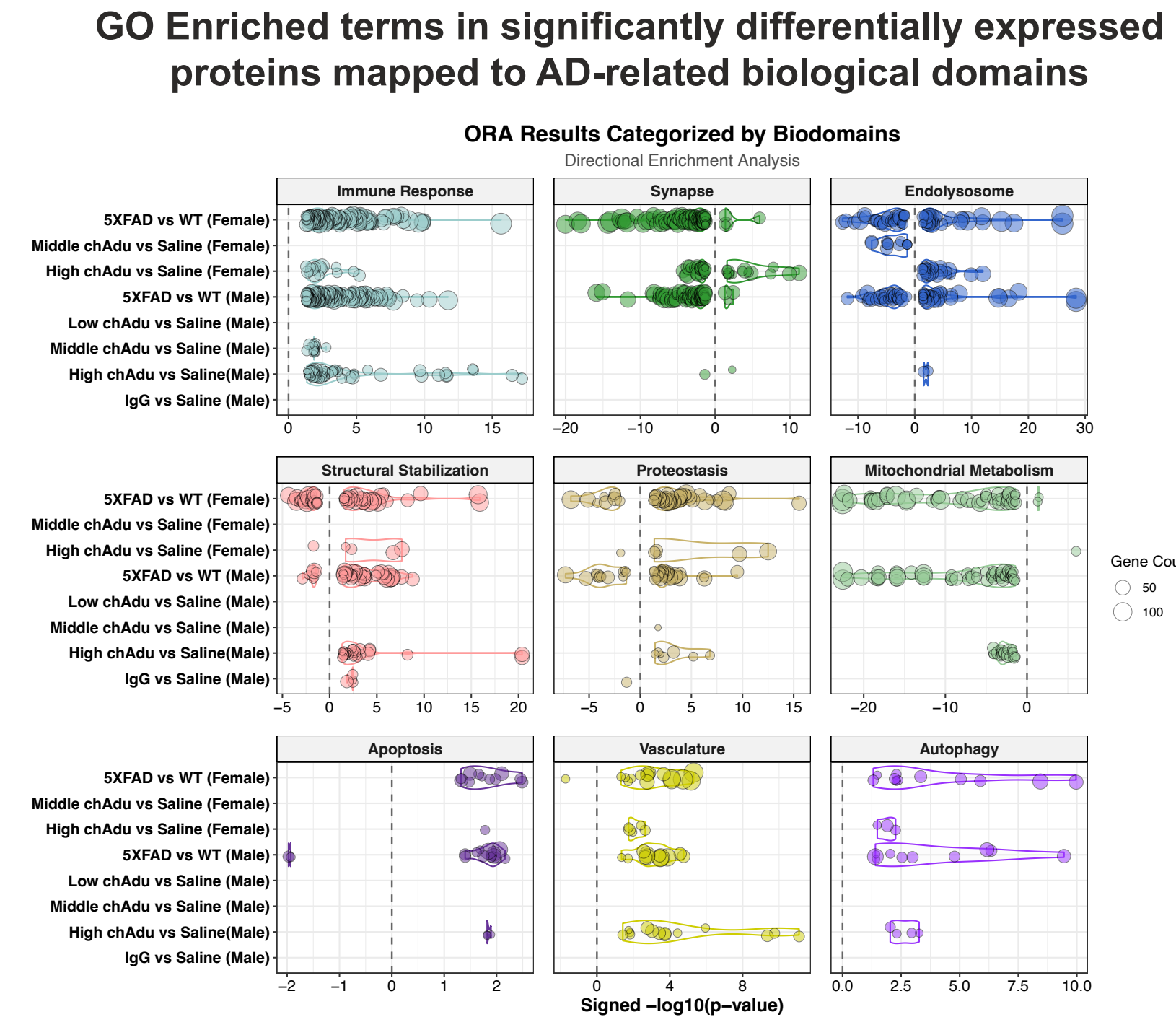
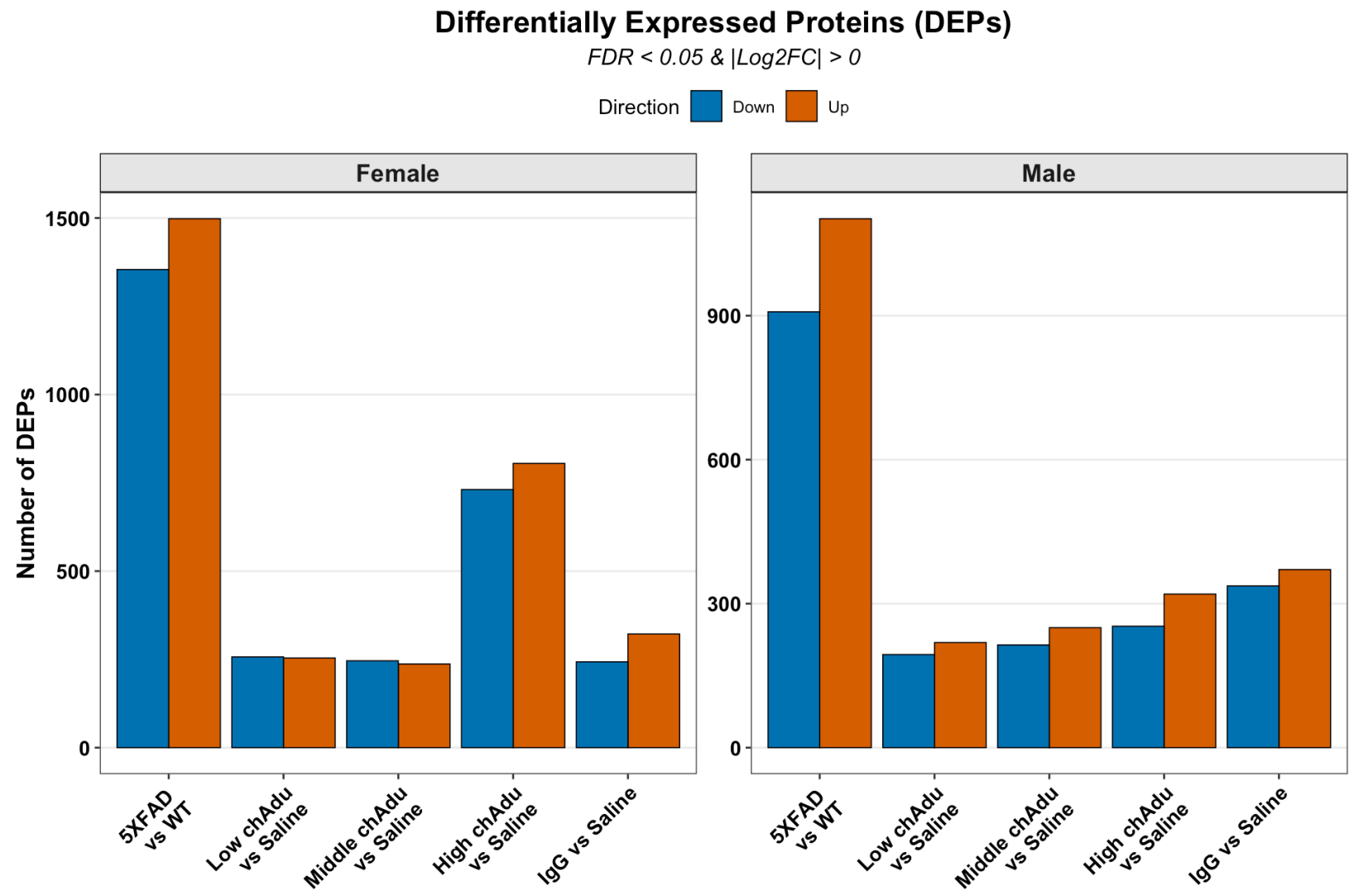
We compared molecular alterations in 5XFAD mice with those seen in human Alzheimer's disease [1-4] and assessed how aducanumab treatment mitigated these changes in the mouse model. Finally, we utilized AD biological domains [5] developed by Emory/Sage/SGC/JAX (<https://treatad.org/emory-sage-sgc/>) TREAT-AD Center to categorized enriched GO terms into biological domains.

BRAIN TRANSCRIPTOMICS

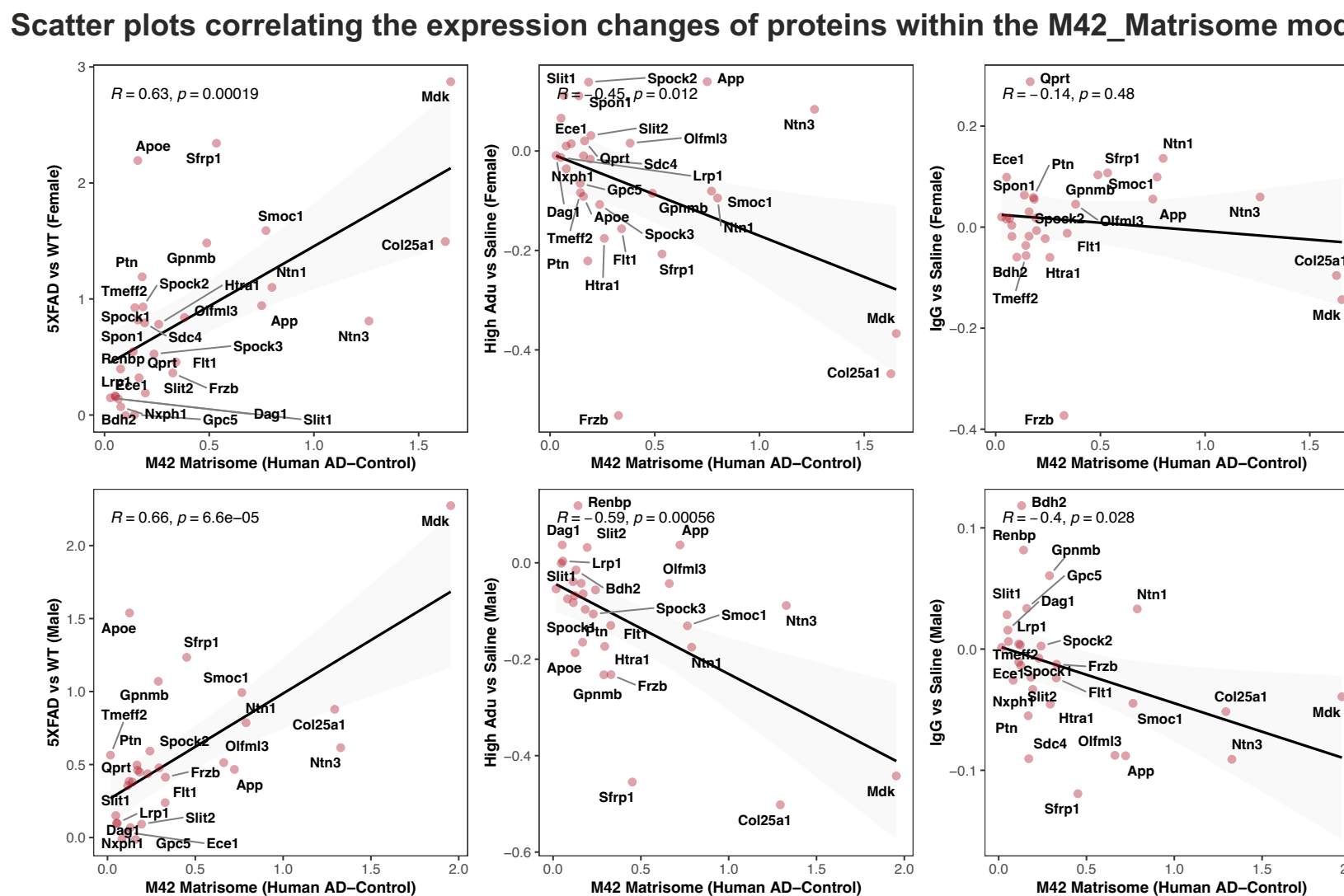
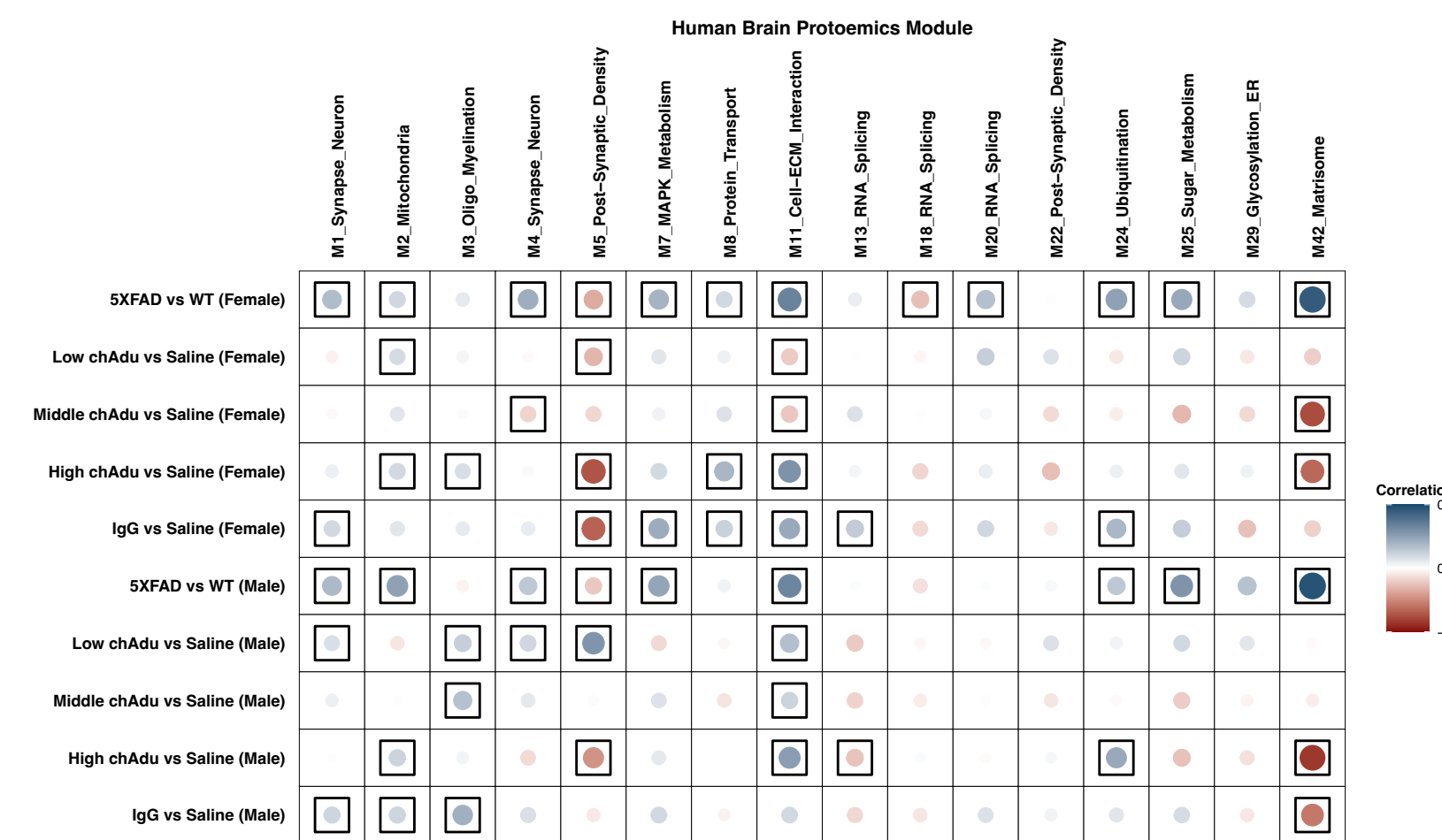


We observed very limited beneficial responses in AD-associated gene modules; increased neuroinflammation, especially in female mice.

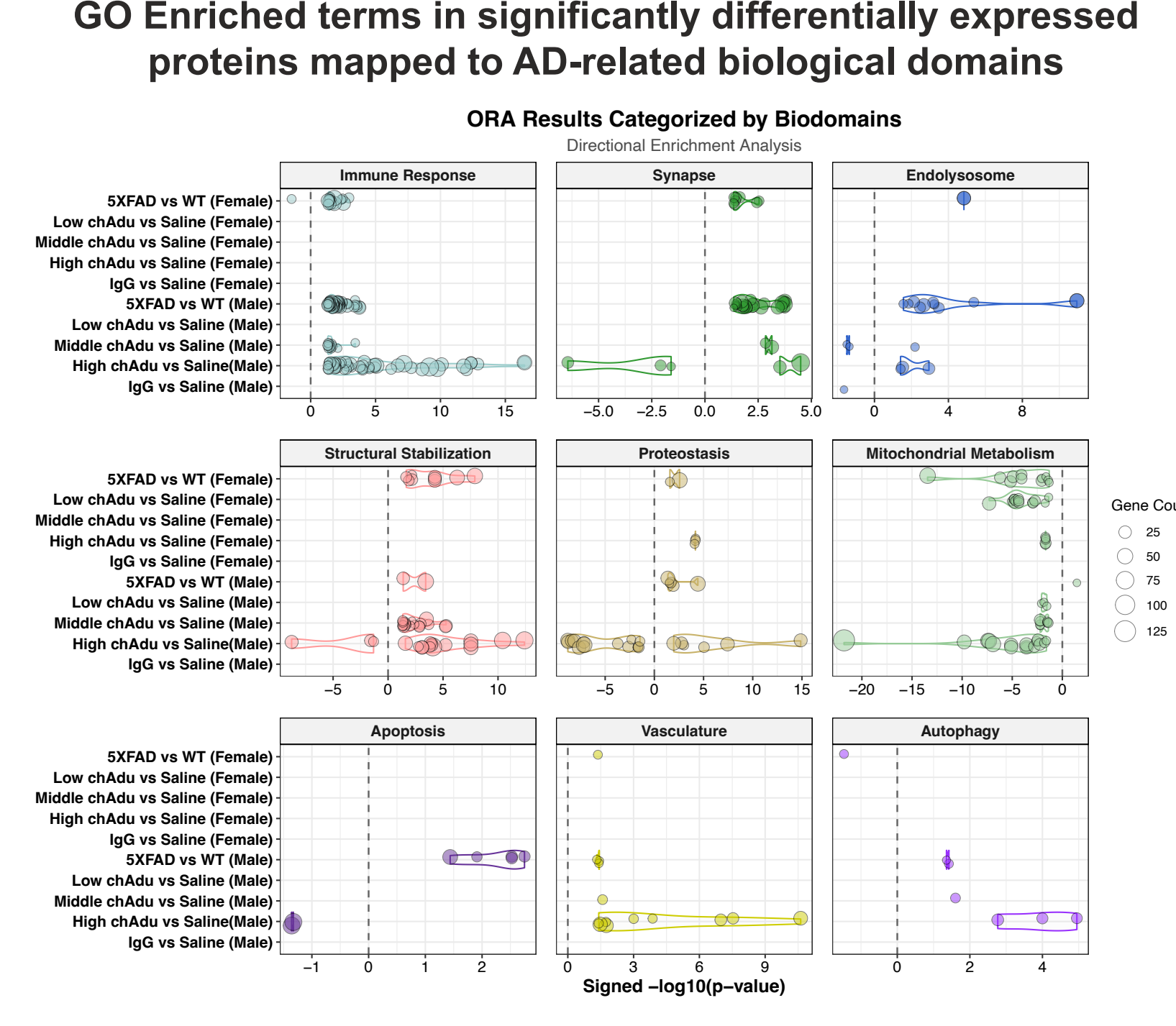
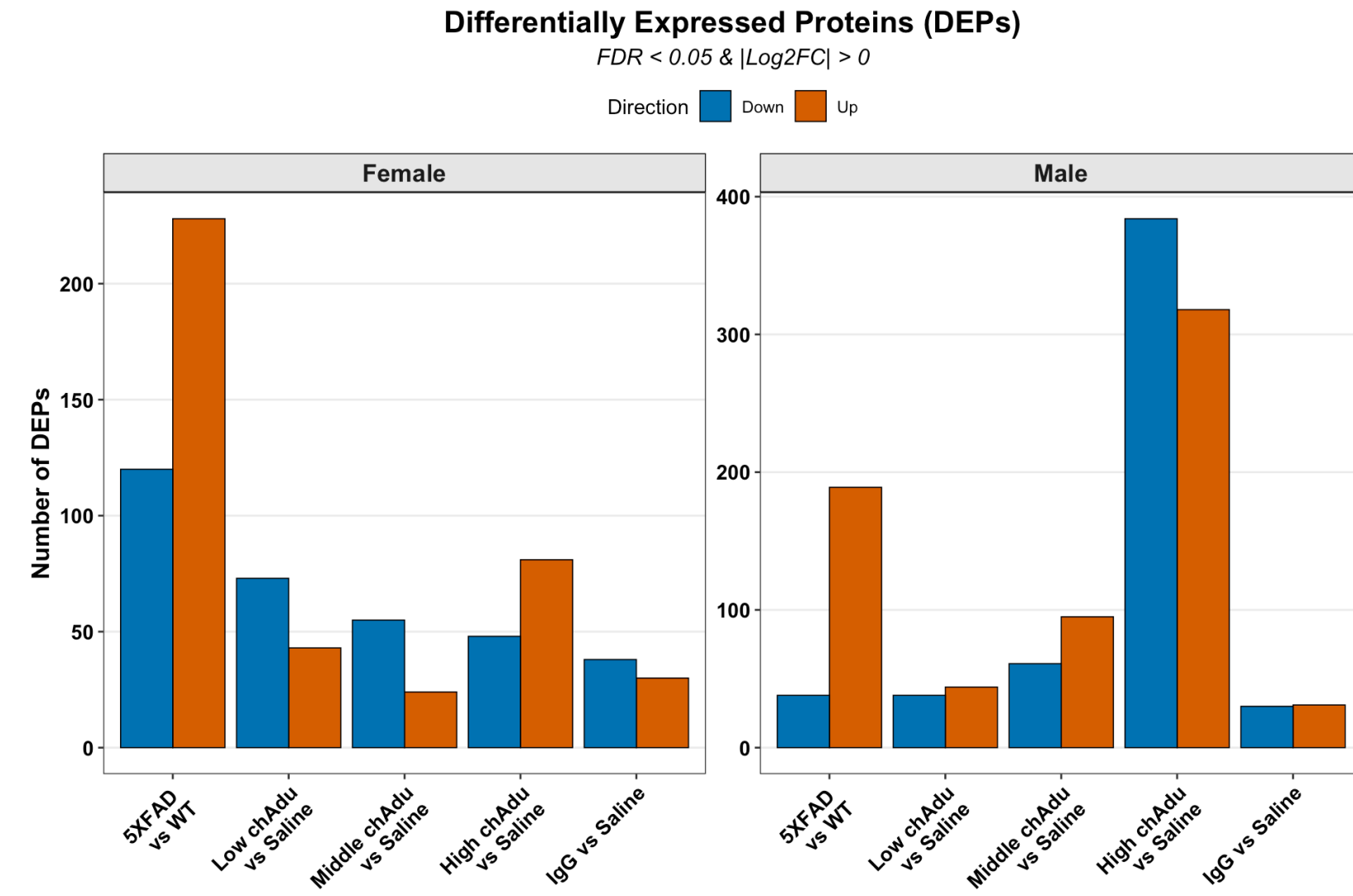
BRAIN TMT PROTEOMICS



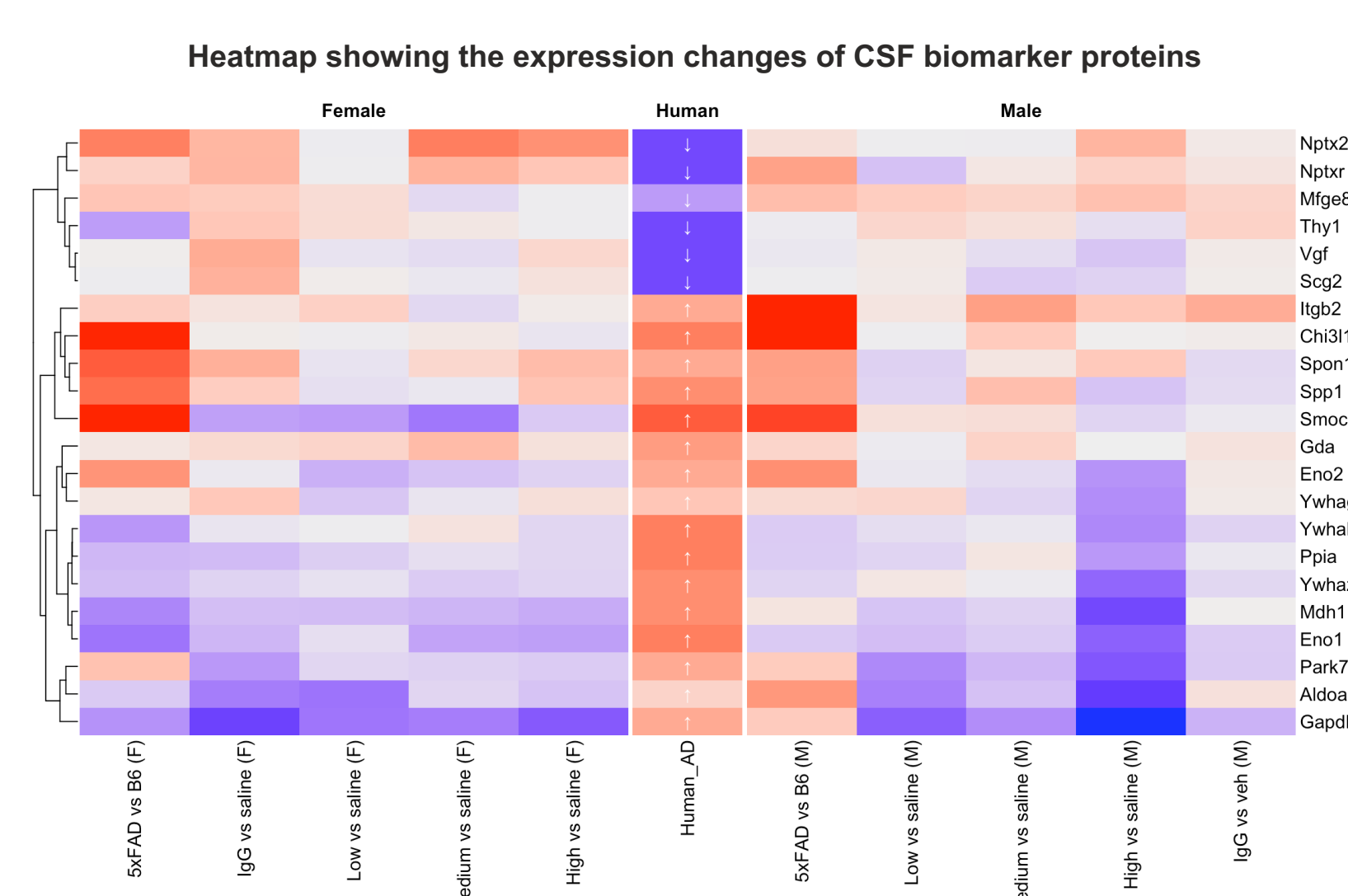
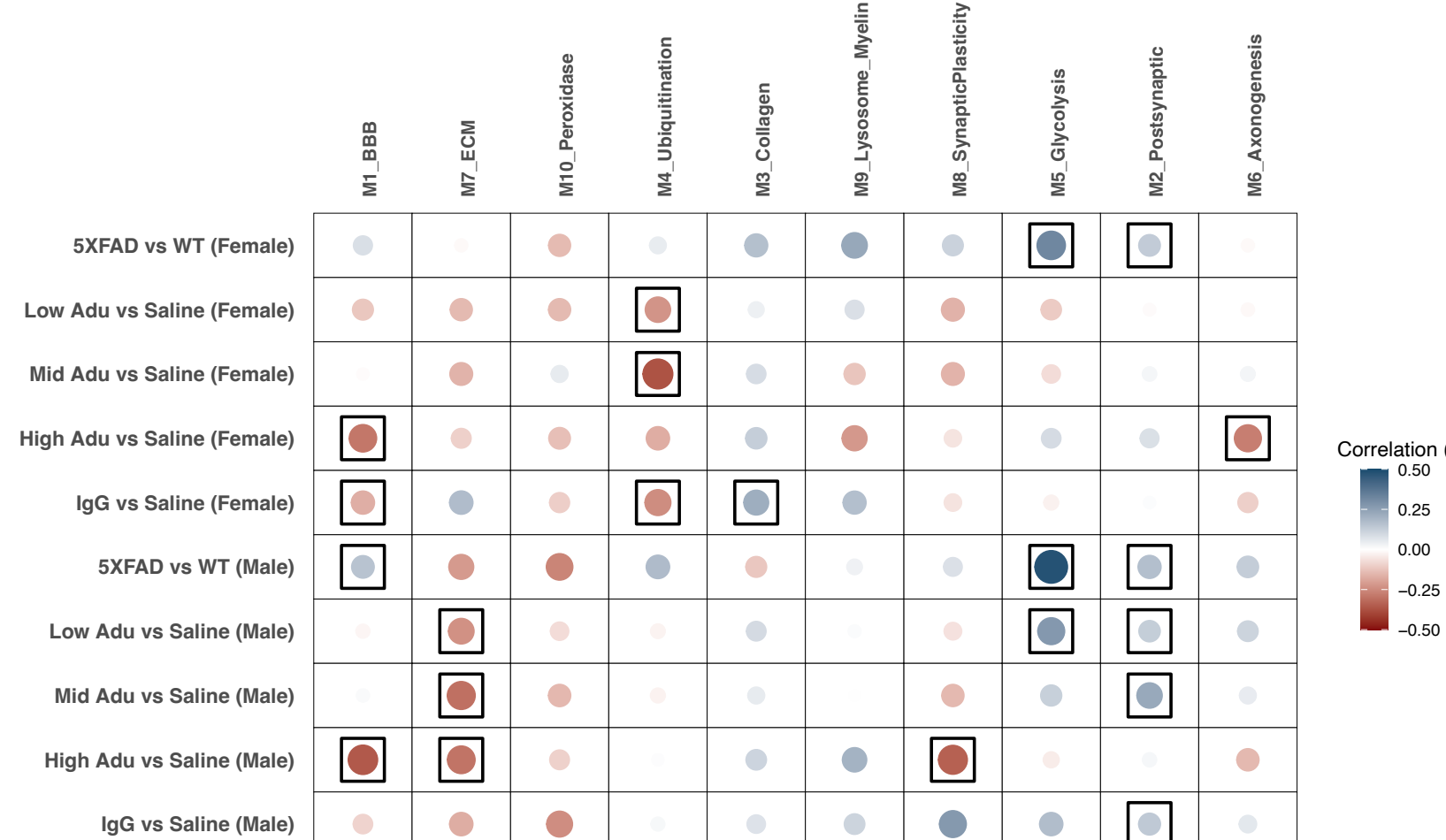
Proteomics Alignment of mouse models to AD-associated Human Brain Proteomics Modules



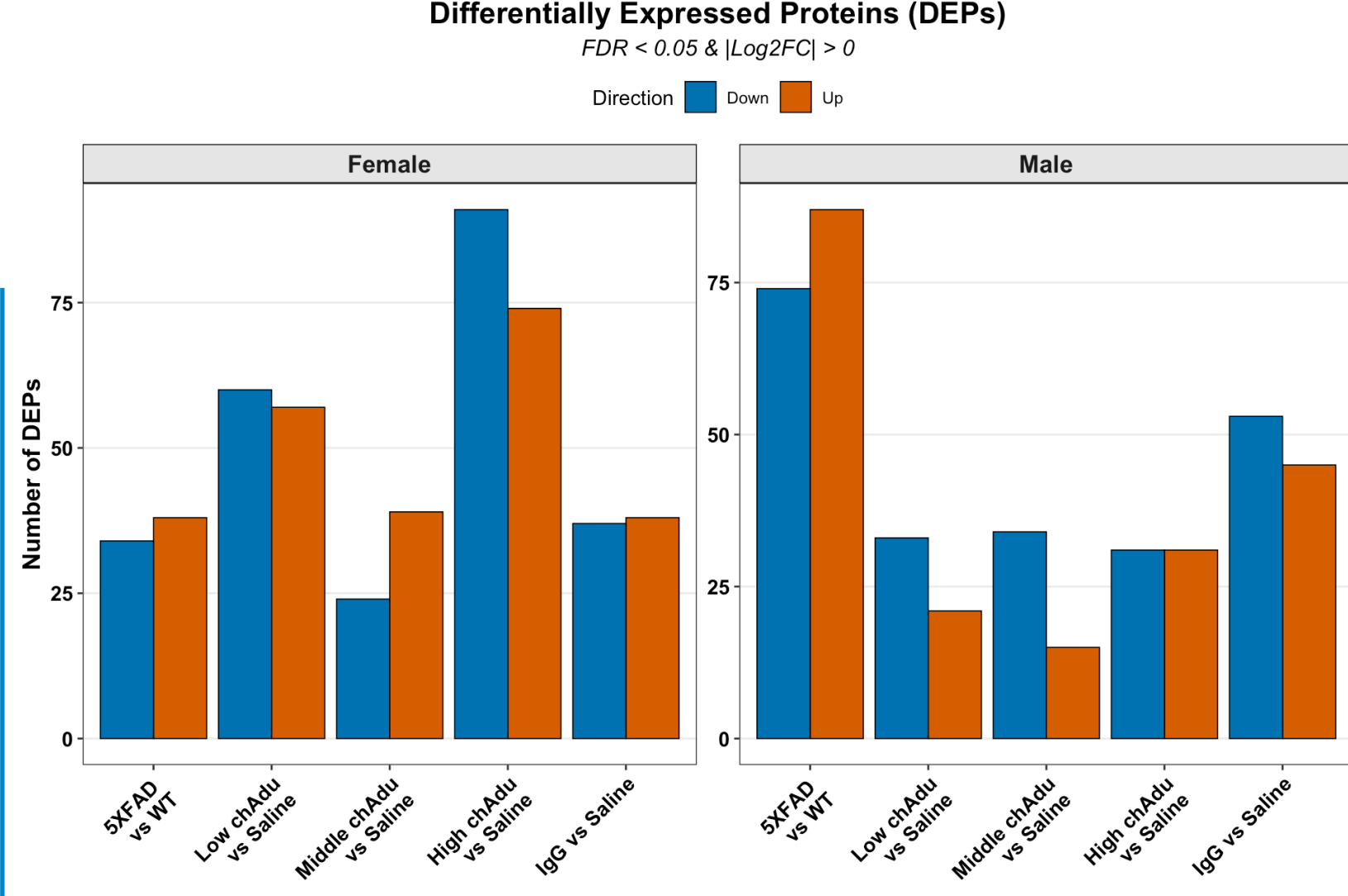
CSF DIA PROTEOMICS



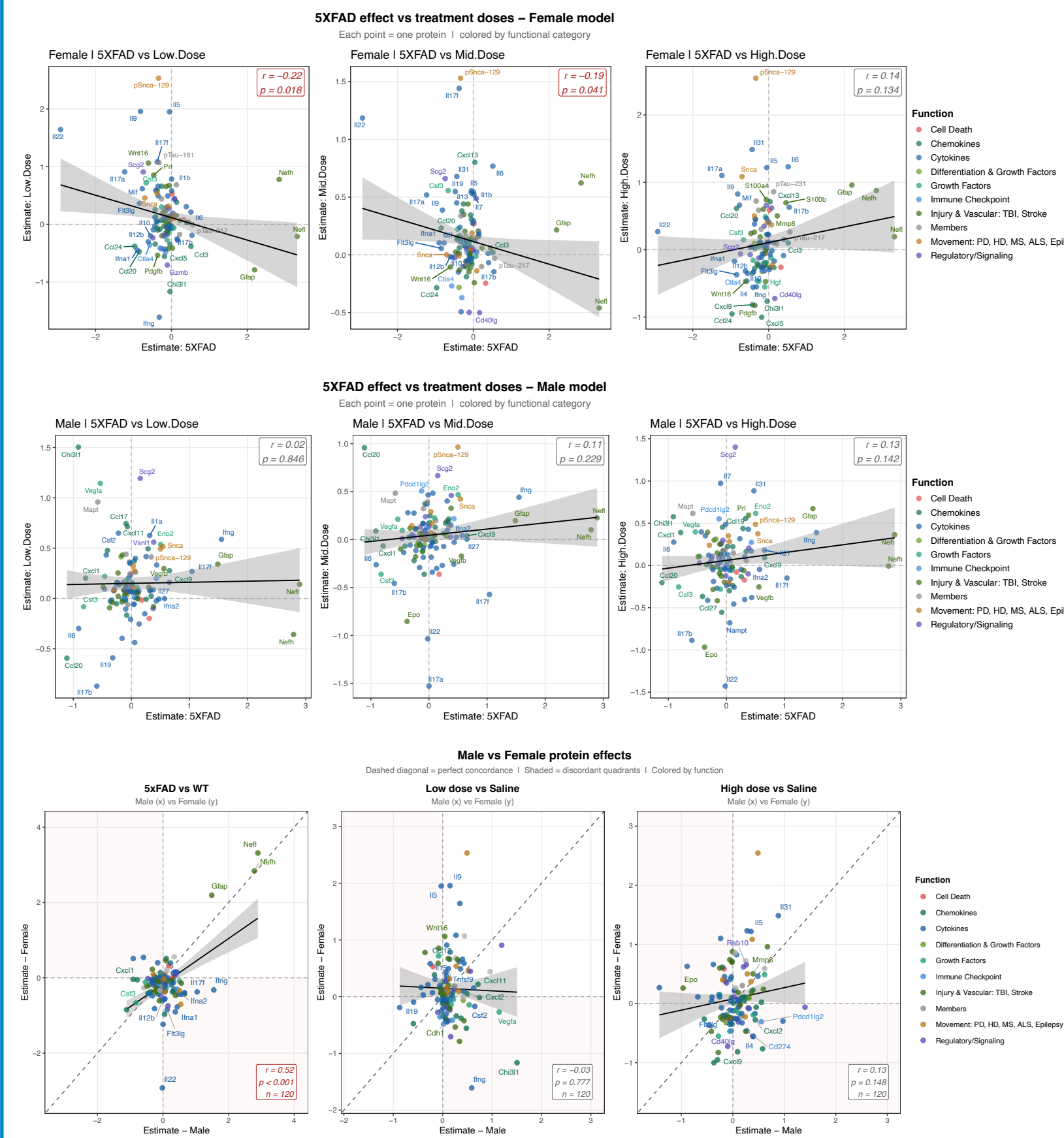
Proteomics Alignment of mouse models to AD-associated Human CSF Proteomics modules



PLASMA DIA PROTEOMICS



PLASMA ALAMAR MOUSE NULISA™ 120 PANEL



SUMMARY

- This study identified the molecular signatures that remain dysregulated even after amyloid clearance.
- Brain proteomes show reduction in amyloid-associated ECM and Matrisome modules after ADU treatment.
- CSF proteomes are not well modeled by 5XFAD, but ADU reverses AD-associated blood-brain barrier signal.
- Plasma Alamar NULISA™ panel shows sex-specific reversal of 5XFAD signatures.
- However, off-target changes across compartments indicate potential risks, emphasizing the need to balance therapeutic benefits with mechanistic liabilities and to consider sex as a critical variable in Alzheimer's disease treatment strategies.

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Acknowledgements

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