**Short-term CSFR1 inhibition by PLX3397 induces phagocytic microglial improving amyloid clearance from presynaptic terminals and rescuing synaptic plasticity.**

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**Background:** (max 50 words)

Ineffective amyloid clearance by compromised microglia is a significant neuroinflammatory contributor to the synaptic deficits typical of neurodegenerative diseases (ND) including Alzheimer's disease (AD). Transplantation of young microglia or deletion/replacement of defective brain microglia by chronic CSF1R inhibition are the main preclinical approaches attempted thus far, with clear translational limits.

**Methods and Results:** (max 100 words)

We investigated the effects of a short-term CSF1R inhibition by PLX3397 on AD neuroinflammation in hippocampal slices. According to electrophysiological results, PLX3397 reverses amyloid-driven impairments on neurotransmission and Long-Term Potentiation (LTP). To address the underlying cellular mechanisms, we resorted to confocal imaging analysis of microglial phenotype by key functional markers. We found that acute PLX3397 treatment does not affect the brain microglia survival, but induces a phenotype shift from homeostatic into phagocytic, thus enhancing amyloid clearance, particularly from glutamatergic terminals. Our data pinpoint mild and non-microglia deleting CSF1R inhibition as an effective drug in neuroinflammation-induced microglial dysfunctions and synaptic impairments.

**Conclusions and Significance:** (max 50 words)

Microglia-related genetic and/or environmental predisposition to neuroinflammation are major risk factors for ND and AD. Current treatments targeting microglia demonstrated to be ineffective or lacks translational value.

Our findings suggest that the pharmacological manipulation of microglial metabolism, phenotype, and function by PLX3397 is a valid therapeutic approach in amyloid-driven neuroinflammation.

**Keywords:** (max 5)

Neuroinflammation, amyloid, phagocytic microglia, CSF1R inhibitor, neurotransmission.

**References**: (max 5 relevant references from the Authors in the following format:

*full authors list*, *title*, *year*, *journal*, *vol.: pages*)

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