TARGETING THE INFLAMMASOME PATHWAY WITH AN ANTI-ASC IMMUNOTHERAPY IN ALZHEIMER'S DISEASE

Davide Basco, PhD – AD/PD 2024

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AC Immune

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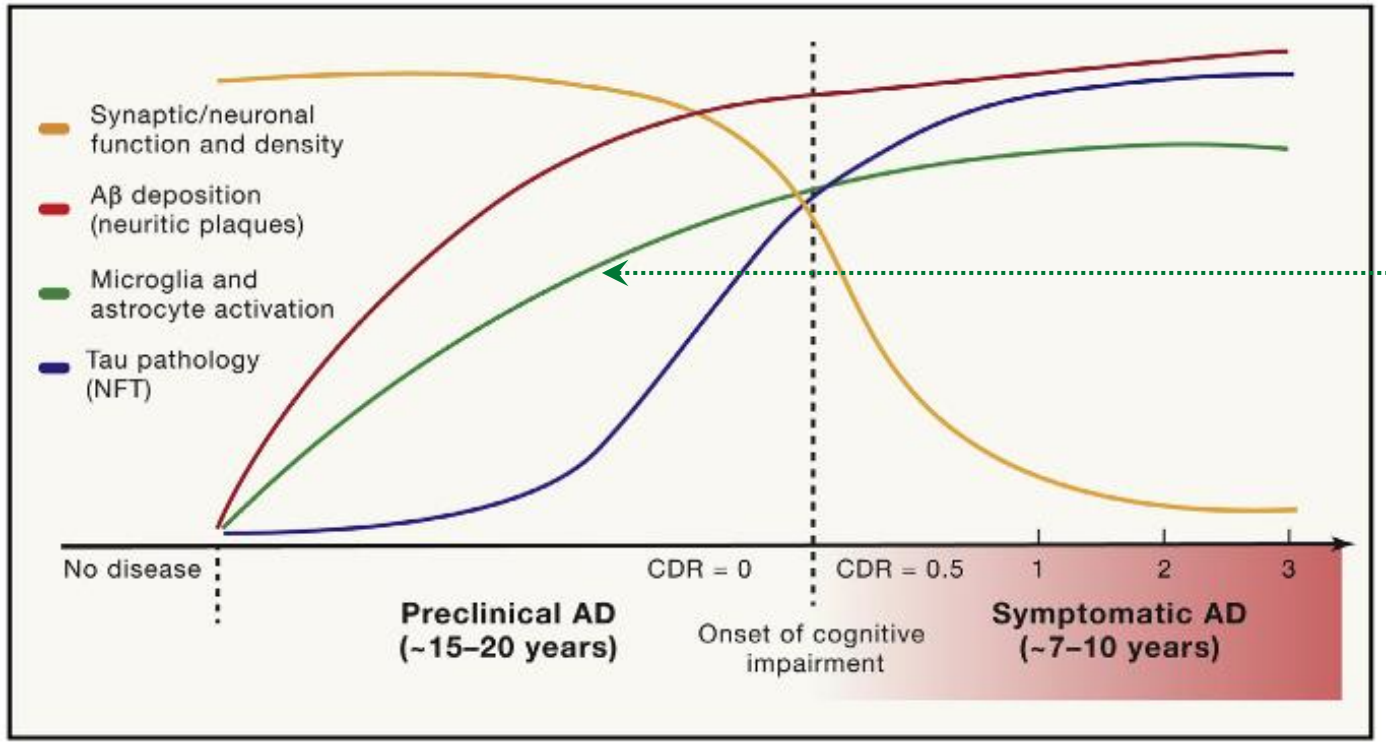
Conflict of interest disclosure

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

Inflammation is a central mechanism in Alzheimer's disease (AD)

In addition to amyloid beta deposition, activation of immune cells manifests early in the pathology



Microglia and astrocyte activation

Long and Holtzman, 2019

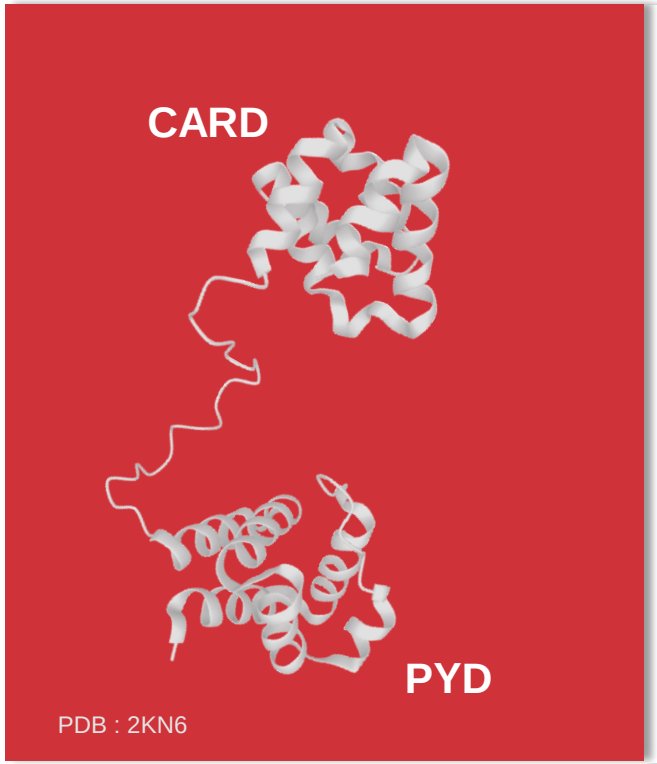
- Aim: target immune cell-mediated pathology via the NLRP3[1]/ASC[2] inflammasome pathway
- Using anti-ASC monoclonal antibodies as an immunotherapy leads to disease amelioration:
  - inhibits pathology driving pro-inflammatory factors
  - while restoring clearance of misfolded proteins (e.g., amyloid beta) and maintaining innate immunity defense

(1) NOD-, LRR- and pyrin domain-containing protein 3; (2) apoptosis associated speck-like protein containing a CARD

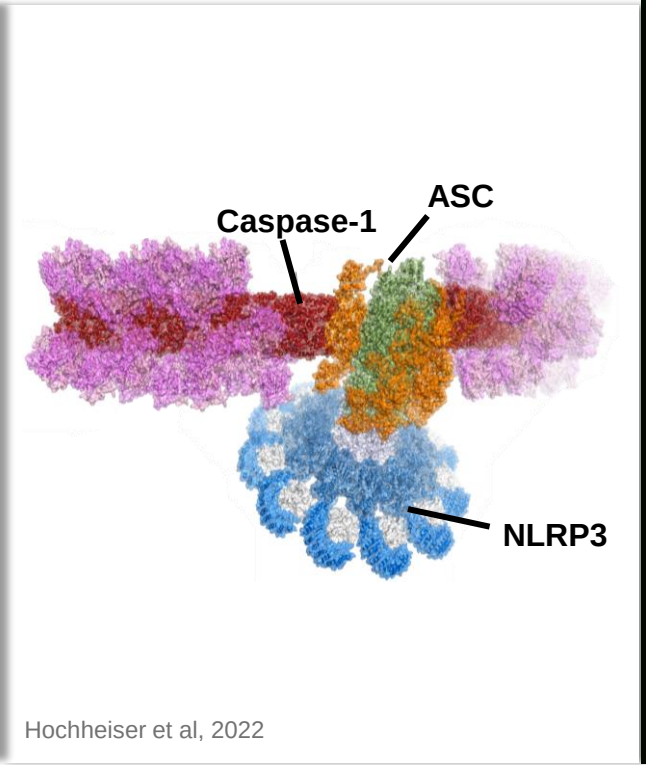
The target: Apoptosis-associated speck-like protein containing CARD (ASC)

A sensor protein part of the pro-inflammatory inflammasome complex

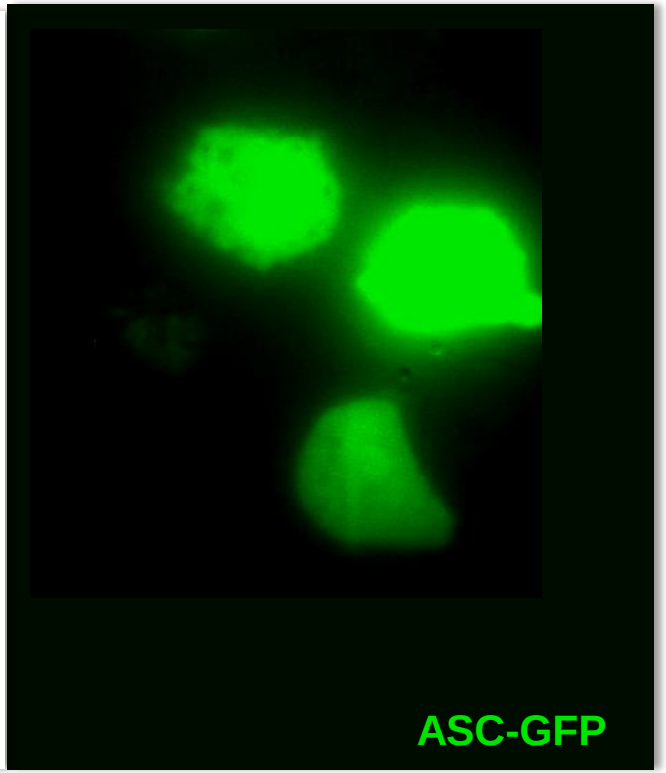
Two globular domains



Part of the inflammasome complex



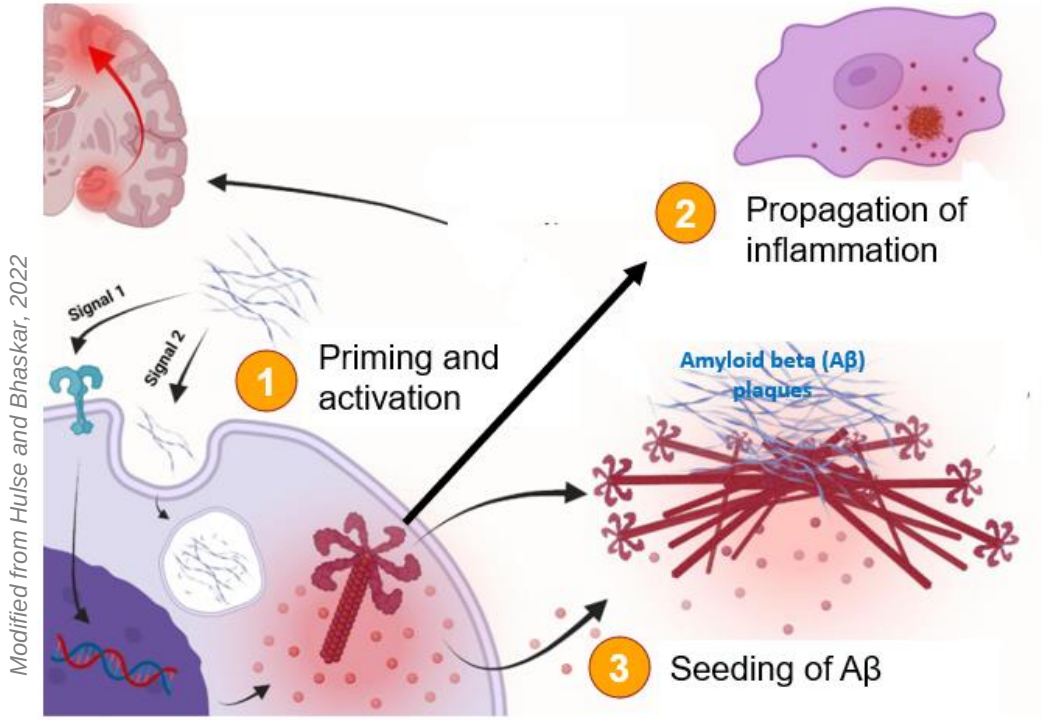
Assembled in specks



- Pro-inflammatory ASC specks are present in multiple CNS related diseases including Alzheimer's

The role of ASC specks in AD as propagators of amyloid pathology

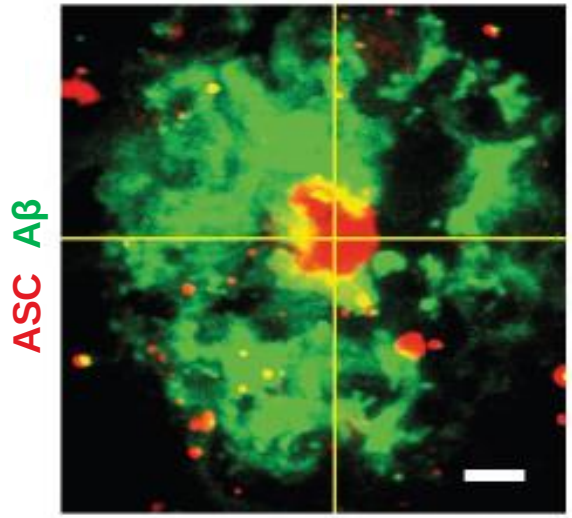
ASC in seeding amyloid beta protein aggregates



Modified from Hulse and Bhaskar, 2022

Alzheimer's disease

Human brain



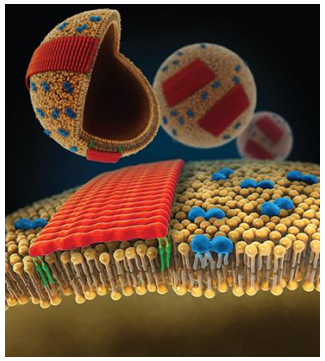
Venegas et al. 2017

- Extracellular ASC specks are detectable in brain of AD patients and seed amyloid beta plaques
- Strong biological rationale for ASC as a new therapeutic target

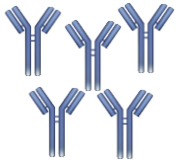
Generating a highly potent anti-ASC mAb: ACI-6635

Cross-reactive on human and mouse ASC

SupraAntigen® vaccine platform

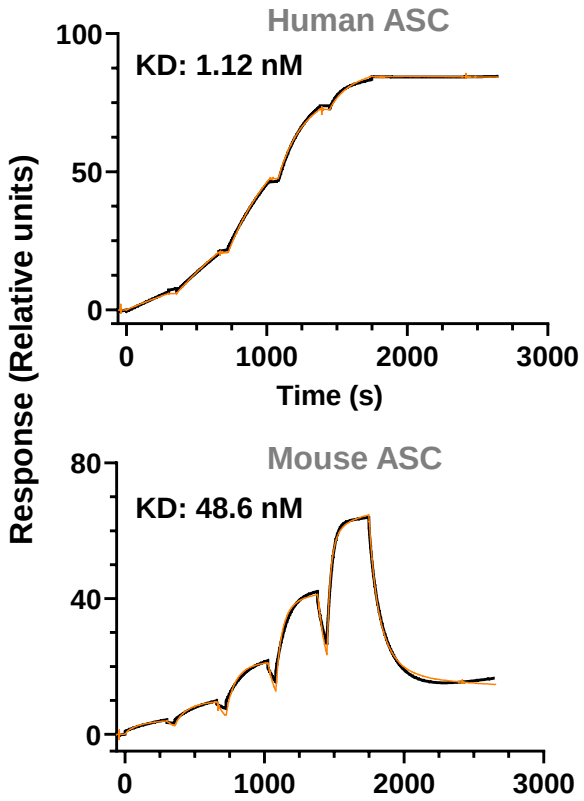


ASC knockout mice

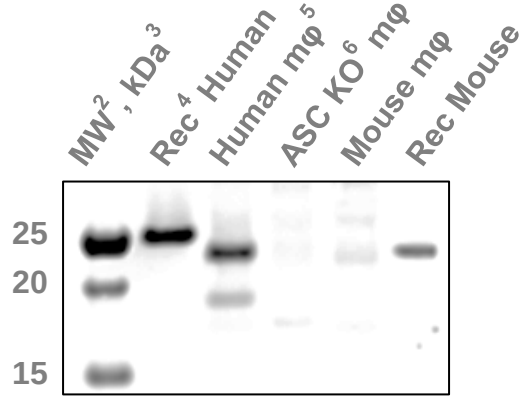


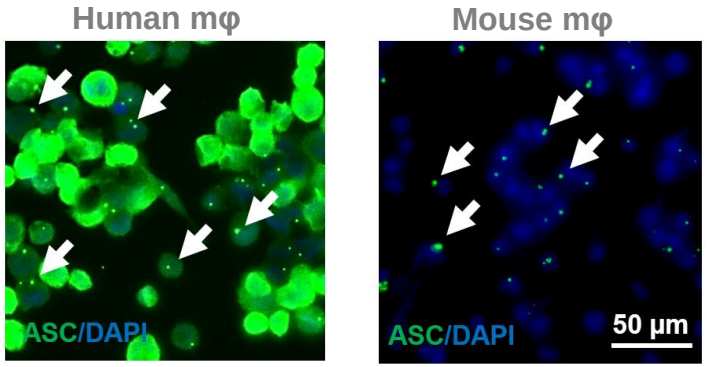
Anti-ASC antibodies

Affinity (SPR[1])



Target engagement (WB & IHC)





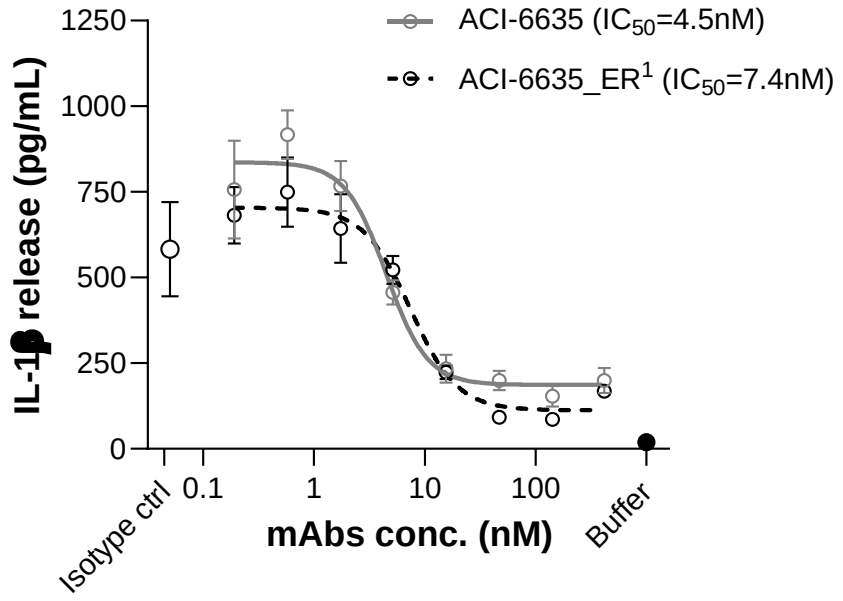
- ACI-6635 selected from >200 clones
- High affinity, specificity and proven target engagement on ASC

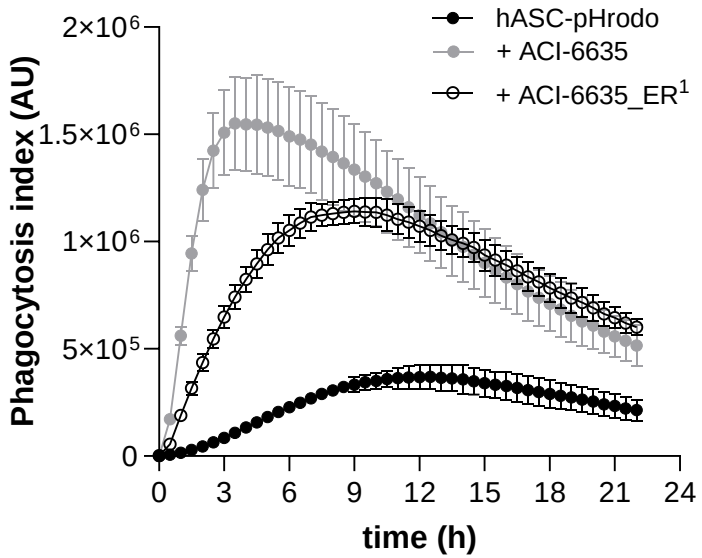
(1) Surface Plasmon Resonance; (2) molecular weight; (3) kilodalton; (4) Recombinant; (5) macrophage; (6) knockout;

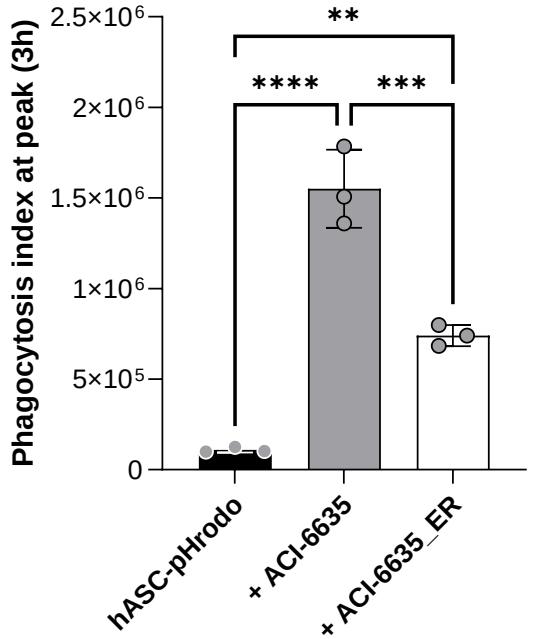
Basco, ITS 2023

ACI-6635: mechanism of action in phagocytosis

Accelerate ASC aggregate uptake with immune complexes using IgG effector function







**p<0.01; ****p<0.0001 vs ACI-6635. One-Way ANOVA

Basco, ITS 2023

- Efficacious mAb-mediated inhibition of ASC-driven inflammasome activation and IL-1β production
- ACI-6635 with full Fc effector function significantly enhances target internalization (phagocytosis) as compared to the effector reduced variant or ASC aggregates alone

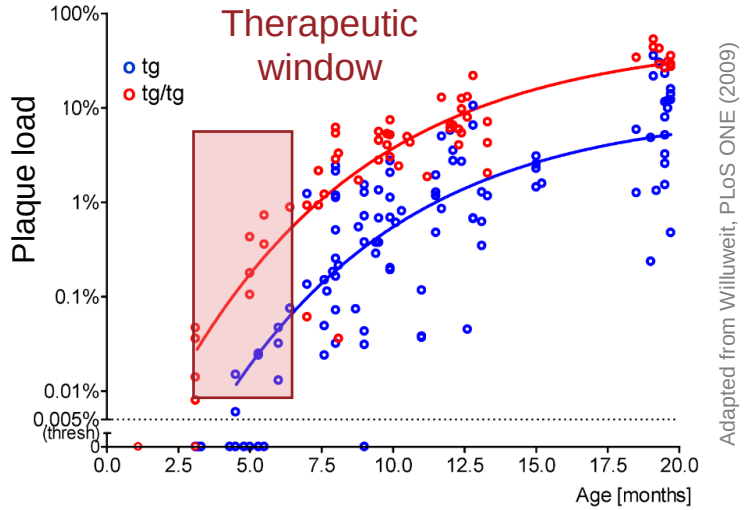
(1) Effector reduced

ACI-6635: efficacy in a mouse model of AD

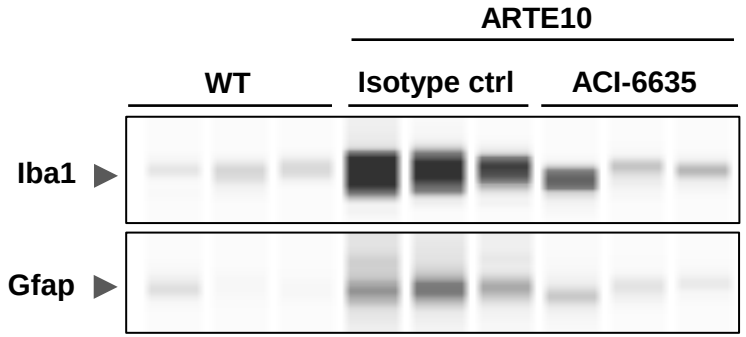
Reduces neuroinflammation in the ARTE10 amyloidosis mouse model

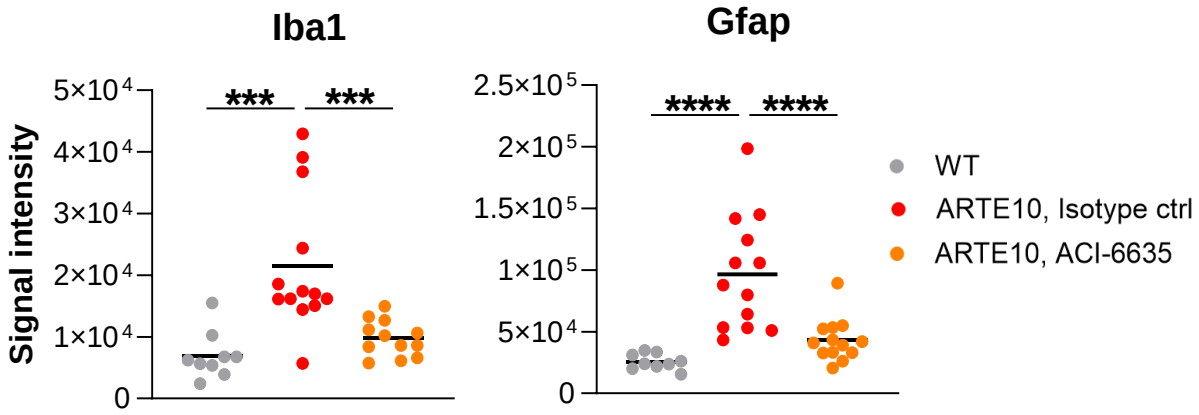
Readouts

- Biochemistry
- Histology
- Exposure



Adapted from Willuweit, PLoS ONE (2009)





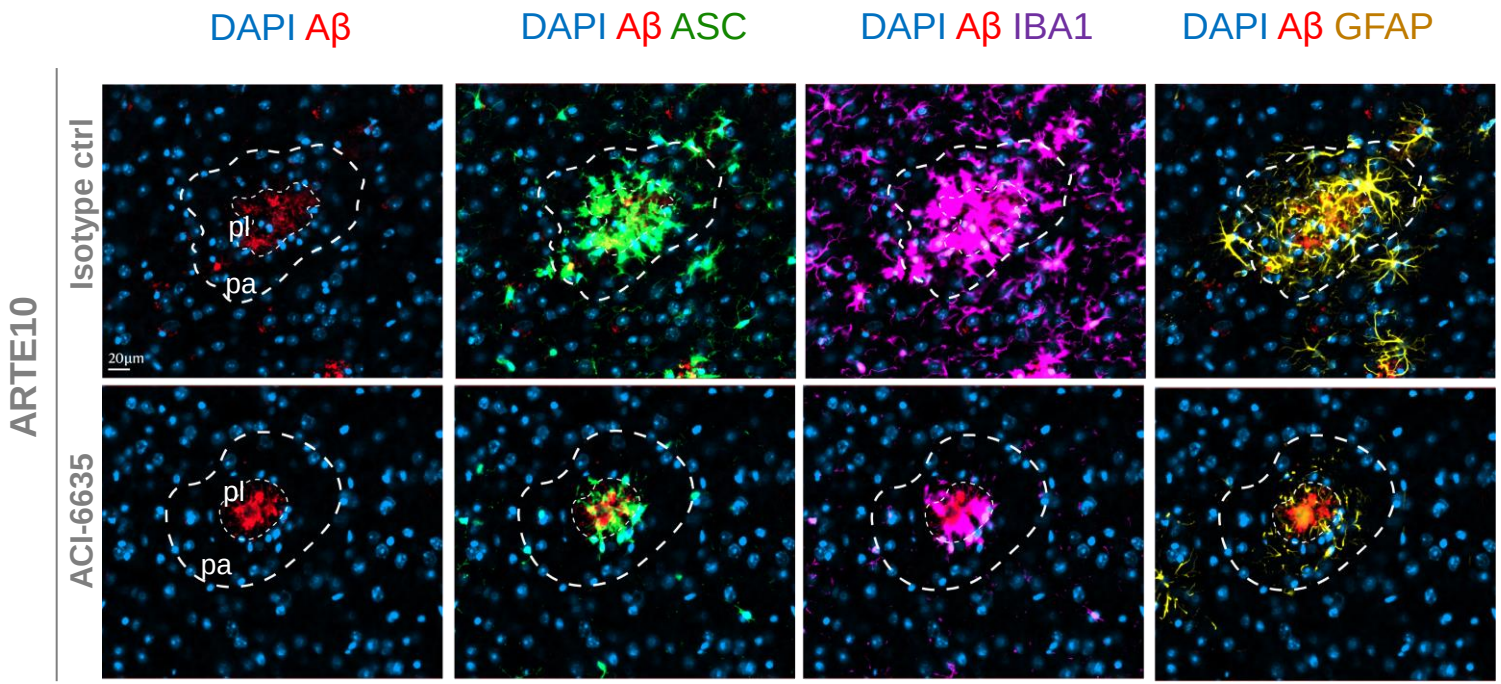
AC Immune unpublished data

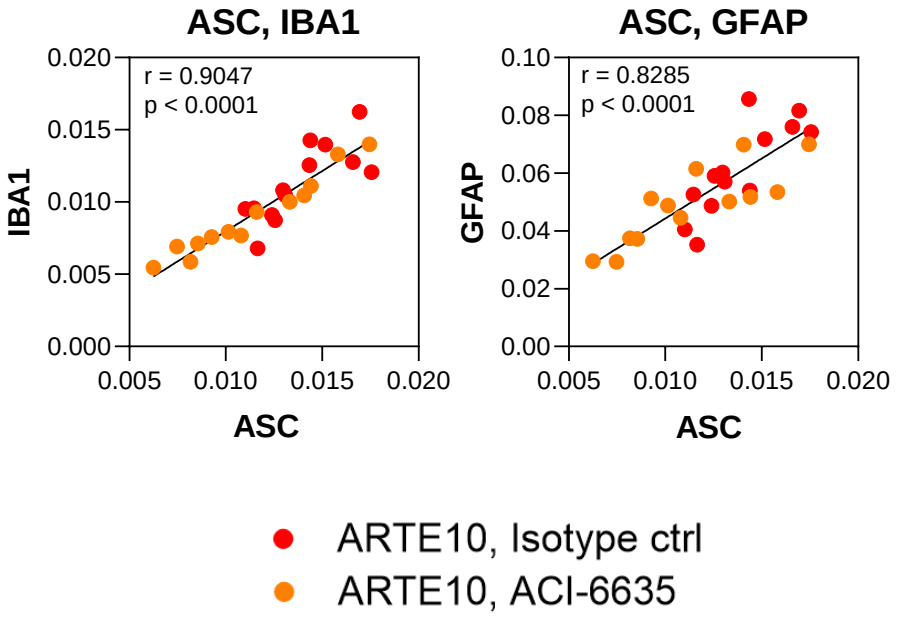
***p<0.001; ****p<0.0001 vs ARTE10, Isotype ctrl. One-Way ANOVA

- Therapeutic window established to assess efficacy in treating neuroinflammation and plaque formation
- ACI-6635 significantly reduces pathogenic microgliosis and astrocytosis

ACI-6635 decreases neuroinflammation via reduction of ASC spreading

mAb-mediated ASC removal mitigates gliosis and plaque engulfment





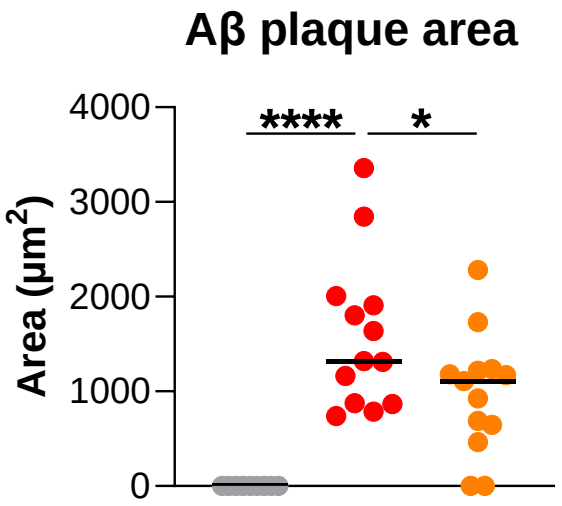
AC Immune unpublished data

- Treatment with ACI-6635 reduces microgliosis and astrocytosis in the peri-plaque areas
- Decreased level of ASC correlates with and may be responsible for reduced gliosis

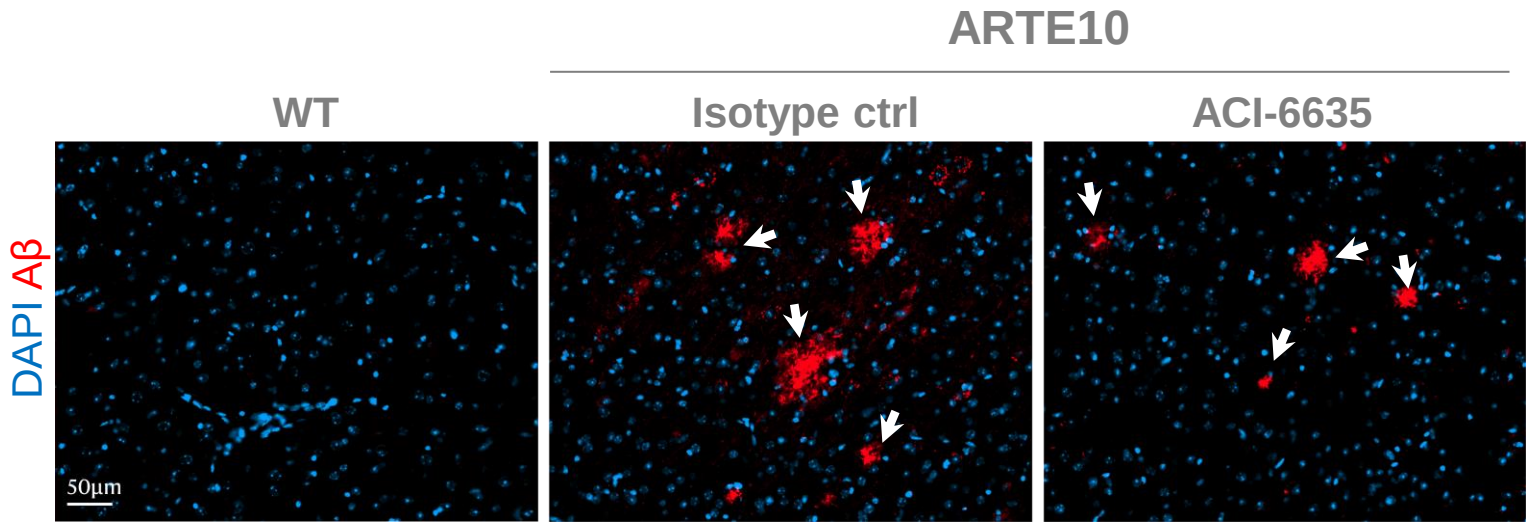
pl: amyloid plaque, pa: plaque-associated region (pl + 25 µm surrounding region)

ACI-6635: efficacy in a mouse model of AD

Reduces cortical amyloid plaque load amyloidosis



*p<0.05; ****p<0.0001 vs ARTE10, Isotype ctrl. One-Way ANOVA



AC Immune unpublished data

- WT
- ARTE10, Isotype ctrl
- ARTE10, ACI-6635

- ACI-6635 significantly reduced plaque size that correlates with improved glial function

Arrows: amyloid plaques

Summary and conclusions

1

- A broad panel of ASC mAbs were generated using our proprietary SupraAntigen® vaccine platform
- ACI-6635 identified as lead mAb with pM binding affinity, potent in *in vitro* assays and cross-reactive to human and mouse ASC

2

- Using mAb, ACI-6635, demonstrates that immunotherapy has the potential to:
  - Accelerate pathological ASC aggregate uptake via immune complexes when exploiting the full effector function of an IgG
  - Substantially reduce neuroinflammation in AD patients as ASC-induced plaque pathology and gliosis was significantly ameliorated in the ARTE10 amyloidosis mouse model of AD

3

- ACI-6635 ready for IND/CTA enabling studies
- With the era of successful disease-modifying treatments such as Lecanemab and Donanemab, therapeutics targeting neuroinflammation as well as plaques may be the next wave of interventional trials

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AC Immune

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