



# TREAT-AD

TaRget Enablement to Accelerate  
Therapy Development for AD

## IUSM-Purdue TREAT-AD Center Target Enabling Component Bioinformatics PTPN6 (SHP-1)

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PTPN6 (protein tyrosine phosphatase non-receptor type 6), also called SHP1, is a member of the protein tyrosine phosphatase (PTP) family, expressed primarily in hematopoietic cells, and functions as an important regulator of multiple signaling pathways in hematopoietic cells. Phagocytosis of aggregated amyloid- $\beta_{1-42}$  and bacterial particles were increased after knockdown of PTPN6 in microglia [4]. Knockout of CD33 as well as knockdown of the CD33 signaling-associated protein PTPN6 led to constitutive activation of inflammation-related pathways [4]. Aggregated  $\alpha$ -syn binding to Fc $\gamma$ RIIB on microglia and activating PTPN6, resulted in inhibited microglial phagocytosis. PTPN6 activation was also observed in A53T  $\alpha$ -syn transgenic mice Parkinson's disease model [5].

PTPN6 is one of the marker genes for microglia. It mediates ITIM signaling downstream of CD33 and other Siglecs inhibitory pathways, while CD33 is a disease-associated microglia (DAM) marker gene and a highly ranked Agora nominated drug target. Functions reversely to LYN, which is another AD drug target proposed, PTPN6 dephosphorylates SYK, which in turn phosphorylates PLCG2 in microglia signaling. It also directly dephosphorylates LYN. In our recent GWAS study using ROSMAP cohort, PTPN6, along with three other genes including LYN, was found to be marginally associated with AD risk (p value 0.0659).

PTPN6 was identified together with other microglia drug target INPP5D, PLCG2, HCK, TYROBP, CSF1R in the core microglia coexpression module (AD3) only from AD patient brains of five AD brain transcriptomic datasets [1] and later on eight large AD transcriptomic datasets (Table-1). In a meta gene coexpression study [2], it was found to be coexpressed in consensus modules of immune response in TCX, FP, PHG, IFG, CBE and DLPFC region of the AD brain [2].