

Antibody-mediated inhibition of ASC attenuates inflammasome activation *in vitro* and in a mouse model of demyelination



Davide Basco, PhD – ADPD 2023, March 29<sup>th</sup>

### Disclaimer

This presentation may contain statements that constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Forward-looking statements are statements other than historical fact and may include statements that address future operating, financial or business performance or AC Immune's strategies or expectations. In some cases, you can identify these statements by forward-looking words such as "may," "might," "will," "should," "expects," "plans," "anticipates," "believes," "estimates," "predicts," "projects," "potential," "outlook" or "continue," and other comparable terminology. Forward-looking statements are based on management's current expectations and beliefs and involve significant risks and uncertainties that could cause actual results, developments and business decisions to differ materially from those contemplated by these statements. These risks and uncertainties include those described under the captions "Item 3. Key Information—Risk Factors" and "Item 5. Operating and Financial Review and Prospects" in AC Immune's Annual Report on Form 20-F and other filings with the Securities and Exchange Commission. Forward-looking statements speak only as of the date they are made, and AC Immune does not undertake any obligation to update them in light of new information, future developments or otherwise, except as may be required under applicable law. All forward-looking statements are qualified in their entirety by this cautionary statement.

SupraAntigen<sup>®</sup> is a registered trademark of AC Immune SA in the following territories: AU, EU, CH, GB, JP and RU.

### Conflict of interest disclosure

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



# ASC is the adaptor protein for numerous inflammasomes

Consists of sensor-interacting PYD and effector-interacting CARD domains

ASC-dependent inflammasomes<sup>1</sup>



ASC specks propagate pathology in CNS<sup>2</sup> diseases



(1) Ravichandran and Heneka, 2021; (2) Central Nervous System; (3) Amyloid beta

- ASC speck propagates inflammation
  - Extracellular ASC specks are detectable in brain of AD patients and seed Aβ plaques
  - Strong biological rationale for ASC as a new therapeutic target

3

ASC specks seed amyloid beta

🕜 AC Immune

Venegas et al. 2017

# Discovery of a highly potent lead candidate ASC antibody

A robust screening cascade for functional characterization of ASC mAbs

### AC Immune's proprietary SupraAntigen<sup>®</sup> technology



(1) pharmacokinetics; (2) proof-of-concept; (3) enzyme-linked immunosorbent assay; (4) surface plasmon resonance

- Generated > 200 anti-ASC hybridoma clones cross-reactive on human and mouse ASC
  - Selected clones for efficacy analysis *in vitro* and *in vivo*



# In vitro characterization of selected anti-ASC antibodies

Binding profile and affinity



(1) enzyme-linked immunosorbent assay; (2) Surface Plasmon Resonance

Anti-ASC mAbs bind human and mouse ASC with picomolar affinity

![](_page_4_Picture_10.jpeg)

## In vitro characterization of selected anti-ASC antibodies

Target engagement

![](_page_5_Figure_2.jpeg)

ASC/DAPI

(1) Recombinant; (2) macrophage; (3) knockout; (4) molecular weight; (5) kiloDalton

• Anti-ASC mAbs are specific for human and mouse ASC and show target engagement on ASC specks

![](_page_5_Picture_9.jpeg)

🕖 AC Immune

### In vitro functional assays

Evaluation of ASC uptake by human macrophages and downstream IL-1ß production

#### Inhibition of recombinant ASC polymerization

#### Inhibition of propagation of inflammation in human macrophages

![](_page_6_Figure_4.jpeg)

- Selected mAbs inhibit ASC polymerization and cytokine release
- Using anti-ASC mAbs substantially increase the uptake and neutralization of immuno-complexes by human macrophages reducing IL-1β production

AC Immune

AC Immune unpublished data

# In vivo efficacy for ASC mAb in a mouse model of demyelination

![](_page_7_Figure_1.jpeg)

 ASC mAb administered before the onset of the pathology protects from demyelination and improves the clinical score

📿 AC Immune

## Targeting ASC decreases T cell infiltration

![](_page_8_Figure_1.jpeg)

(1) hematoxylin eosin; (2) immunohistochemistry; (3) Body Weight; (4) not significant

 Anti-ASC mAb decreases CD4+ cell infiltration in the spinal cord possibly by limiting T cell egress from spleen

![](_page_8_Picture_5.jpeg)

![](_page_8_Picture_7.jpeg)

🕜 AC Immune

# Targeting ASC decreases microgliosis and inflammasome activation

![](_page_9_Figure_1.jpeg)

IR - immunoreactive

- ASC mAb shows target engagement by strongly reducing inflammasome markers in the spinal cord
  - Efficacy supported by reduction of microgliosis in the spinal cord

## Conclusions

1

- Generated a panel of ASC monoclonal antibodies with picomolar binding affinity, broad epitope coverage and cross-reactive to human and mouse ASC
- Enable exploration of ASC biology, therapeutic and biomarker potential
- Proven *in vitro* efficacy in reducing ASC polymerization and propagation of ASCdriven inflammation
- Proven *in vivo* efficacy for proprietary ASC mAbs shown by improvement of clinically relevant readouts supported by molecular markers in a mouse model of neuroinflammation and demyelination
- 4 Completed humanization activities for the antibody with proven in vivo efficacy

Inhibiting ASC function via immunotherapy provides amelioration of neuroinflammatory processes via multiple mechanisms relevant to various CNS macrophage- and microglia-mediated as well as peripheral inflammatory diseases.

### Acknowledgements

![](_page_11_Picture_1.jpeg)

Alexandra Casel Chantal Alliod Roger Moser Christopher Dumayne Romain Ollier Monisha Ratnam Florence Gauye Alessio Mylonas Tania Melly Alberto Silva Samjhana Thapa Tamar Ziehm

Kasia Piorkowska Thomas Jaquier Maria Stella Lombardi

Web:

Presenter:

Tamara Seredenina Marie Kosco-Vilbois Johannes Streffer Andrea Pfeifer

Valérie Eligert Rime Madani Andreia Serra Maxime Ayer Gabi Beuzelin

Damien Nevoltris Greg de Val

https://www.acimmune.com/

www.linkedin.com/company/ac-immune

davide.basco@acimmune.com

![](_page_11_Picture_12.jpeg)

Business development: bd@acimmune.com Investors and Media: communications@acimmune.com

![](_page_11_Picture_17.jpeg)