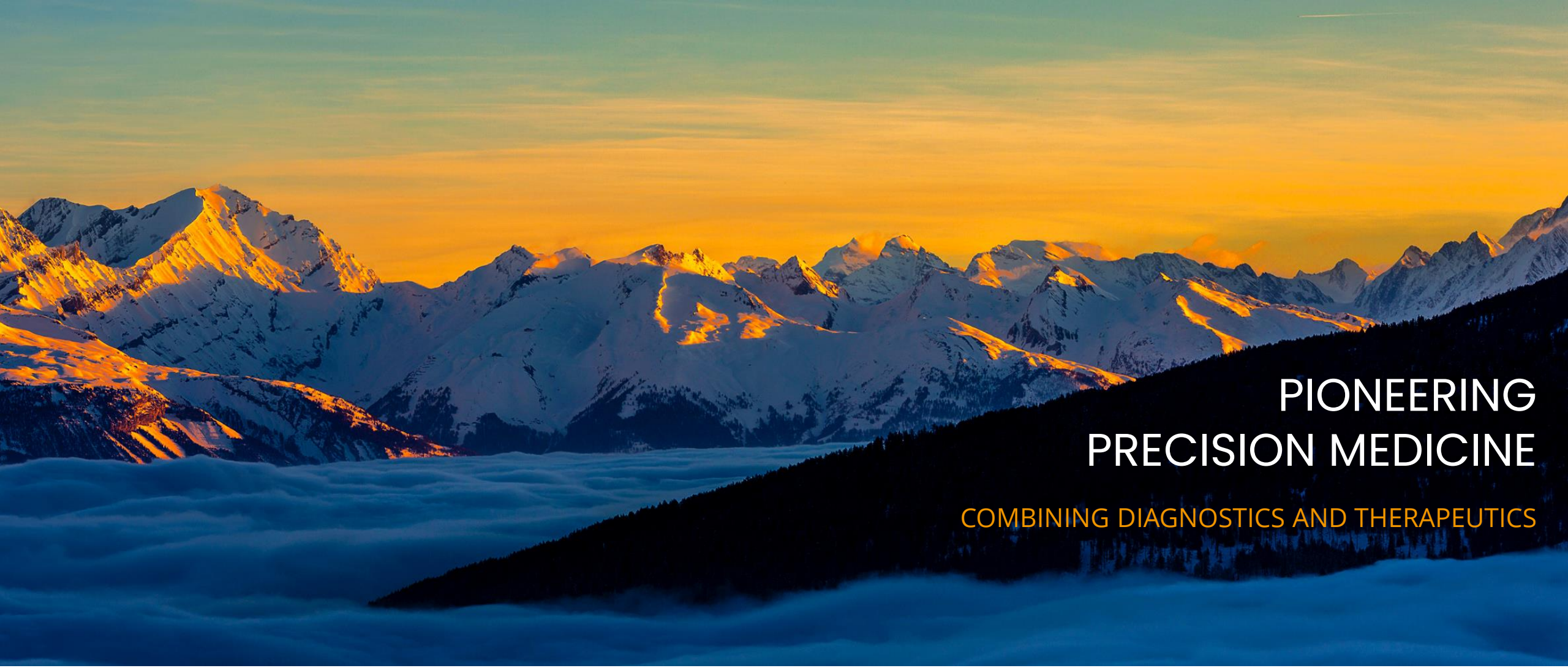

The NLRP3 inhibitor ACI-19764 mitigates obesity-driven neuroinflammation and insulin resistance

Davide Basco, PhD | EASD 2025 | 16 September 2025

AC Immune

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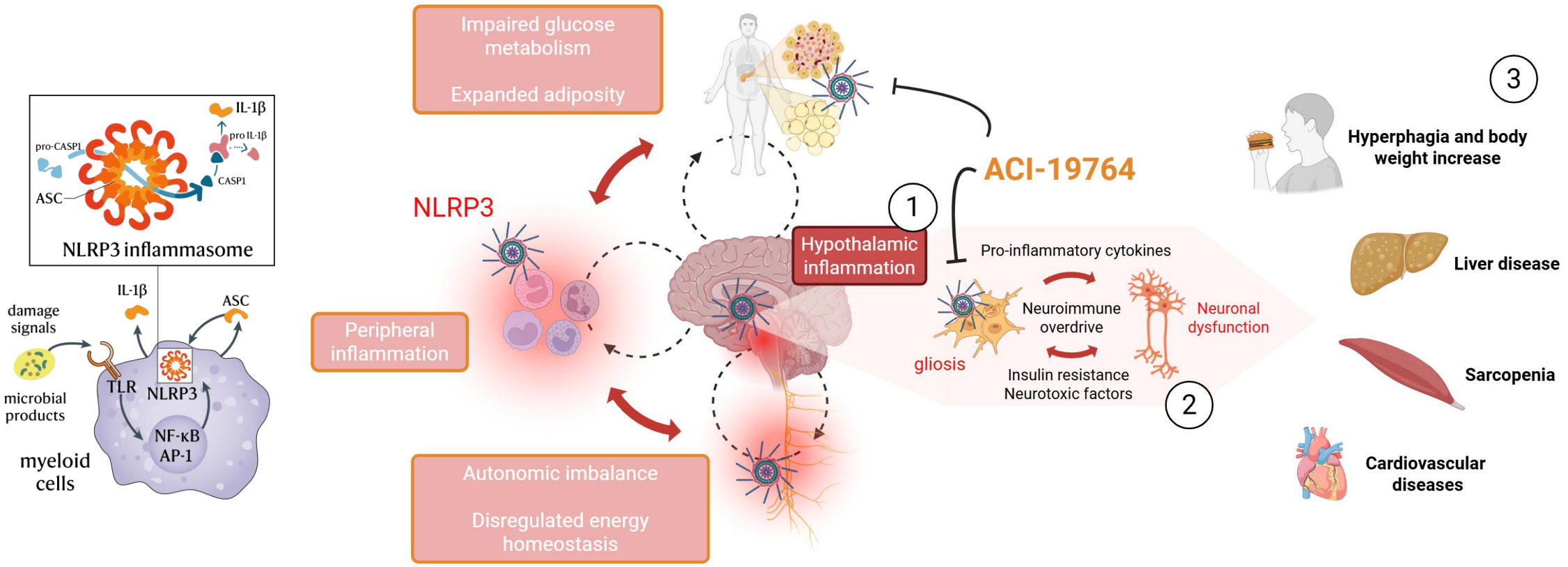
Disclosures

Davide Basco is an employee of AC Immune entitled to stock options

Targeting obesity with the CNS-penetrant NLRP3[1] inhibitor ACI-19764



1. **NLRP3-mediated inflammatory crosstalk links peripheral to hypothalamic inflammation**
2. **Pharmacological NLRP3 inhibition in the brain restores hypothalamic regulation of physiological functions**
3. **Therapeutic impact extended to peripheral systems by addressing obesity-related complications**

- A brain penetrant NLRP3 inhibitor may restore physiological functions in the hypothalamus and other regions controlling food intake and energy homeostasis

(1) NOD-like receptor protein 3

Efficacy of the NLRP3 inhibitor ACI-19764 in a mouse model of obesity

Reduced body weight and improved insulin sensitivity

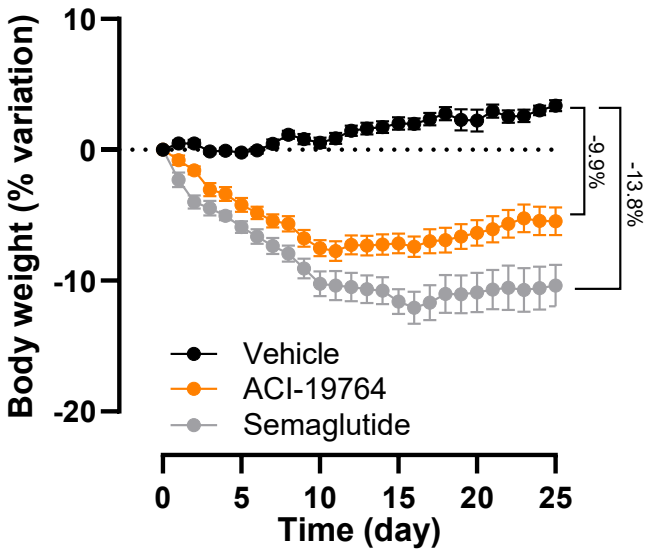
C57BL6/J mice
5 weeks

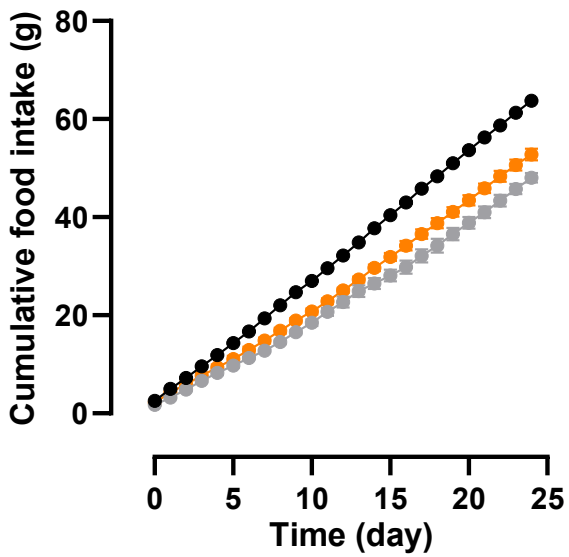
Diet-induced obesity model
+ High-fat diet (24 weeks)

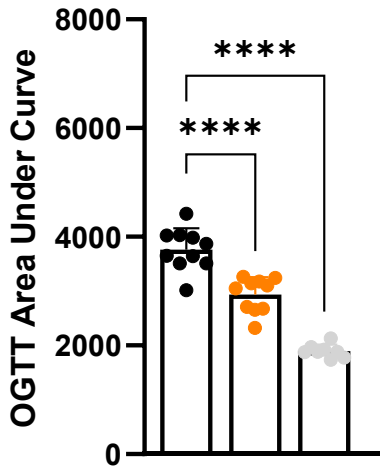
In-life readouts
Body weight
Food intake
Blood glucose/insulin
OGTT[1]

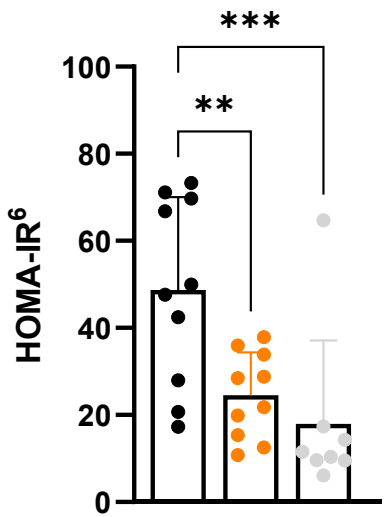
Endpoints
Brain histology (IBA1, GFAP)
Liver weight
Biomarkers
Exposure

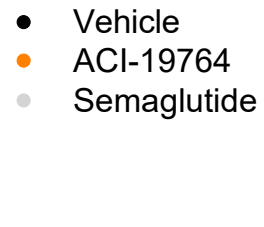
Treatment (4 weeks)
+ ACI-19764 (5 mg/kg BID[2]; PO[3])
+ Semaglutide (10 µg/kg, QD[4], SC[5])











**p<0.01; ***p<0.001; ****p<0.0001 vs vehicle. One-way ANOVA

- ACI-19764 significantly improved key metabolic readouts in diet-induced obesity (DIO) mouse model

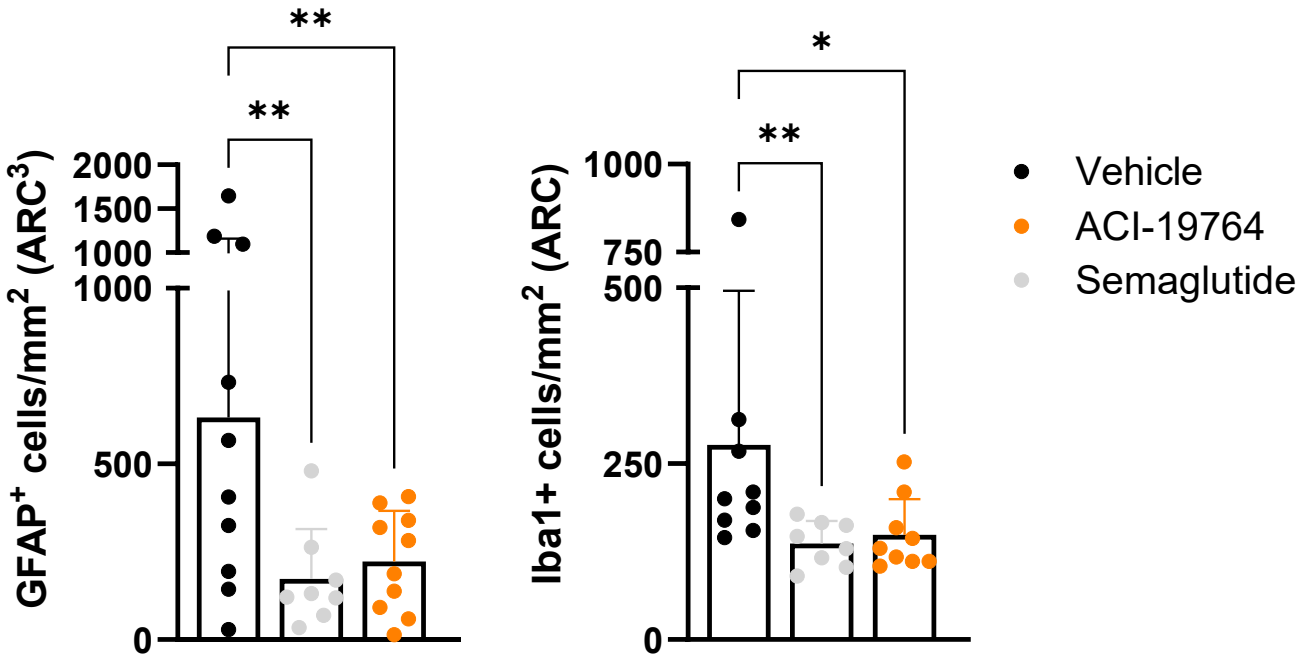
(1) Oral Glucose Tolerance Test; (2) Twice daily; (3) per os; (4) once daily; (5) subcutaneously; (6) Homeostatic Model Assessment of Insulin Resistance

AC Immune, unpublished data

ACI-19764 reduced neuroinflammation in the hypothalamus

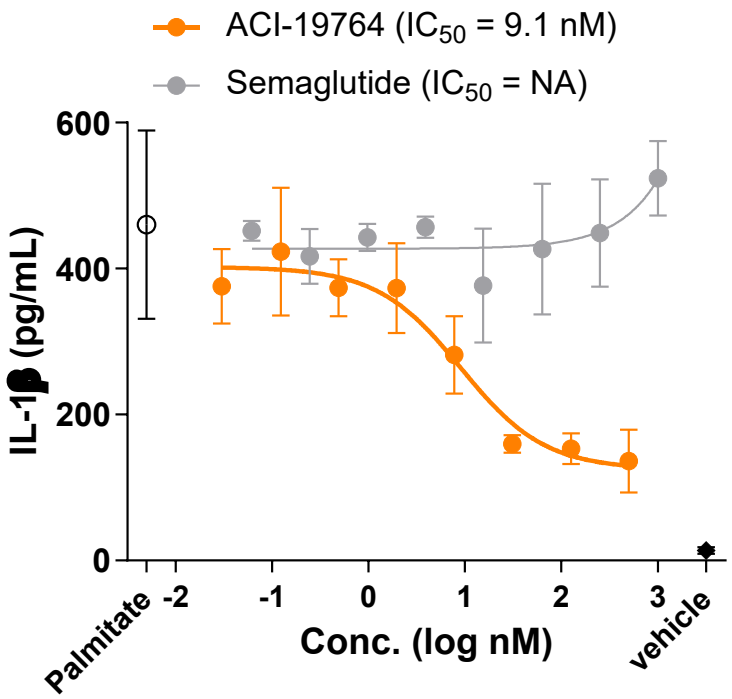
A different mechanism of action as compared to semaglutide

IHC[1] analysis in DIO[2] mouse brains



*p<0.05; **p<0.01 vs vehicle. One-way ANOVA

Palmitate-induced IL-1β secretion in human macrophages



AC Immune, unpublished data

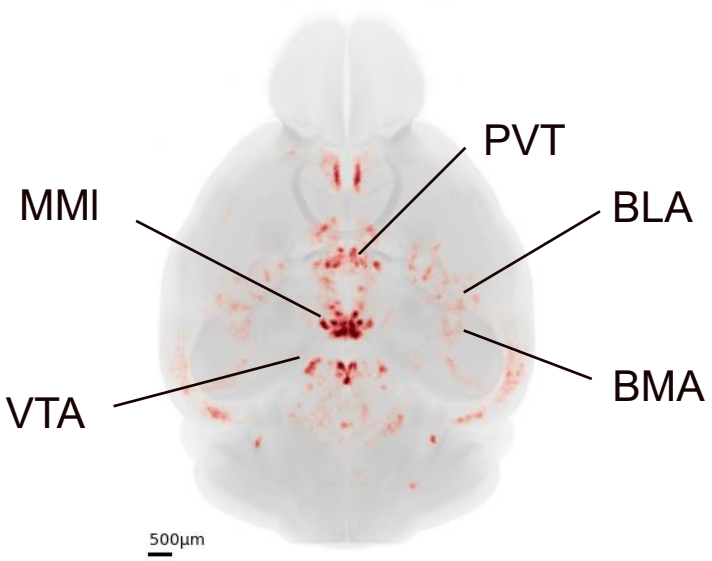
- ACI-19764 and semaglutide significantly reduced neuroinflammation in the brain region regulating food intake through a different mechanism of action than semaglutide

(1) Immunohistochemistry; (2) Diet-Induced Obesity; (3) Arcuate Nucleus of the Hypothalamus

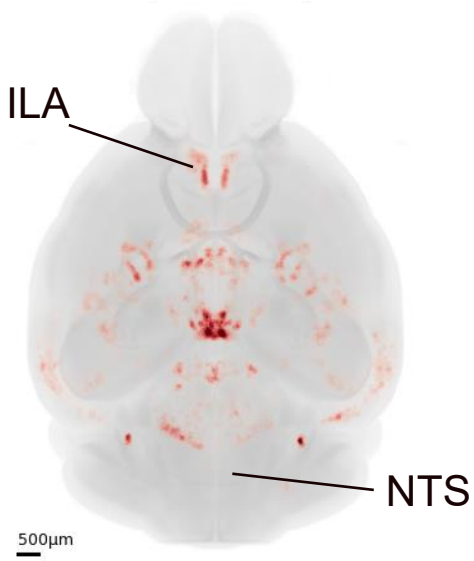
Compound effect on neuronal activity in DIO brains

c-Fos activation brain mapping by light sheet microscopy

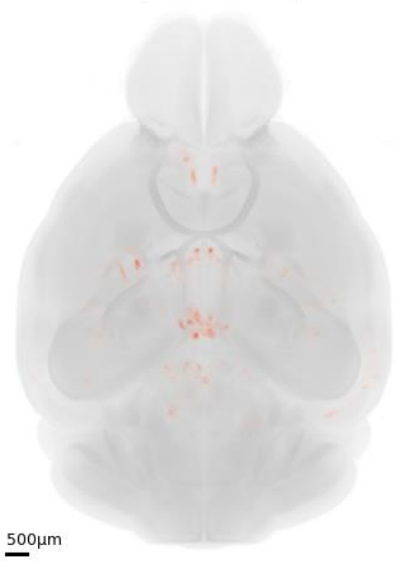
ACI-19764 acute vs vehicle
Single dose



ACI-19764 chronic vs vehicle
10 days



Sema chronic vs vehicle
10 days



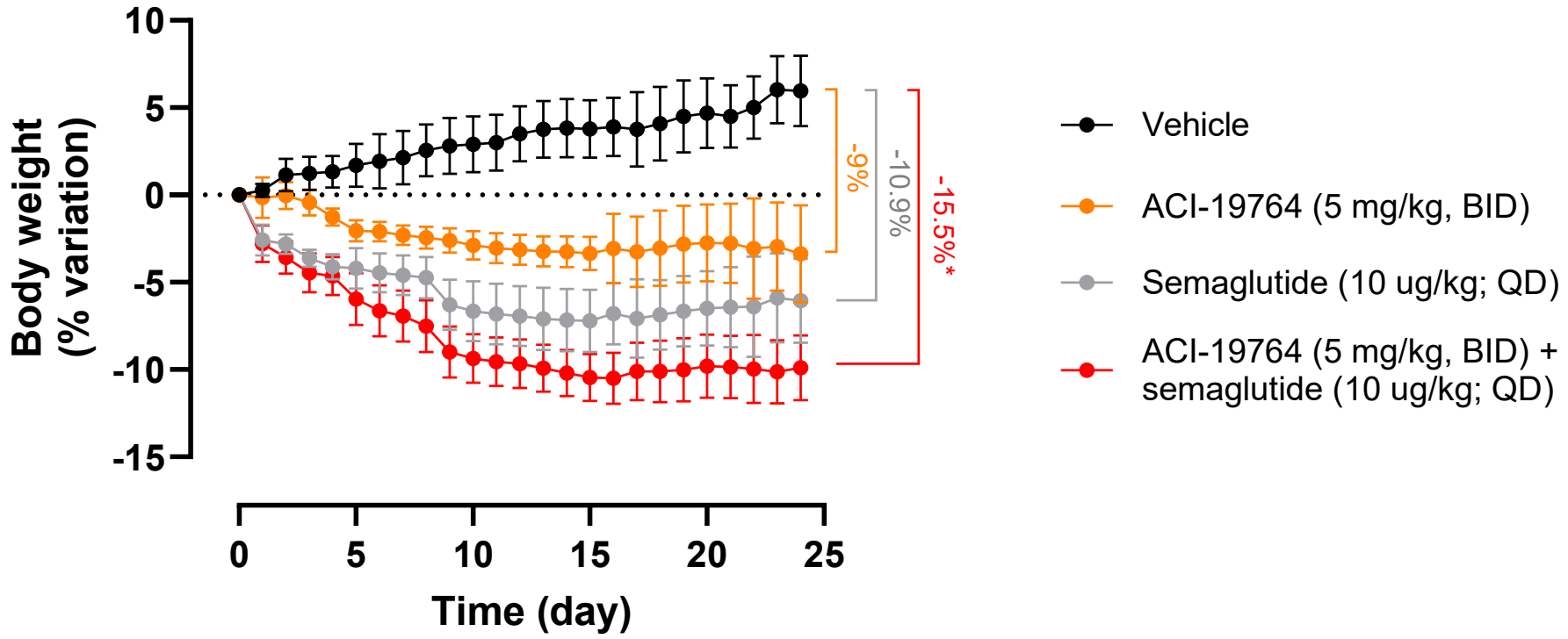
- ACI-19764 activated multiple brain regions involved in the regulation of homeostatic feeding, food reward sensitivity, and energy expenditure
- The broader effect of ACI-19764 as compared to the non-CNS penetrant semaglutide provides biological rationale for combination therapy

PVT: Paraventricular nucleus of the Thalamus; MMl: Medial mammillary nucleus, lateral; ILA: Infralimbic Area; BLA/BMA: BasoLateral/BasoMedial Amygdala; VTA: Ventral Tegmental Area; NTS: Nucleus of the Solitary Tract

AC Immune, unpublished data

ACI-19764 combined with semaglutide maximized body weight loss

Body weight analysis



AC Immune, unpublished data

- ACI-19764 significantly reduces body weight showing cumulative effect when combined with semaglutide suggesting a synergy of the two mechanisms of action

(1) bis in die; (2) per os; (3) quaque die; (4) subcutaneously. *at least p<0.05 vs other monotherapies

Conclusions

- The CNS-penetrant NLRP3 inhibitor ACI-19764 showed efficacy in DIO mouse model of obesity reducing body weight and key metabolic biomarkers
- ACI-19764 exerts a broad influence on neuronal activation in key circuits governing food intake, energy expenditure and reward system
- ACI-19764 mechanism of action is different and complementary to the one of semaglutide, supporting the rationale for a combination therapy for obesity and other metabolic disorders
- Based on excellent efficacy, safety and tolerability data, along with low predicted efficacious doses in human, ACI-19764 has the potential to be best-in-class CNS NLRP3 inhibitor

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