# Defining Pharmacodynamic Gene Markers and the Biological Processes of INPP5D Modulation Across Experimental Models

**Roma Matharu[1],** Disha Soni[2], Peter Lin[2], Isaac Caballero-Floran[2], Bruce Lamb[2,3], Claudia Rangel-Barajes[2], Adrian Oblak[2,4]

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

## Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by the accumulation of extracellular amyloid-β plaques and intracellular neurofibrillary tau tangles. Microglia respond to these pathological features but often become functionally impaired as the disease advances. INPP5D (also known as SHIP1), a phosphatase broadly expressed in hematopoietic cells and restricted to microglia within the brain, plays a key inhibitory role in regulating microglial activity. It acts through receptors such as TREM2, Dectin-1, and FcγR via the PI3K/AKT signaling axis. Preclinical studies suggest that inhibiting INPP5D enhances microglial function and reduces AD-related pathology. To advance INPP5D-targeted therapies, it is essential to characterize the downstream transcriptional effects of inhibition. Identifying consistent gene expression changes across experimental models can help establish pharmacodynamic markers and clarify biological pathways to guide therapeutic development.

## Methods

We investigated transcriptomic alterations associated with INPP5D inhibition using four models: (1) primary mouse microglia from Inpp5d haplodeficient versus wild-type mice (in vitro), (2) TAD32-treated versus vehicle-treated primary microglia (in vitro), (3) TAD32-treated versus vehicle-treated C57BL/6J mice (in vivo), and (4) INPP5D-targeting siRNA versus scrambled RNA-treated C57BL/6J mice (in vivo). Gene expression was profiled using Nanostring's neuroinflammation and glial panels. Differentially expressed genes (DEGs) were compared across models to identify shared molecular signatures, and enrichment analysis was performed.

## Results

Despite a limited overlap of individual DEGs, we observed consistent enrichment of key biological pathways related to phagocytosis (including FcγR signaling, lysosomal function, and complement activation), inflammatory regulation (TLR, IL-17, and TNF signaling), and PI3K/AKT signaling. These findings suggest that INPP5D inhibition elicits conserved functional effects across diverse experimental contexts.

## Conclusion

Our findings identify convergent transcriptional and biological responses to INPP5D inhibition that may serve as pharmacodynamic indicators. These results support the utility of INPP5D

modulation in therapeutic development, offering potential biomarkers for drug selection and efficacy monitoring across preclinical models.