

Morphomer-Antibody Drug Conjugates (MorADCs)  
A new class of drugs for Neurodegenerative diseases

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ADPD 2025 | 1–5 April 2025

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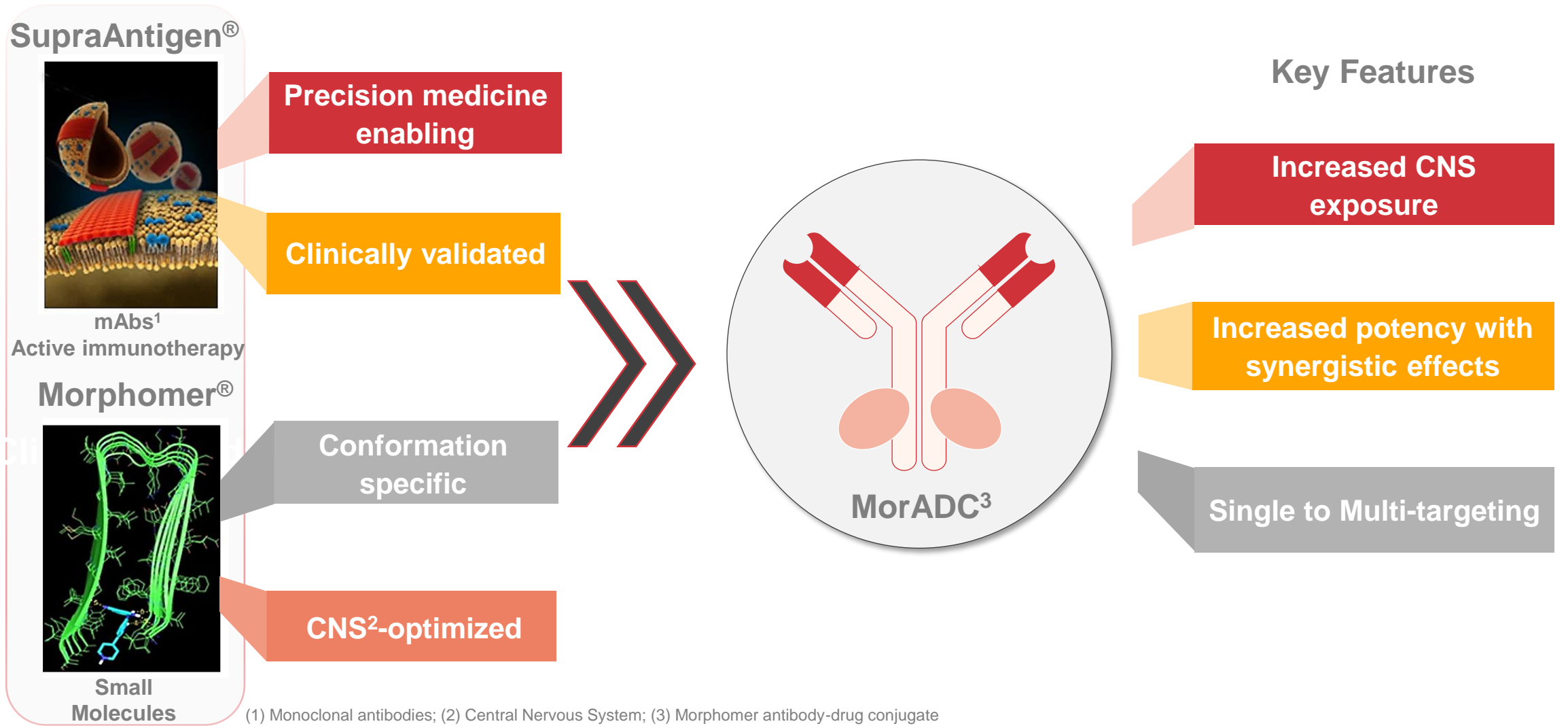
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## Conflict of interest disclosure

Sreenivasachary Nampally is an employee of AC Immune SA entitled to stocks and stock options.

# Synergistic combination of the SupraAntigen<sup>®</sup> and Morphomer<sup>®</sup> platforms

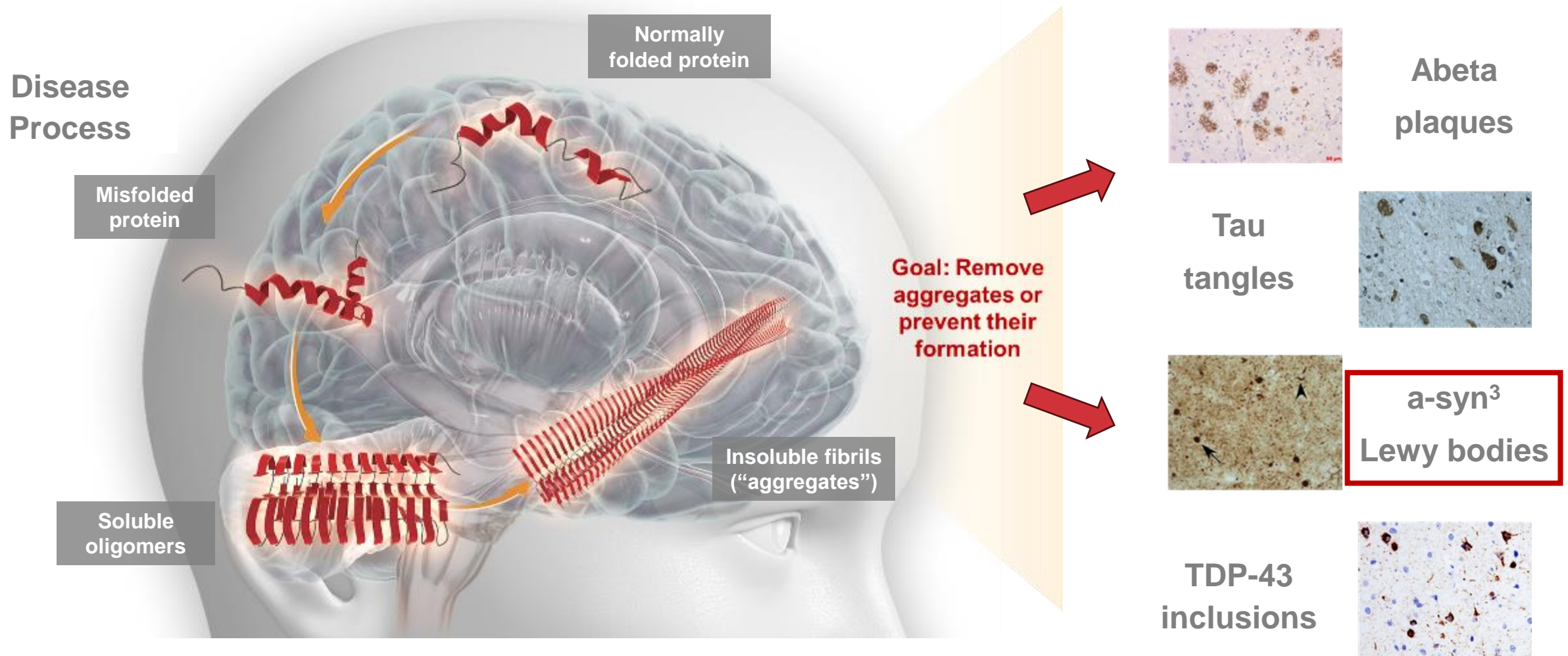
Combination of two clinically validated platforms to improve brain penetration and potency





# Misfolded proteins: Leading targets in neurodegenerative diseases

Abeta, Tau, a-synuclein and TDP-43<sup>1</sup> drive pathology in NDD<sup>2</sup>

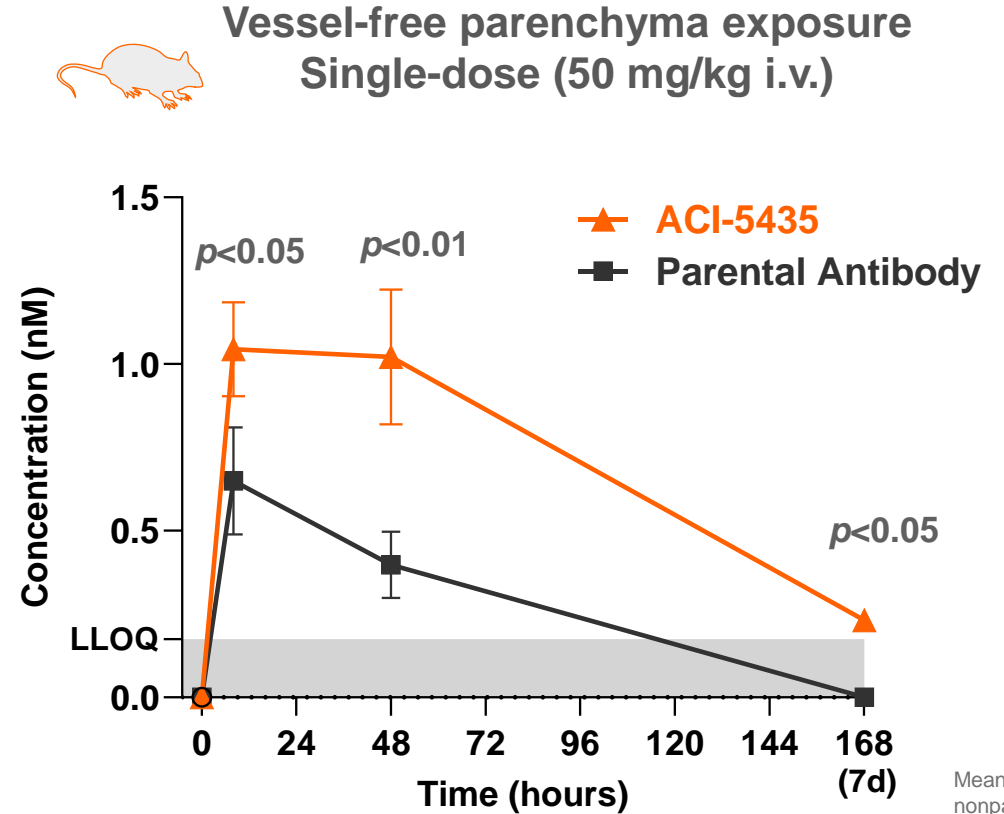
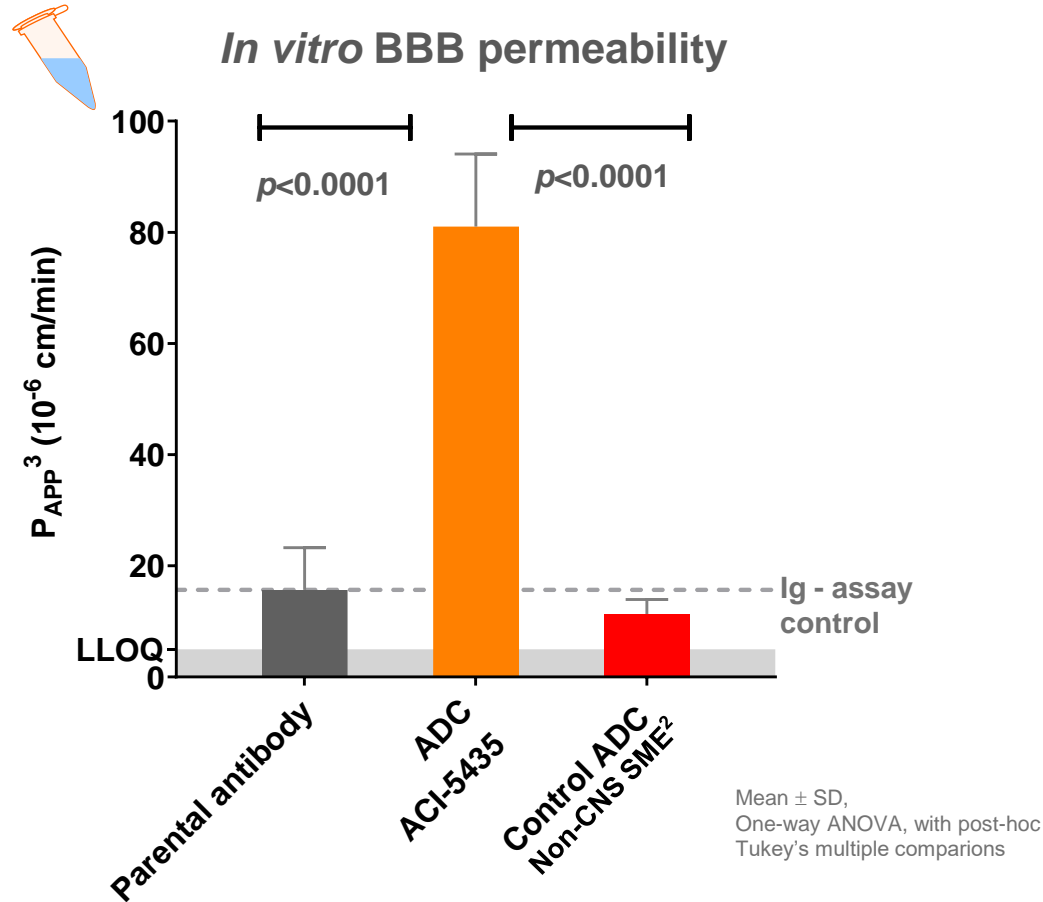


(1) TAR DNA-binding protein 43; (2) Neurodegenerative disease; (3) a-synuclein



# MorADCs display increase brain penetration

*In vitro* BBB<sup>1</sup> permeability and CNS exposure of MorADC ACI-5435



**3-fold increase in brain uptake over 7 days**

- Conjugation of the antibody to a brain penetrant Morphomer significantly increases BBB permeability and CNS penetration

(1) Blood Brain Barrier; (2) Control ADC with non-brain-penetrant small molecule; (3)  $P_{APP}$ : Apparent permeability



# MorADCs display synergistically improved potency

Inhibition of alpha-synuclein aggregation *in vitro* monitored by Thioflavin T

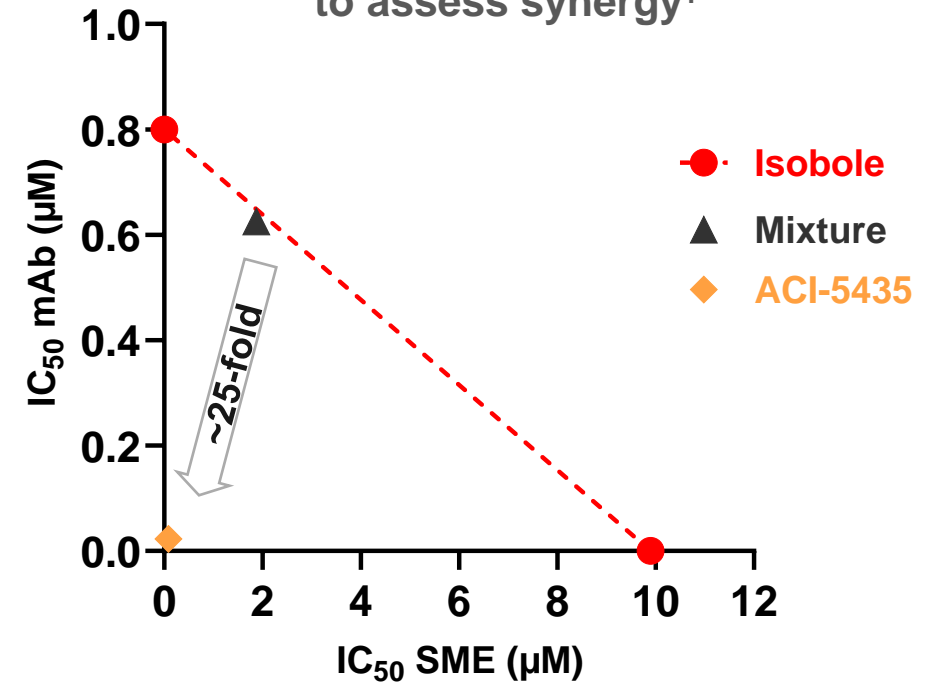
## Inhibition of aggregation



Inhibition of a-syn aggregation (IC <sub>50</sub> )			
Parental Antibody	Parental Morphomer	Mixture of parental drugs (1:3 ratio)	morADC ACI-5435-1
800 nM	9926 nM	2528 nM	103 nM

$$\text{Combination index (C.I.)} = \frac{a}{IC_{50 A}} + \frac{b}{IC_{50 B}}$$

## Analysis of drug combinations to assess synergy<sup>1</sup>



AC Immune unpublished data

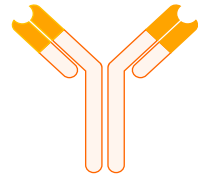
- ACI-5435 is 25-fold more potent than the mixture of the two parental entities
- These data reveal the synergistic effect of the mAb and SME when combined in one therapeutic molecule

(1) Chou TC. Drug combination studies and their synergy quantification using the Chou–Talalay method. Cancer Res 2010



# MorADCs are more potent inhibitors *in vitro*

a-syn aggregation monitored by beta-sheet and filament structures

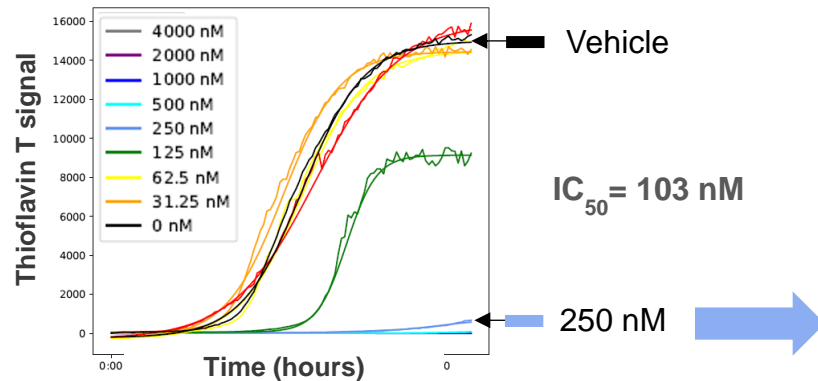
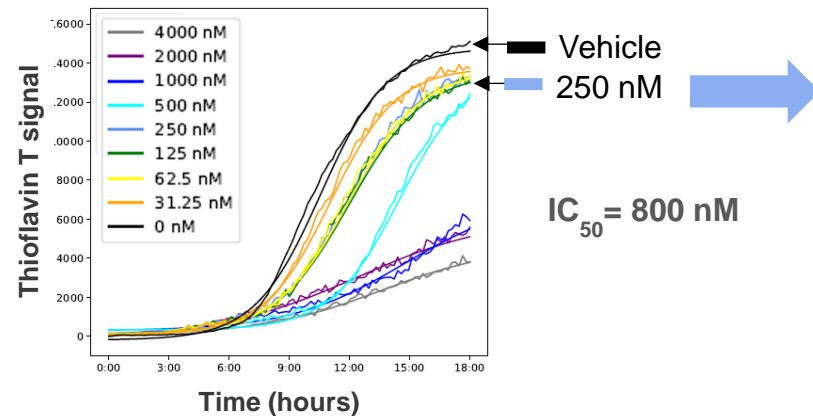


Parental Antibody



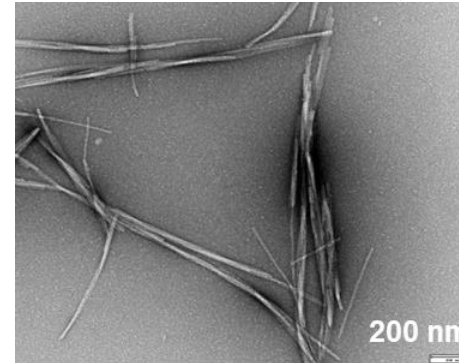
ACI-5435

## ThT<sup>1</sup> assay

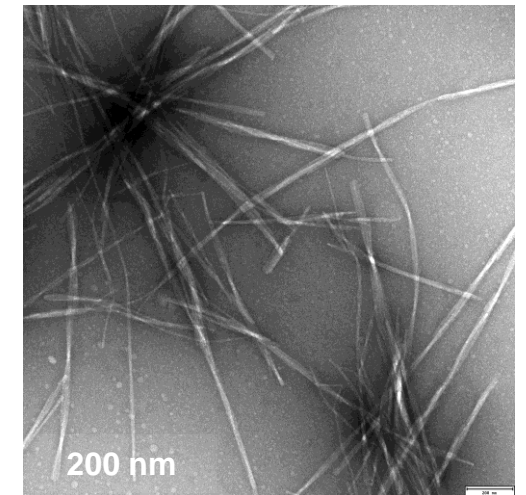


## Filament formation<sup>2</sup>

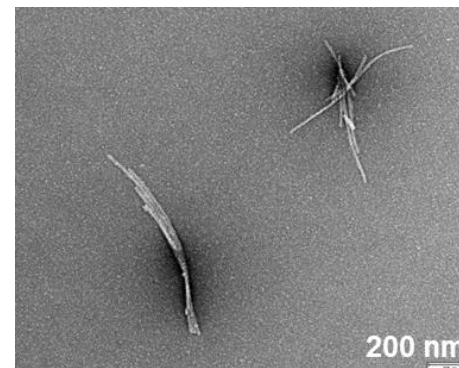
Parental antibody



Vehicle control



ACI-5435



AC Immune unpublished data

- MorADCs are highly potent as able to completely inhibit a-syn aggregation formation confirming the synergism when combined as one therapeutic molecule

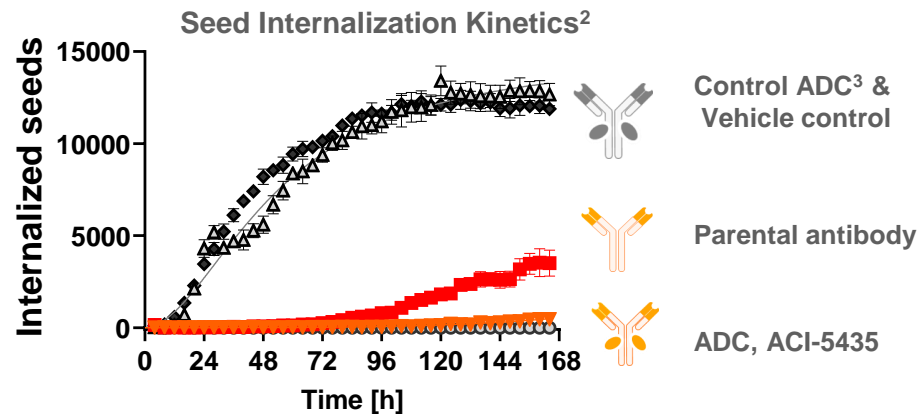
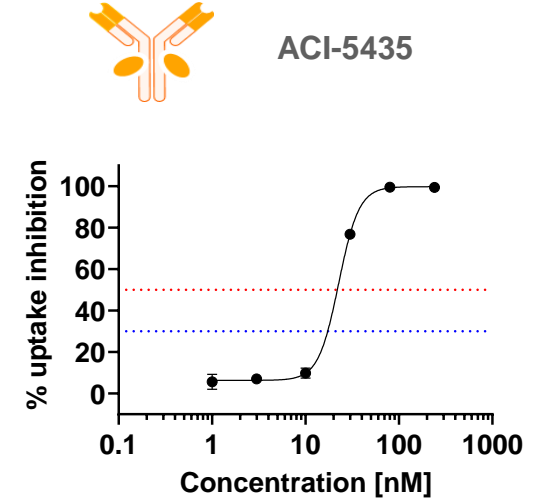
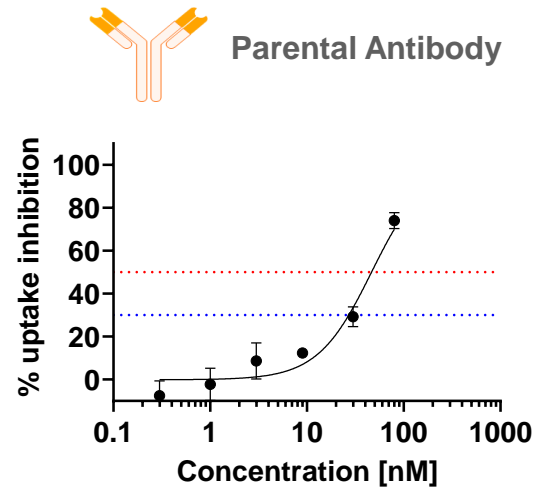
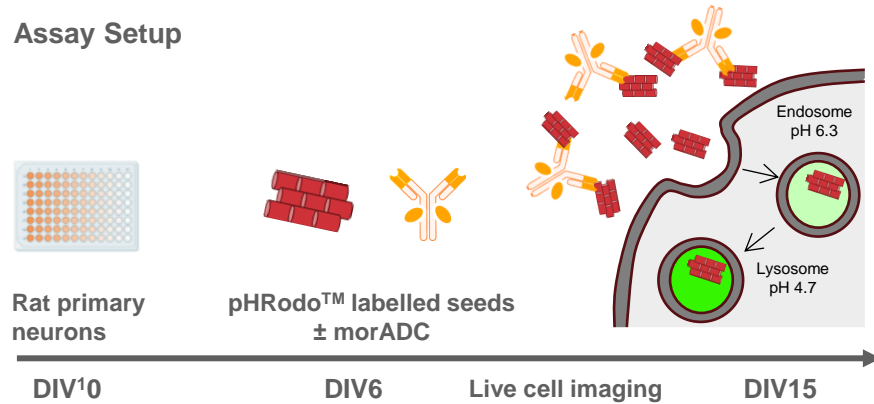
(1) Thioflavin T; (2) images generated by electron microscopy



# MorADCs inhibit a-syn seed internalization into neurons

## Kinetics of seed uptake in neurons

### Assay Setup



■ MorADCs have higher potency than parental antibody at reducing a-syn seed uptake

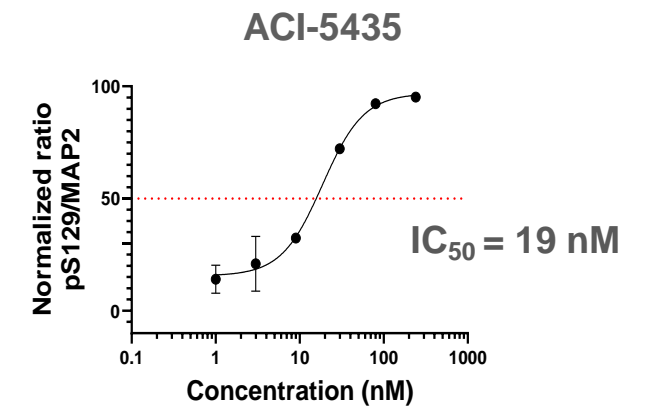
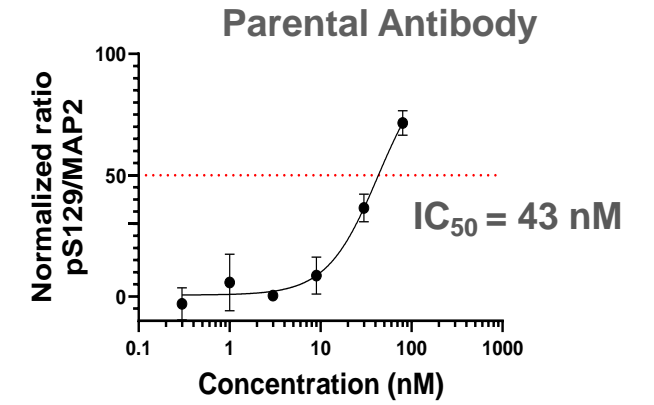
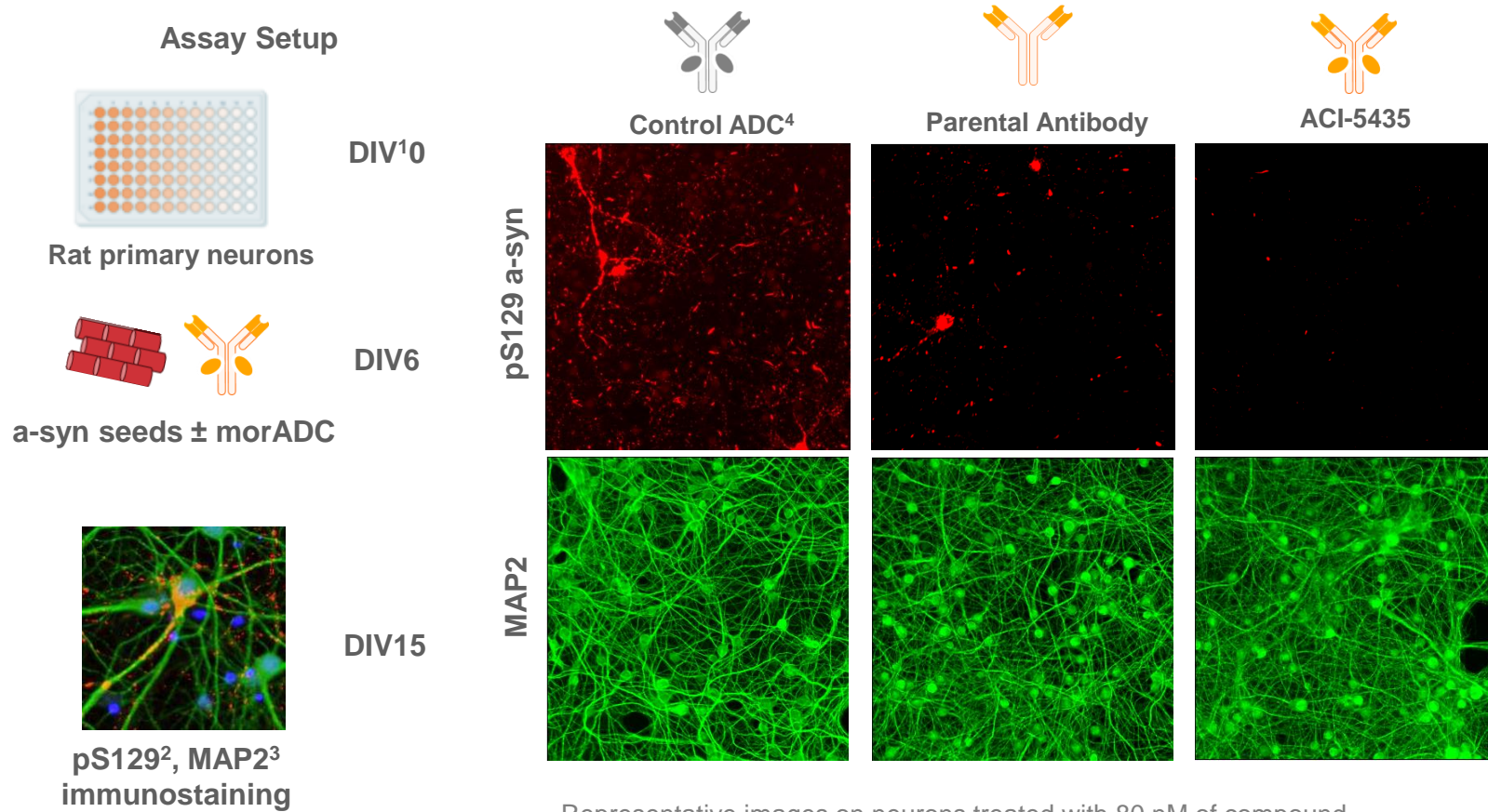
(1) Days *in vitro*; (2) Test articles used at 80nM; (3) Non-a-syn binding antibody conjugated to non-a-syn binding small molecule





# MorADCs inhibit intracellular pS129 a-syn accumulation

Treatment effects on *de novo* aggregates formed at endpoint



AC Immune unpublished data

- MorADCs have higher potency than parental antibody at reducing intracellular accumulation of pS129 a-syn

(1) Days *in vitro*; (2) pS129 a-syn; (3) Microtubule Associated Protein 2; (4) Non-a-syn binding antibody conjugated to non-a-syn binding small molecule

# Key take away messages

MorADCs: a game changing opportunity for NDD<sup>1</sup> therapies

## First-in-class

- A groundbreaking platform that integrates two clinically validated approaches into a single therapeutic molecule

## Brain exposure

- CNS exposure improved for morADCs compared to the parental mAbs

## Synergy

- The morADCs synergistically inhibit pathological a-syn aggregation

## Therapeutic potential

- MorADCs represent an innovative therapeutic approach with a broad application potential for the treatment of NDDs

(1) Neurodegenerative diseases



# Acknowledgements

Oskar Adolfsson  
Camille Martin  
Romain Ollier  
Sebastien Menant  
Elpida Tsika  
Alexis Fenyi  
Nadine Ait-Bouziad  
Lorene Aeschbach  
Sylvain Pautet  
Johannes Brune  
Aline Fuchs  
Nicolas Dreyfus  
Aurélien Davranche  
David Ribas  
Madiha Derouazi  
Marie Kosco-Vilbois  
Francesca Capotosti  
Günther Staffler  
Andrea Pfeifer



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We continue to shape the future of neurodegeneration by discovering and developing breakthrough therapies through pioneering science and precision medicine



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