



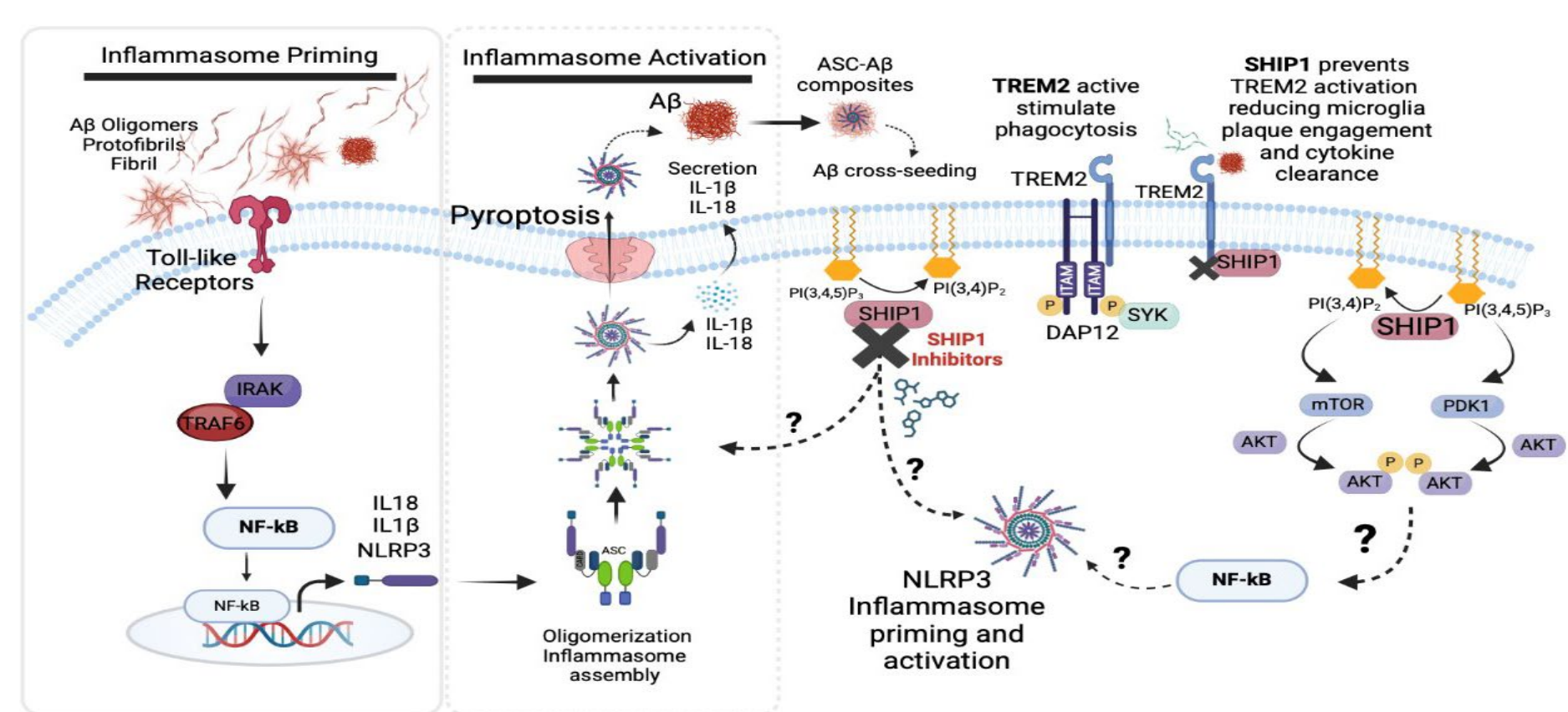
Pharmacodynamic gene and pathway profiling of INPP5D modulation across models

Roma Matharu¹, Disha M. Soni, PhD², Peter Lin, PhD², Isaac H Caballero-Floran, PhD², Bruce T. Lamb, Ph.D^{2,3}, Claudia Rangel-Barajas, PhD², Adrian L. Oblak, PhD^{2, 4}

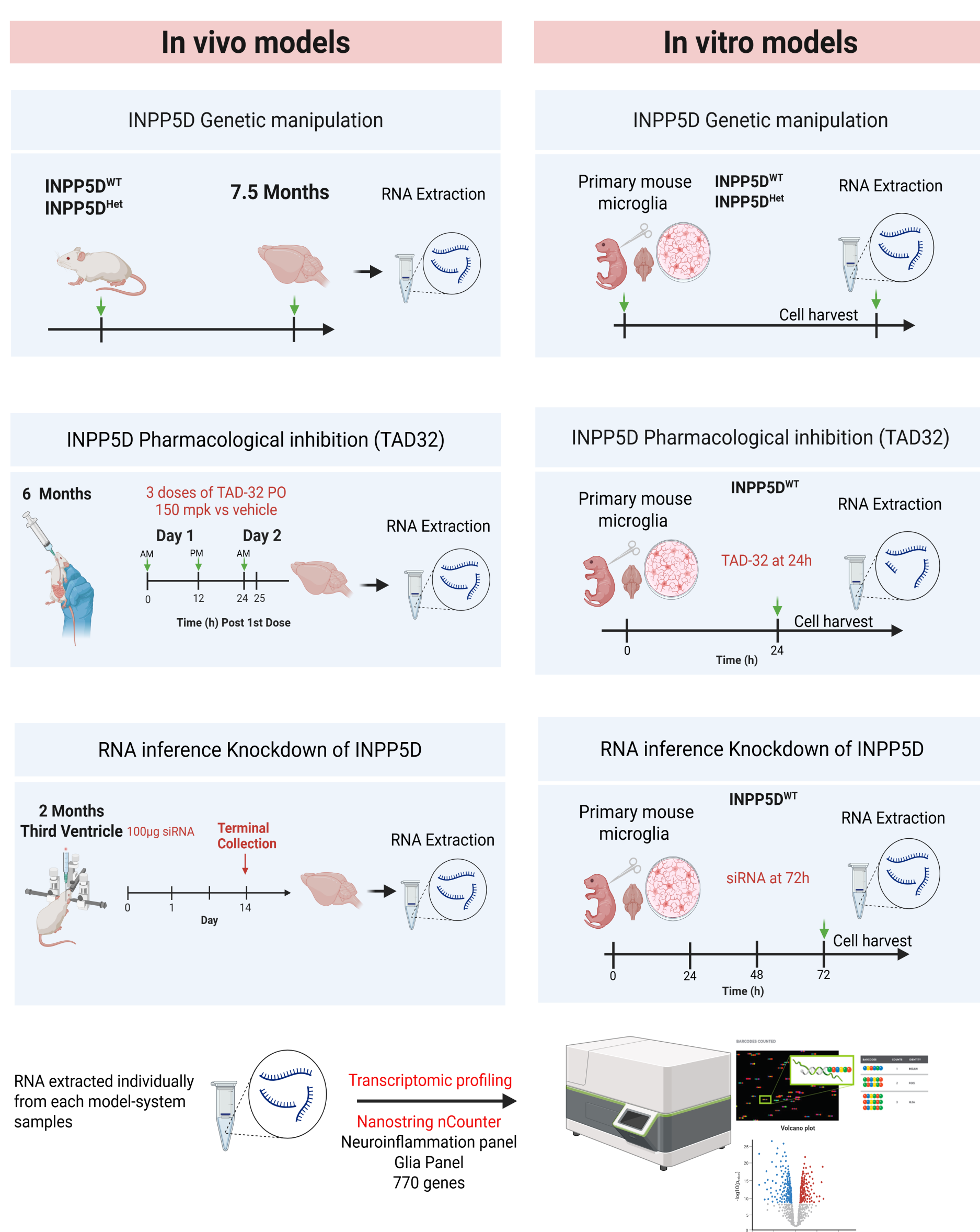
¹Indiana University School of Medicine, ²Indiana University School of Medicine, Stark Neuroscience Research Institute, ³Indiana University School of Medicine, Department of Medical and Molecular Genetics, ⁴Indiana University School of Medicine, Department of Radiology & Imaging Sciences

Background

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by amyloid- β plaques and tau tangles, with microglia playing a critical role in response to these pathologies. INPP5D, a phosphatase, is a significant immune response regulator specific to microglia in the brain. INPP5D inhibition has been found to enhance microglial function, but the consistency of transcriptional alterations across different experimental models remains unclear. **We aim to define conserved gene expression and pathway-level responses across *in-vivo* and *in-vitro* models, which can help guide therapeutic development targeting INPP5D inhibition.**



Materials & Methods



Results

INPP5D inhibition in *in-vivo* models show shared pathways despite distinct differential gene alteration profiles

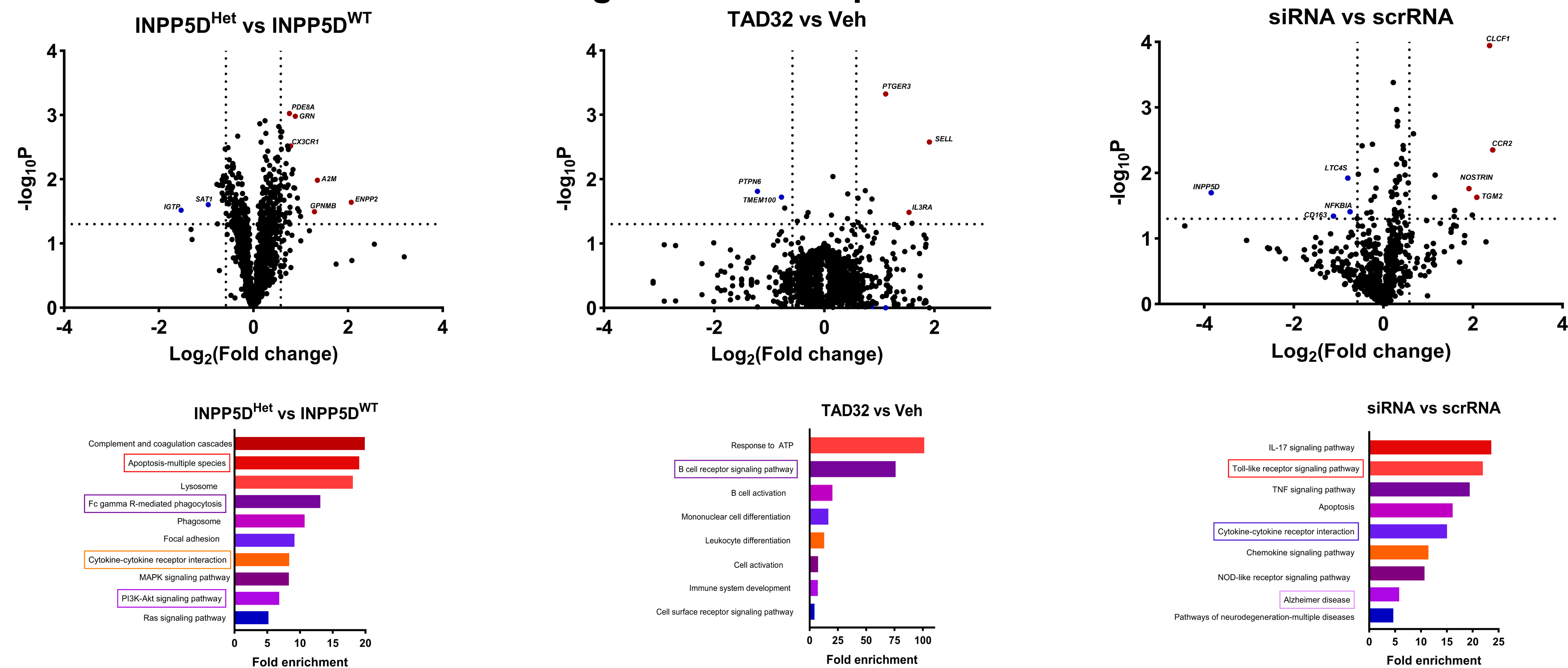


Figure 1. Each volcano plot represents differentially expressed genes (DEGs) among *in-vivo* models. Above, left to right respectively: INPP5D^{Het} vs. INPP5D^{WT} glial panel, TAD32 vs. Vehicle, siRNA vs. scramble RNA. Each line graph below, left to right, represents enriched biological processes found within *in-vivo* models with respect to the volcano plots above from left to right.

Microglia – specific inhibition of INPP5D models show distinct transcriptomic profile but shared immune pathways overlap with *in-vivo* models

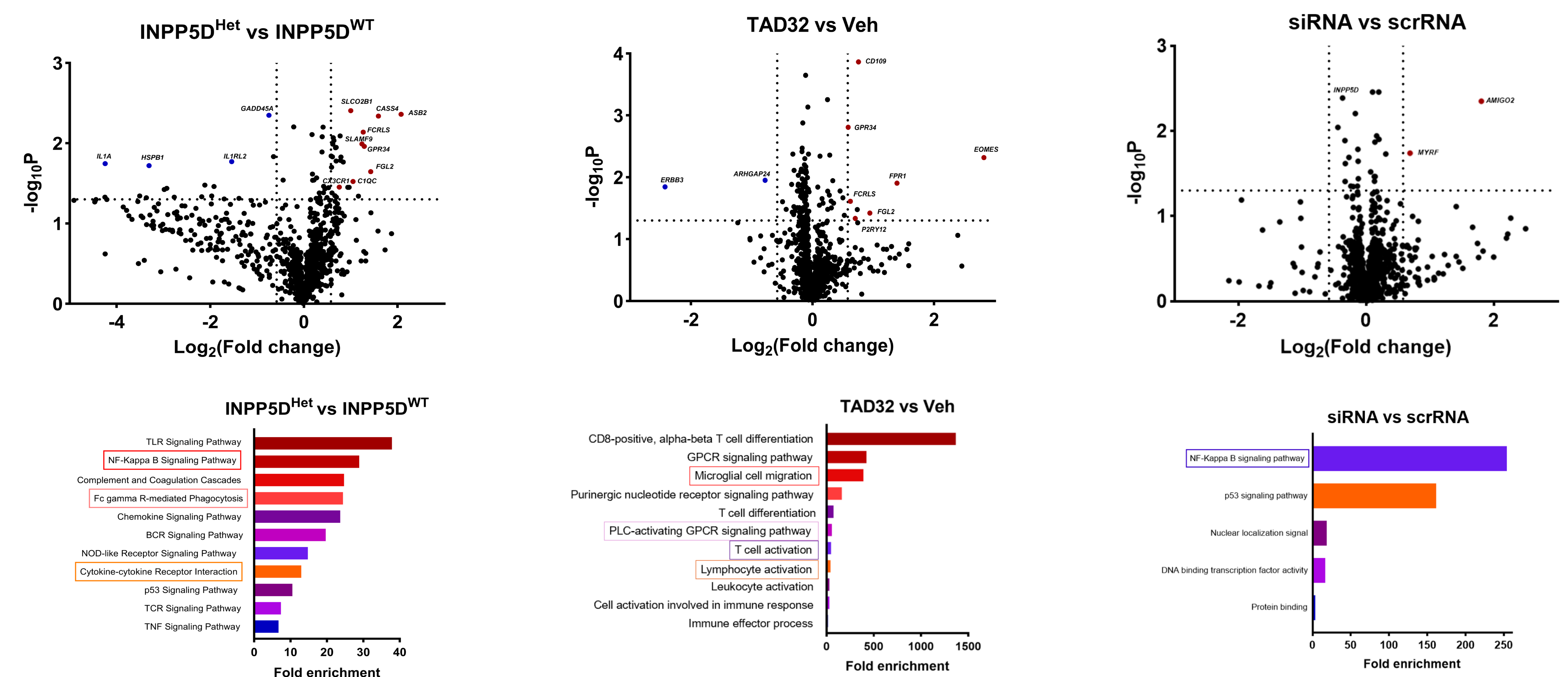


Figure 2. Each volcano plot represents DEGs among *in-vitro* models. Above, left to right respectively: INPP5D^{Het} vs. INPP5D^{WT}, TAD32 vs. Vehicle, siRNA vs. scramble RNA. Each line graph below, left to right, represents enriched biological processes found within *in-vitro* models with respect to the volcano plots above from left to right.

Results

Gene overlap across INPP5D-targeted models

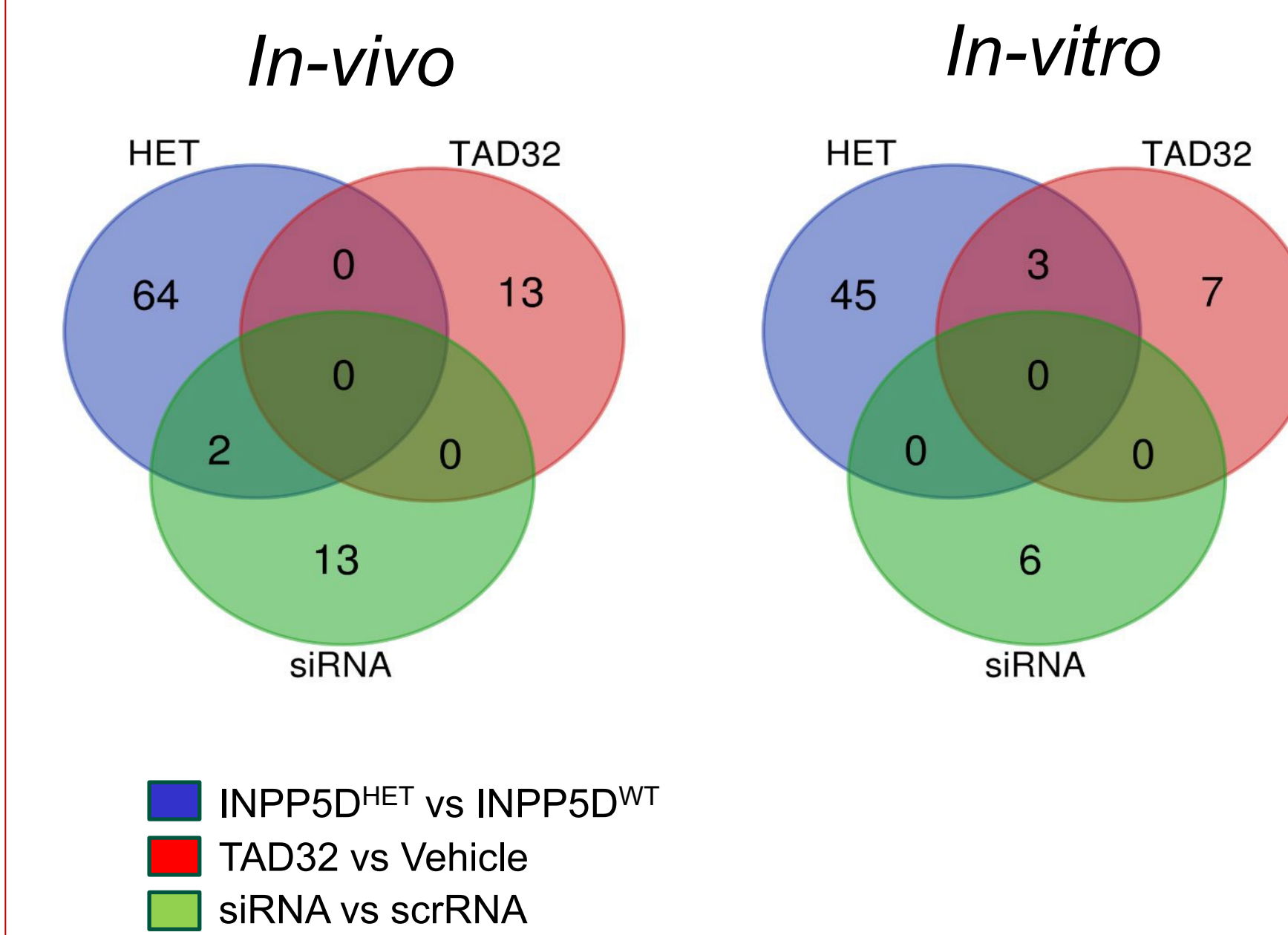


Figure 3. Both Venn diagrams show DEG overlap between INPP5D^{Het}, TAD32, and siRNA in *in-vivo* studies (common genes: TGM2, NOSTRIN) and *in-vitro* studies (common genes: FGL2, FCRL5, GPR34).

Summary

- Despite limited overlap in individual DEGs across INPP5D-targeted models, there is robust convergence of key biological pathways, including phagocytosis, immune modulation, and PI3K/AKT signaling which highlights a conserved functional response to INPP5D inhibition.
- Furthermore, the consistent activation of immune-related pathways across genetic (INPP5D^{Het}), pharmacological (TAD32), and loss-of-function (siRNA) animal models underscores a shared pharmacodynamic signature. This alignment supports the translational potential of both small-molecule and gene-silencing approaches in modulating INPP5D-related neuroimmune signaling.

Future Directions

- Systematically validate key pathway markers across diverse INPP5D models, both in the presence and absence of Alzheimer's pathology, to delineate context-dependent molecular signatures.
- Leverage these mechanistic insights to inform the development of more precise, stage-specific therapeutic strategies targeting INPP5D-related pathways in neurodegenerative disease.

Acknowledgements

This project was funded, in part with support from MODEL-AD U54AG054345 and TREAT-AD U54AG065181 from Monument Biosciences.