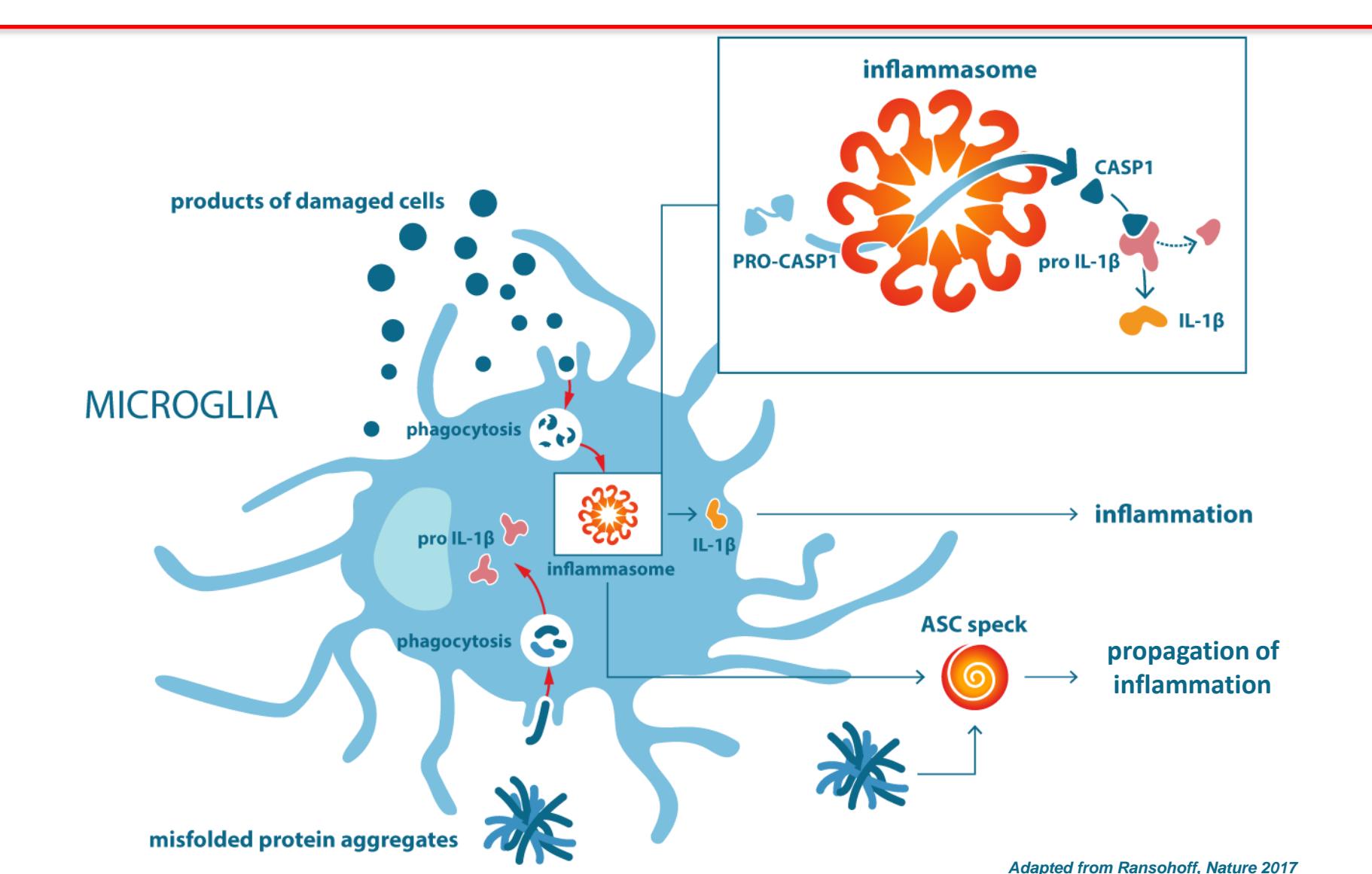


DISCOVERY AND OPTIMIZATION OF NOVEL POTENT BRAIN PENETRANT NLRP3 INHIBITORS

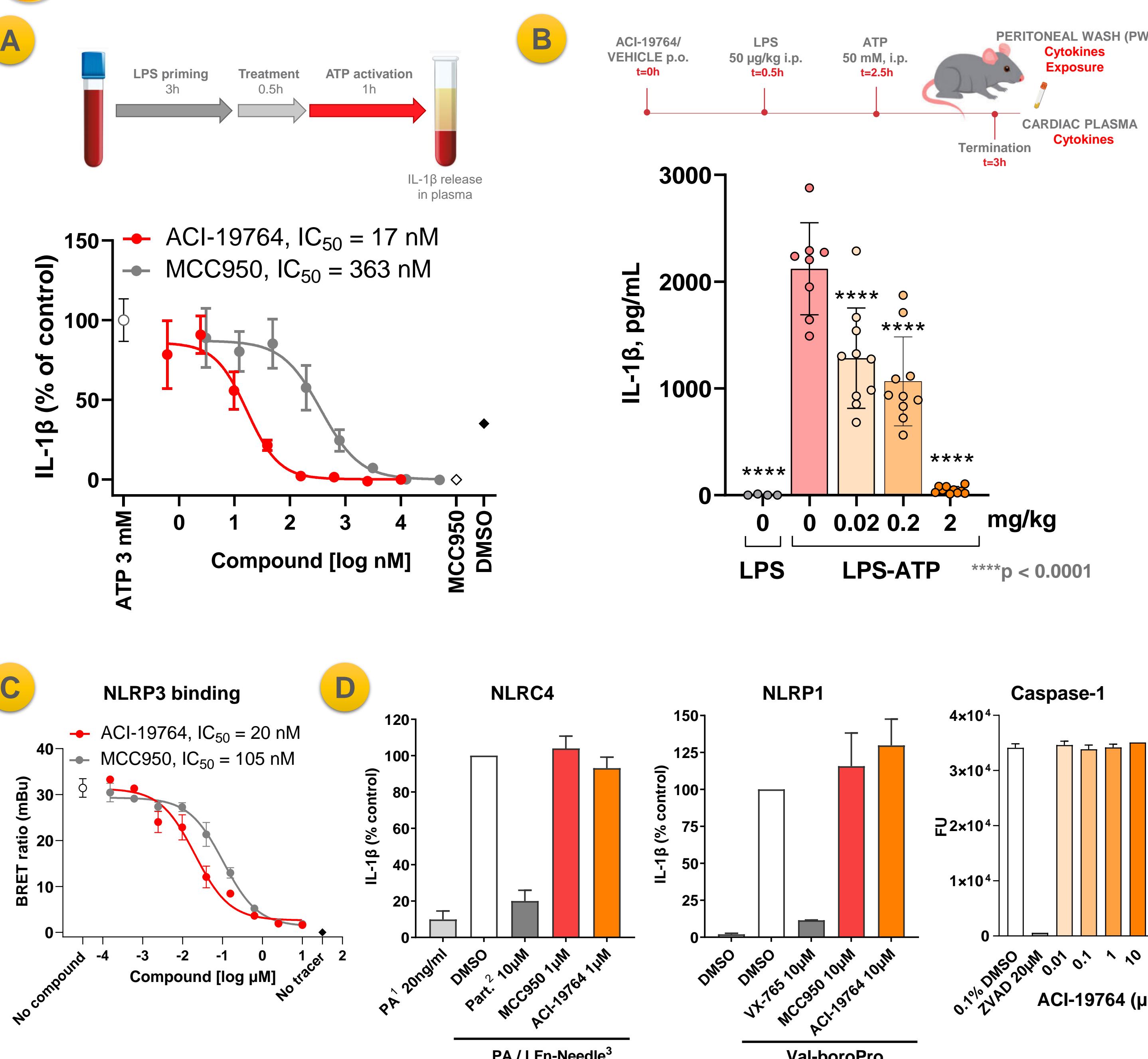
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Background

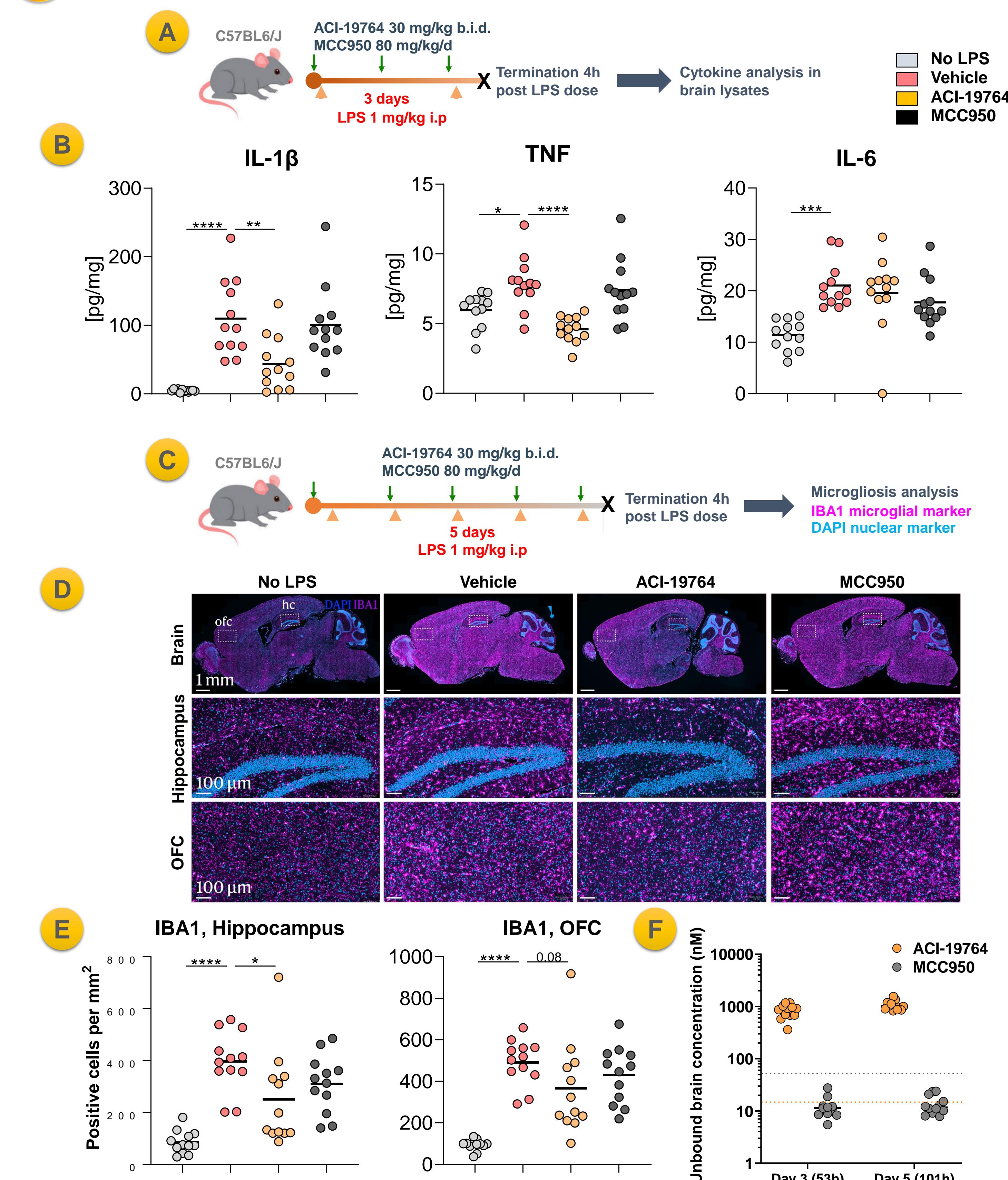
- NLRP3 inflammasome activation exacerbates neuronal dysfunction in multiple neurological diseases including Alzheimer's, Parkinson's disease and multiple sclerosis
- ACI targets the NLRP3 inflammasome pathway to:
 - Inhibit brain inflammation
 - Restore phagocytosis of misfolded proteins
 - Selectively target pathogenic pathways in the brain
- Potent brain penetrant NLRP3 inhibitors needed to provide proof-of-concept for NLRP3 inhibition in neurological disorders



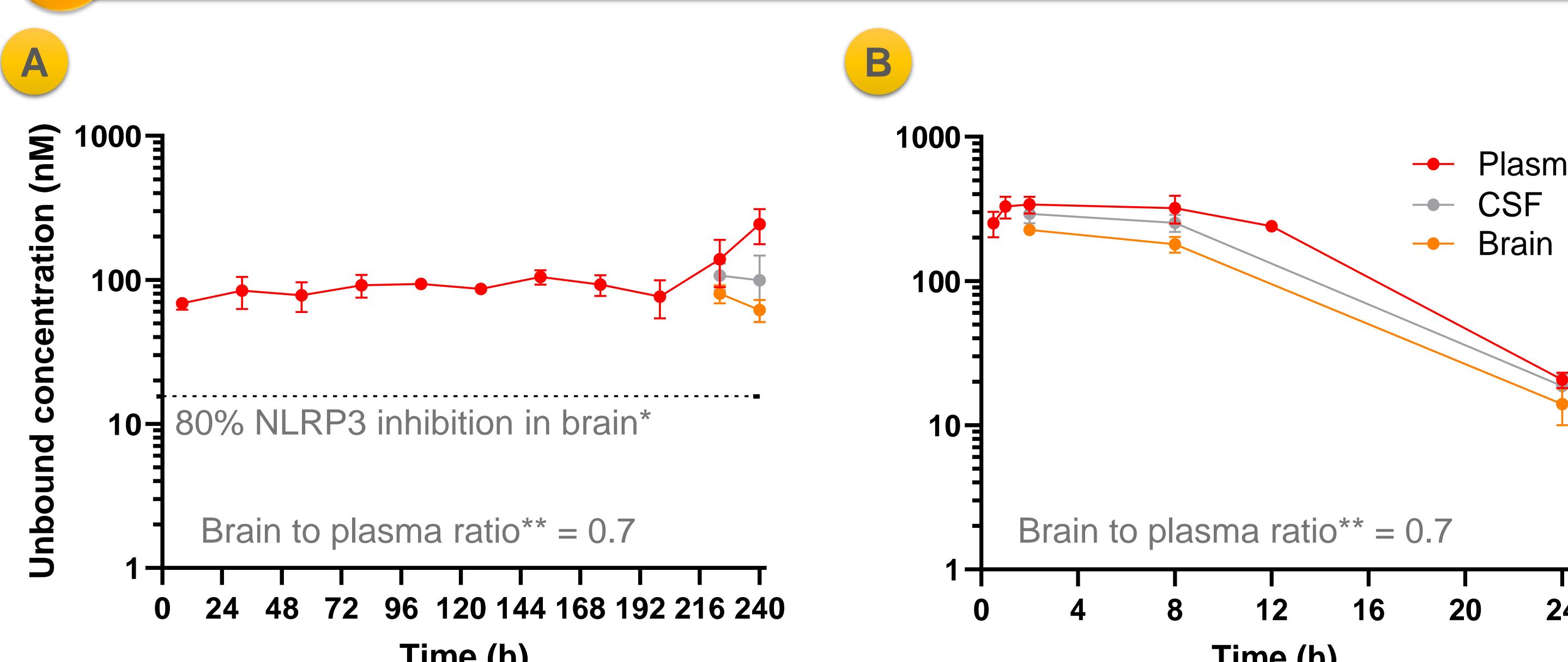
1 ACI-19764 efficacy *in vitro* and *in vivo* and selectivity



4 ACI-19764 efficacy in LPS brain inflammation model



2 ACI-19764 pharmacokinetic profile

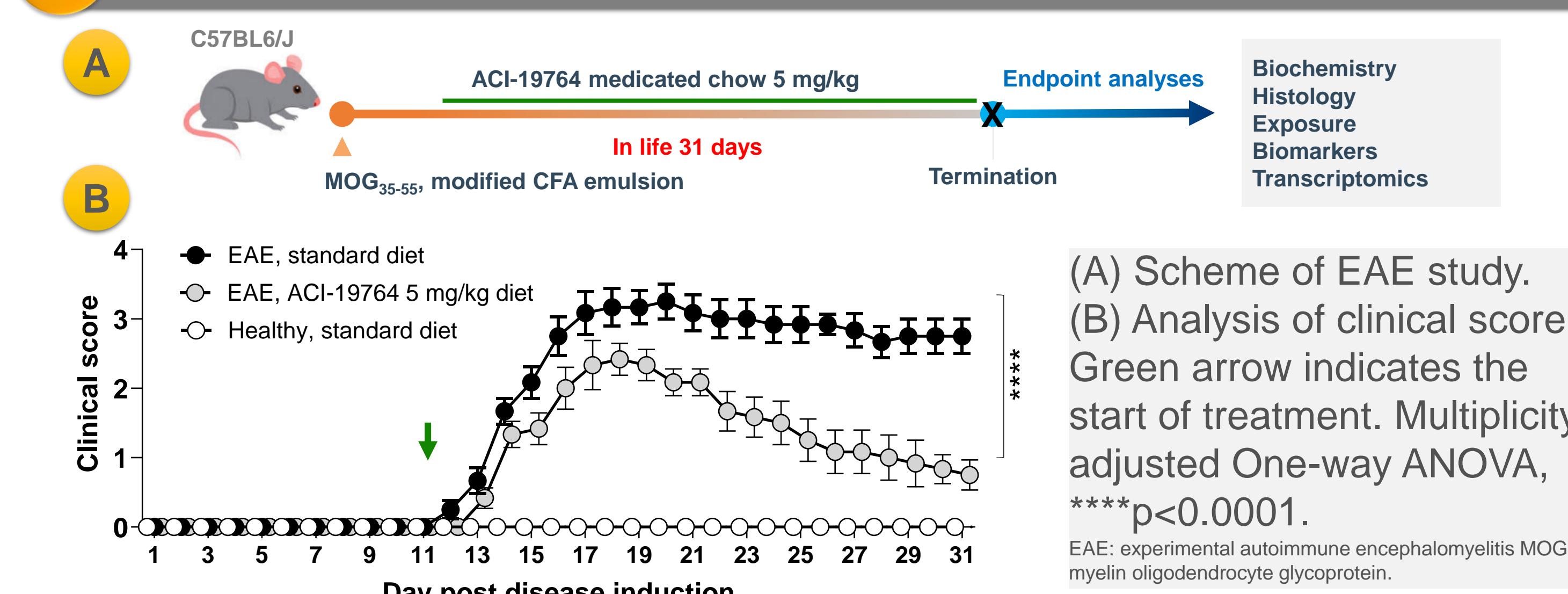


(A) Scheme of repeated LPS-induced brain inflammation study (acute phase). **(B)** Quantification of pro-inflammatory cytokines, n=12/group. **(C)** Scheme of repeated LPS-induced brain inflammation study (chronic phase). **(D)** Analysis of microgliosis, Iba1 immunofluorescence (magenta), DAPI nuclear dye (blue). **(E)** Quantification of Iba1-positive cells, n=12/group. OFC – orbitofrontal cortex. One-way ANOVA, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. **(F)** Compound exposure in brain. Dotted lines show NLRP3 IC₈₀ in mouse microglia for ACI-19764 (orange) and MCC950 (grey).

3 ACI-19764 safety and developability profile



5 ACI-19764 efficacy in the model of multiple sclerosis



Conclusions

- ACI's medicinal chemistry approach and inventive drug design identified a novel lead compound NLRP3 inhibitor, ACI-19764:
 - Active *in vitro* and *in vivo* in 2 models of neuroinflammation
 - Optimal exposure for sustained NLRP3 inhibition in the brain
 - Excellent safety and developability profile
 - Best-in-class brain penetrant molecule applicable for a broad range of neurological indications
 - To develop alone or in combination with other therapies