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

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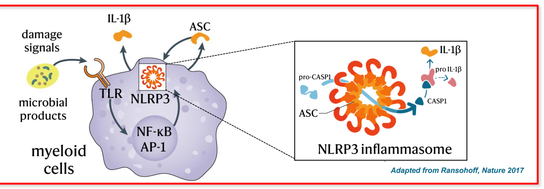
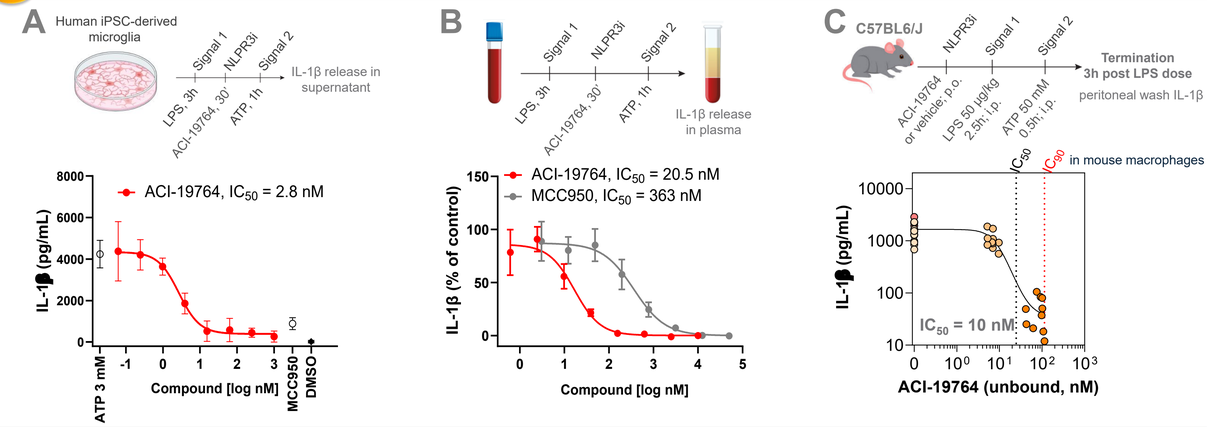
Background

- 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

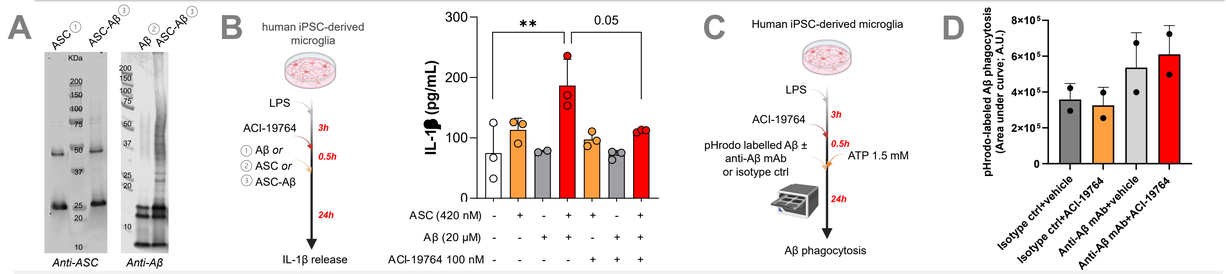


1 ACI-19764 potently inhibits IL-1β release *in vitro* and *in vivo*



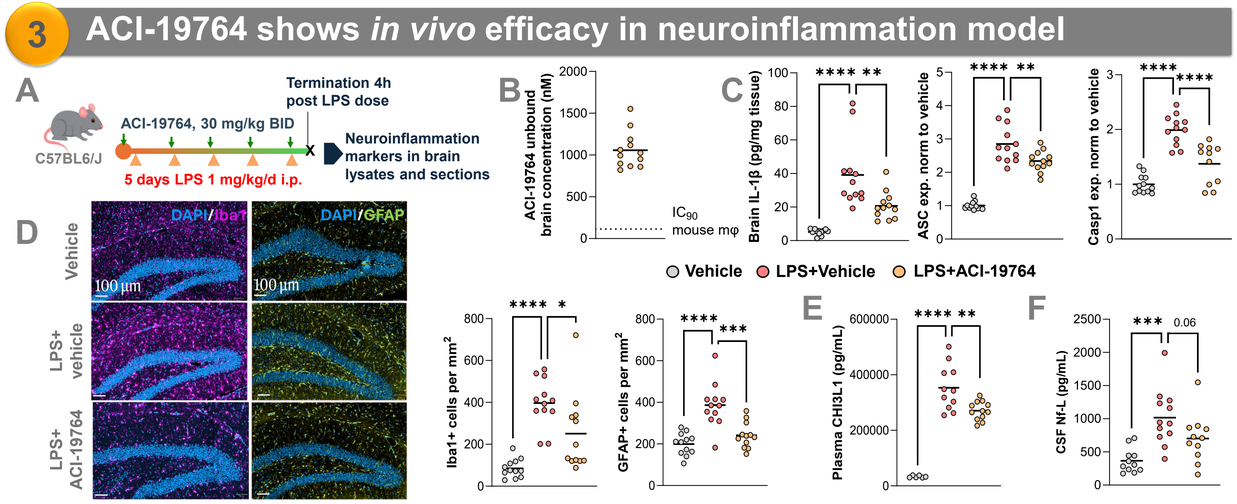
Potency of NLRP3 inhibition in (A) human iPSC-derived microglia and (B) human whole blood. ATP: adenosine triphosphate; LPS: lipopolysaccharide. (C) Efficacy in acute peritonitis mouse model; n=10/group.

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



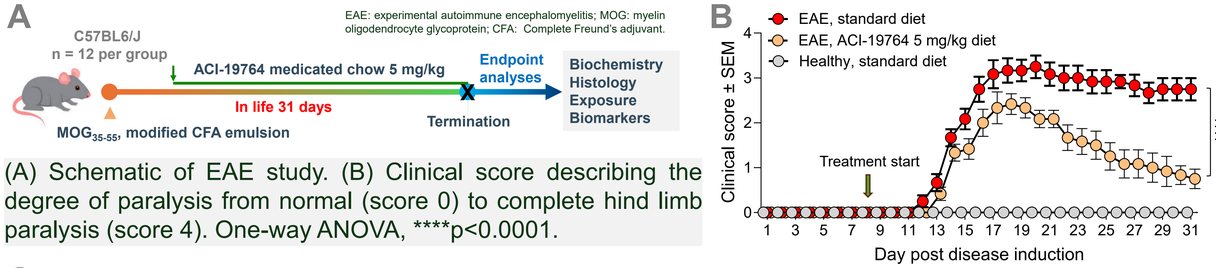
(A) Western blot analysis of ASC and Aβ proteins used as AD-related stimuli for human iPSC-derived microglia. (B) *In vitro* model and ACI-19764 efficacy in inhibiting IL-1β release. One-way ANOVA, **p<0.01. (C) Schematic of Aβ phagocytosis *in vitro* assay. (D) Effect of ACI-19764 on anti-Aβ mAb-mediated 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. **DAPI** nuclear dye, **IBA1** microglia, and **GFAP** astrocytes immunofluorescence; (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. mφ: 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]

Compound	Species	Kp,uu[2] CSF[3]
ACI-19764	Dog	1
VTX3232[13]	Human	0.5
BGE-102[12]	Human	0.7

High potency IL-1β inhibition

Compound	hMφ[4], nM	hWBA[5], nM
ACI-19764, IC_{50}	2.7	20.5
VTX3232[13], IC_{50}	2.7	15
BGE-102[12], IC_{90}	2.1	1.8

Therapeutic dose

Compound	Human dose
ACI-19764	≤ 10 mg daily predicted
VTX3232[13]	30 mg daily (in obesity Ph2) 40 mg daily (in PD[6] Ph2)
BGE-102[12]	Up to 90 mg daily (in CV risk Ph2)

High selectivity

Compound	Selectivity
ACI-19764	no action on other inflammasomes[7]
VTX3232	no action on other inflammasomes[7]
BGE-102	no action on other inflammasomes[7]

CNS target engagement and efficacy *in vivo*

Neuroinflammation in ARC[8] of DIO[9] mice

Compound	Microgliosis (IBA1)	Astrocytosis (GFAP)
ACI-19764	-47%*	-65%*
VTX3232[14]	-40%*	-30% (ns[10])
BGE-102	na[11]	na

Safety

Compound	Safety
ACI-19764	Preclinical safety/toxicology package up to 3 months supporting further clinical development
VTX3232	Acceptable safety profile up to 3 mo.
BGE-102	Acceptable safety profile up to 3 mo.

(1) Pharmacokinetics; (2) Optimal brain to plasma ration (Kp,uu) = 1.0; (3) Cerebrospinal fluid; (4) Human macrophages; (5) Human whole blood assay; (6) Parkinson's disease; (7) AIM2, NLRP1, NLRC4; (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.