

Novel potent brain penetrant NLRP3 inhibitor ACI-19764 demonstrates efficacy in models of neuroinflammation

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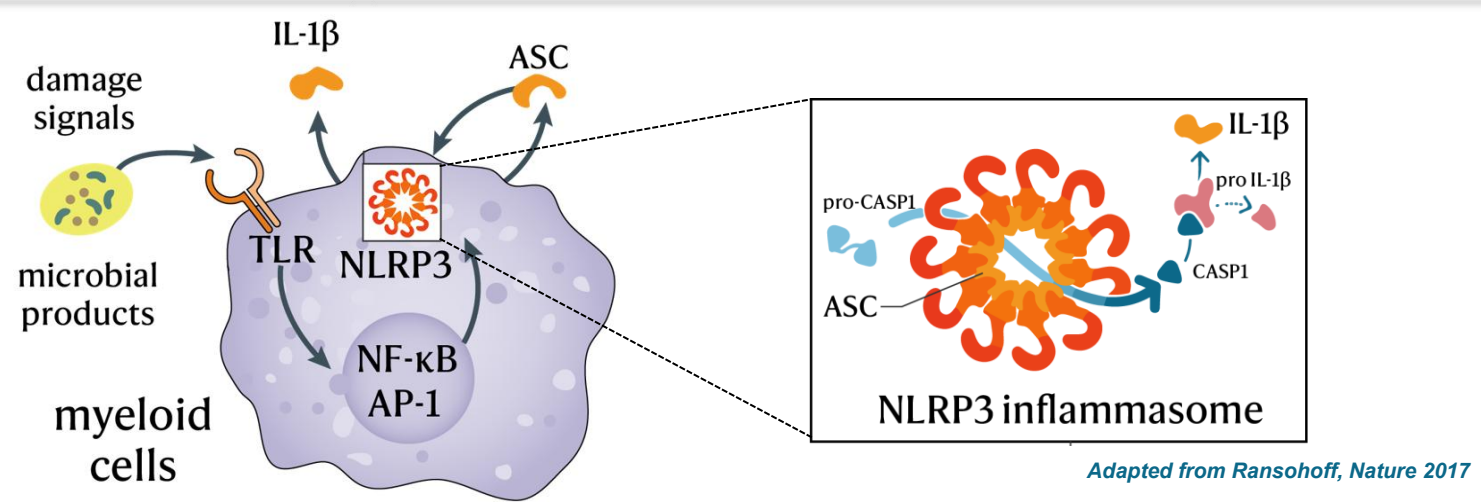
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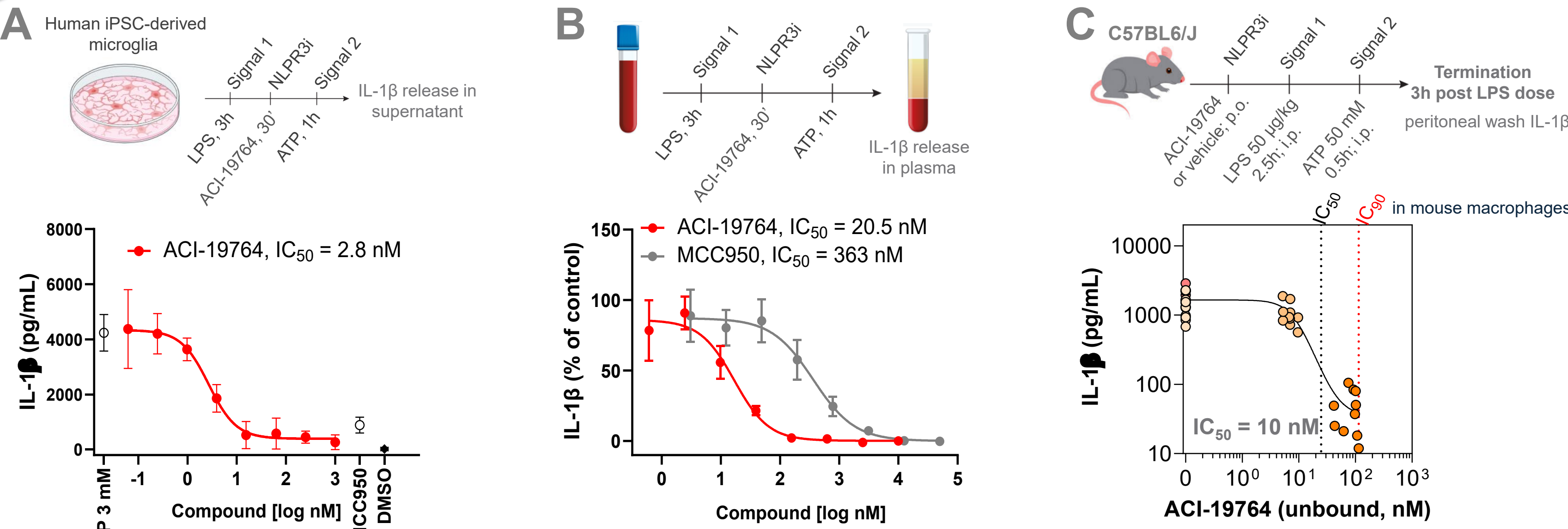


Background

- NLRP3 inflammasome activation exacerbates neuronal dysfunction in multiple neurological diseases including Alzheimer's, Parkinson's disease and multiple sclerosis
- NLRP3 inhibition in the CNS represents a promising therapeutic target in several neurological disorders, alone or in combination with other therapies

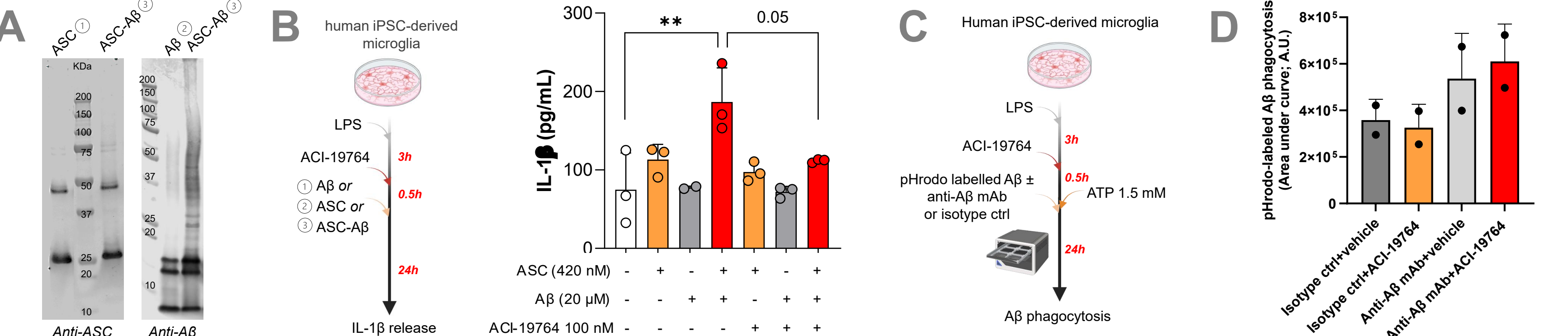


1 ACI-19764 potently inhibits IL-1β release *in vitro* and *in vivo*



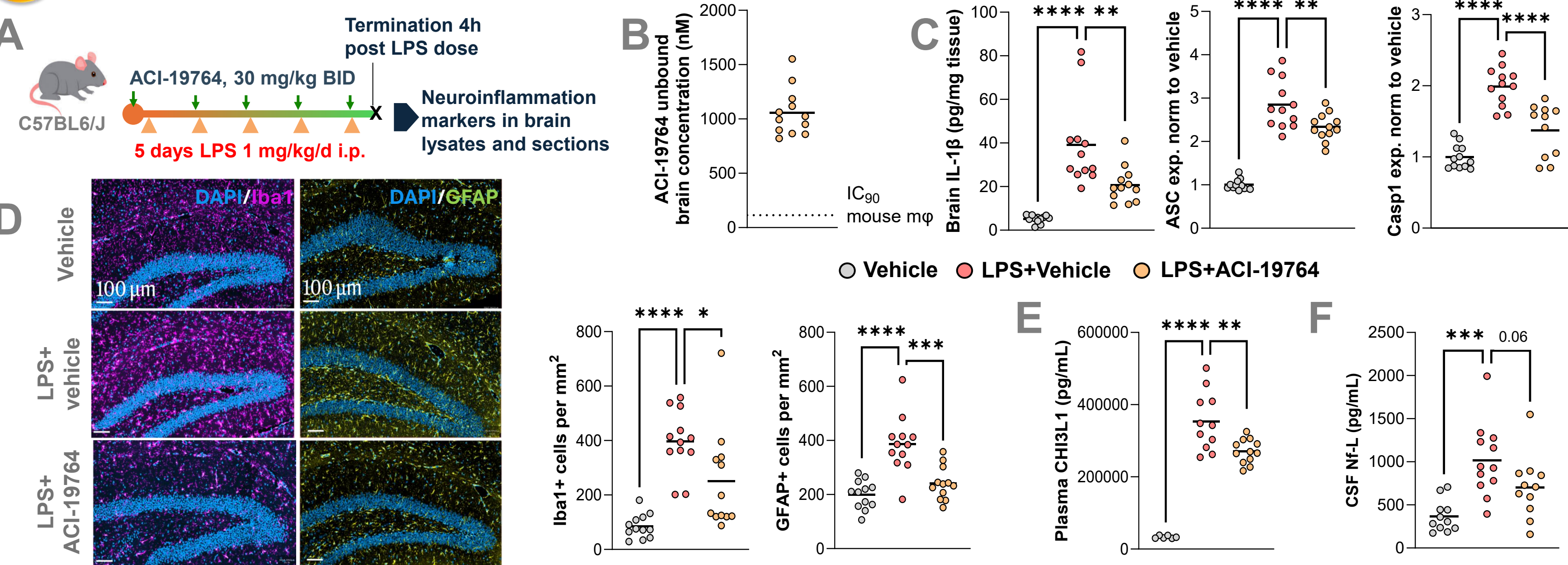
Potency of NLRP3 inhibition in (A) human iPSC-derived microglia and (B) human whole blood. ATP: adenosine triphosphate; LPS: lipopolysaccharide. (C) Efficacy in acute peritonitis mouse model; n=10/group.

2 ACI-19764 dampens IL-1β production triggered by AD-related stimuli and preserves antibody-driven amyloid beta clearance



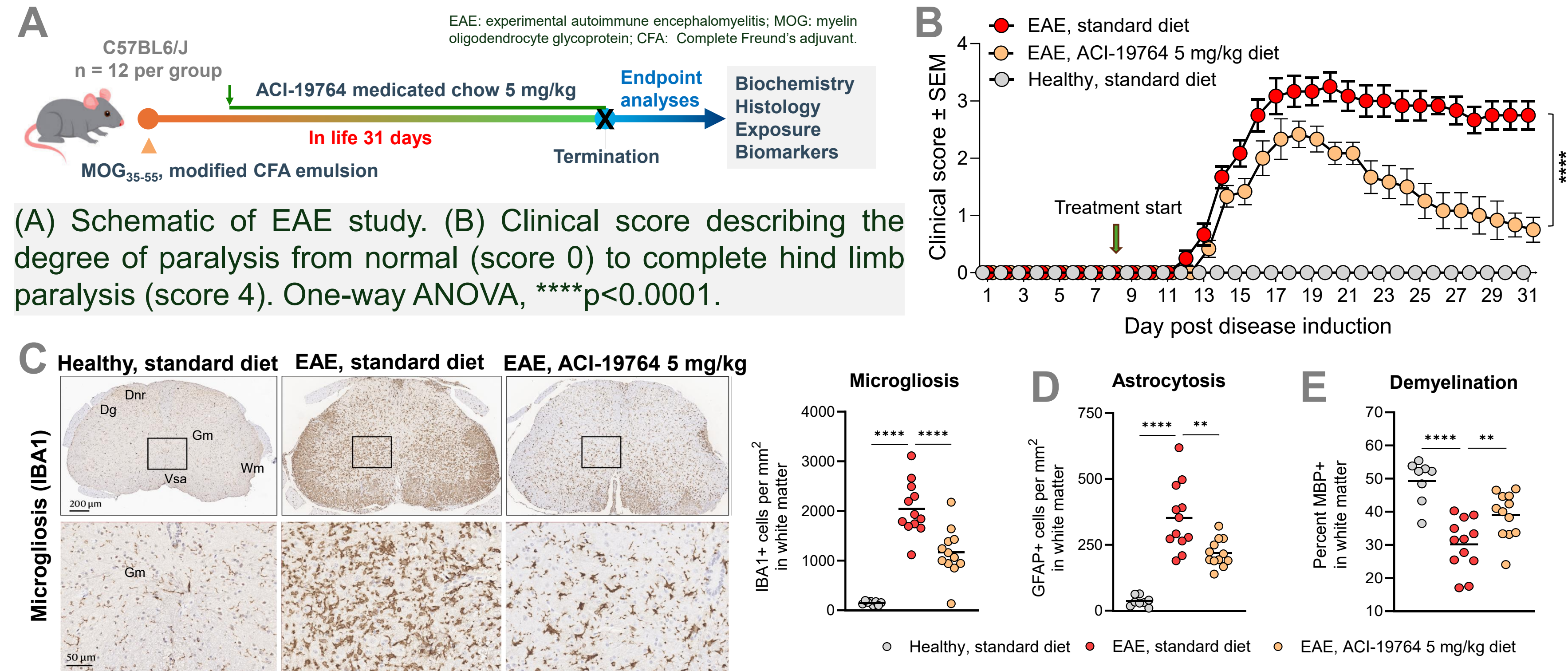
(A) Western blot analysis of ASC and Aβ proteins used as AD-related stimuli for human iPSC-derived microglia. (B) *In vitro* model and ACI-19764 efficacy in inhibiting IL-1β release. One-way ANOVA, **p<0.01. (C) Schematic of Aβ phagocytosis *in vitro* assay. (D) Effect of ACI-19764 on anti-Aβ mAb-mediated Aβ phagocytosis (area under curve after 4 hours; n=2 experiments).

3 ACI-19764 shows *in vivo* efficacy in neuroinflammation model



(A) Study design for LPS-induced brain inflammation mouse model. (B) Terminal exposure in brain. (C) Quantification of target engagement markers in brain lysates. Analysis of pharmacodynamic effect on (D) hippocampal gliosis. (E) plasma neuroinflammatory marker CHI3L1 and (F) CSF neurofilament L chain (Nf-L). N=12/group. One-way ANOVA, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. BID: twice a day. mmp: macrophages

4 ACI-19764 improves clinical score, limits demyelination and neuroinflammation in a model of multiple sclerosis



(A) Schematic of EAE study. (B) Clinical score describing the degree of paralysis from normal (score 0) to complete hind limb paralysis (score 4). One-way ANOVA, ****p<0.0001. (C) IBA1 IHC staining of lumbar spinal cord cross-sections and its quantification. (D) Quantification of astrocytosis by IHC staining of GFAP. (E) Myelination assessment by IHC staining of Myelin Binding Protein (MBP). One-way ANOVA, **p<0.01, ****p<0.0001.

5 Potential best-in-class profile for the clinical candidate ACI-19764: favorable brain penetrance and potency

Optimal brain PK ¹			High potency IL-1β inhibition			Therapeutic dose	
Compound	Species	Kp,uu ² CSF ³	Compound	hMφ ⁴ , nM	hWBA ⁵ , nM	Compound	Human dose
ACI-19764	Dog	1	ACI-19764, IC ₅₀	2.7	20.5	ACI-19764	≤ 10 mg daily predicted
VTX3232 ¹³	Human	0.5	VTX3232 ¹³ , IC ₅₀	2.7	15	VTX3232 ¹³	30 mg daily (in obesity Ph2) 40 mg daily (in PD ⁶ Ph2)
BGE-102 ¹²	Human	0.7	BGE-102 ¹² , IC ₉₀	2.1	1.8	BGE-102 ¹²	Up to 90 mg daily (in CV risk Ph2)
High selectivity			CNS target engagement and efficacy <i>in vivo</i>			Safety	
Compound	Selectivity		Neuroinflammation in ARC ⁸ of DIO ⁹ mice			Compound	Safety
ACI-19764	no action on other inflammasomes ⁷		Compound	Microgliosis (IBA1)	Astrocytosis (GFAP)	ACI-19764	Preclinical safety/toxicology package up to 3 months supporting further clinical development
VTX3232	no action on other inflammasomes ⁷		ACI-19764	-47%*	-65%*	VTX3232	Acceptable safety profile up to 3 mo.
BGE-102	no action on other inflammasomes ⁷		VTX3232 ¹⁴	-40%*	-30% (ns ¹⁰)		
			BGE-102	na ¹¹	na	BGE-102	Acceptable safety profile up to 3 mo.

(1) Pharmacokinetics; (2) Optimal brain to plasma ratio (Kp,uu) = 1.0; (3) Cerebrospinal fluid; (4) Human macrophages; (5) Human whole blood assay; (6) Parkinson's disease; (7) AIM2, NLRP1, NLRP4; (8) Arcuate nucleus of hypothalamus; (9) Diet-induced obesity model; (10) Not significant; (*) p<0.05; (11) not available; (12) BioAge Labs R&D Day, May 8th 2026. (13) Ventyx Biosciences Corporate Presentation, June 2025; (14) Bultinck et al., Mol Metab 2025.

Conclusions

The profile of the clinical candidate NLRP3 inhibitor, ACI-19764 displays:

- Low nanomolar activity *in vitro* and *in vivo*
- Efficacy *in vitro* against AD stimuli while preserving mAb-mediated Aβ phagocytosis, supporting the therapeutic potential of NLRP3 inhibition in AD
- Efficacy *in vivo* in two distinct mouse models of neuroinflammation
- Brain penetration suitable for sustained inhibition in the CNS
- Predicted low human dose compatible with long-term daily oral administration
- Ongoing Phase 1 study in healthy volunteers. Results expected in H2 2026.