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

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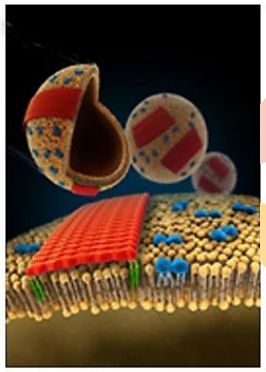
Conflict of interest disclosure

Sreenivasa**chary** Nampally is an employee of AC Immune SA entitled to stocks and stock options.

Synergistic combination of the SupraAntigen® and Morphomer® platforms

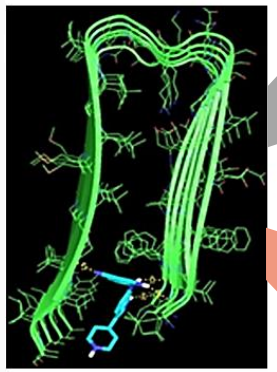
Combination of two clinically validated platforms to improve brain penetration and potency

SupraAntigen®



mAbs[1]
Active immunotherapy

Morphomer®



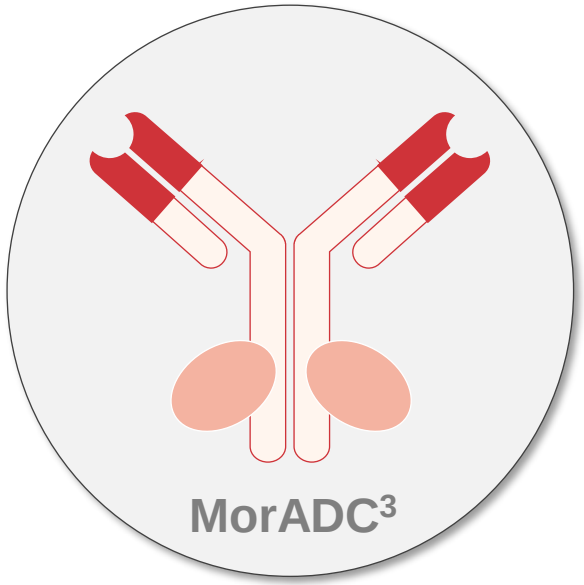
Small Molecules

Precision medicine enabling

Clinically validated

Conformation specific

CNS[2]-optimized



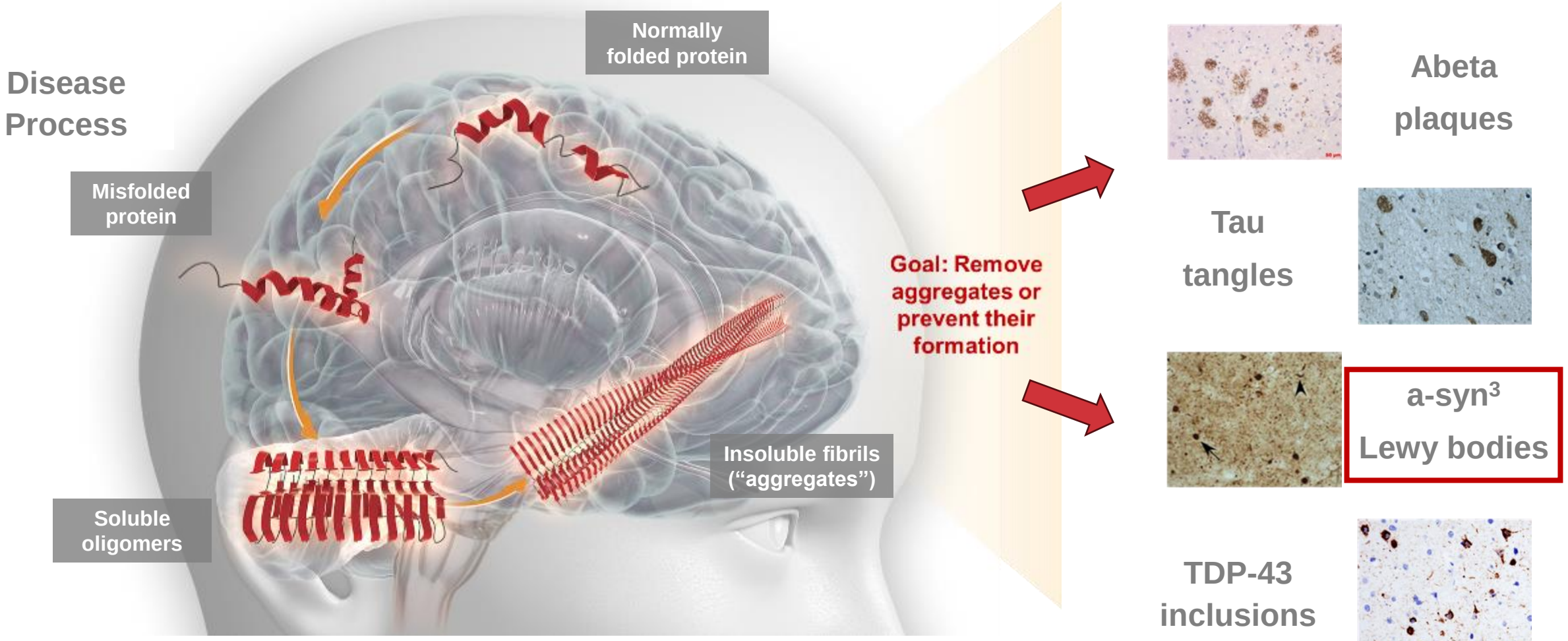
Key Features

- **Increased CNS exposure**
- **Increased potency with synergistic effects**
- **Single to Multi-targeting**

(1) Monoclonal antibodies; (2) Central Nervous System; (3) Morphomer antibody-drug conjugate

Misfolded proteins: Leading targets in neurodegenerative diseases

Abeta, Tau, a-synuclein and TDP-43[1] drive pathology in NDD[2]



Nag *et al.* Acta Neuropathologica Communications 2018

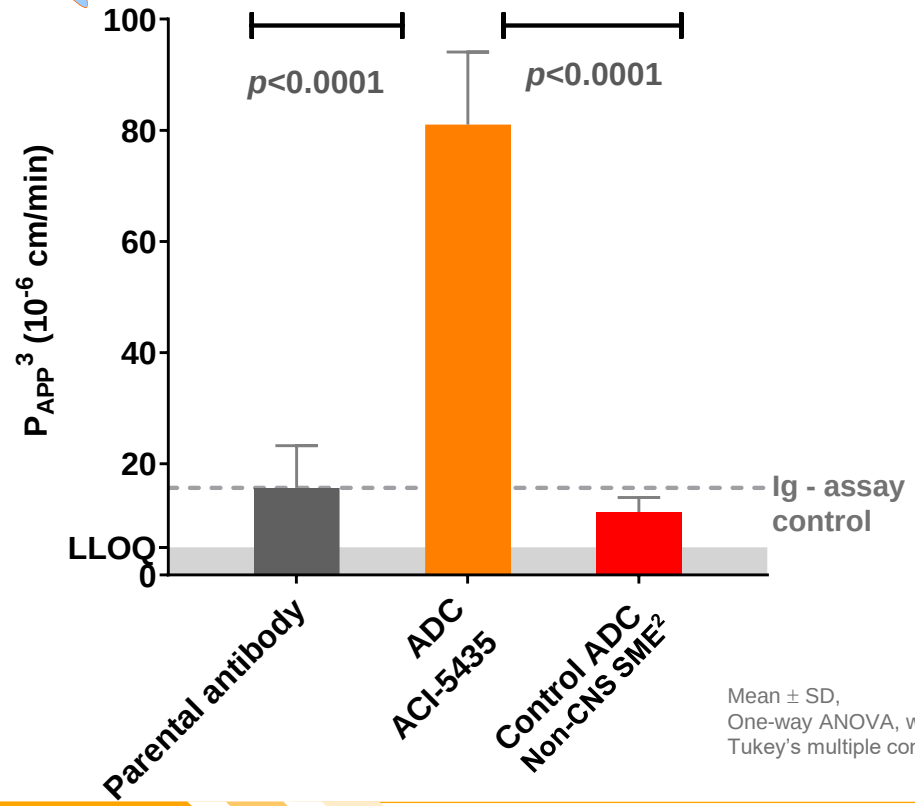
(1) TAR DNA-binding protein 43; (2) Neurodegenerative disease; (3) a-synuclein

MorADCs display increase brain penetration

In vitro BBB[1] permeability and CNS exposure of MorADC ACI-5435

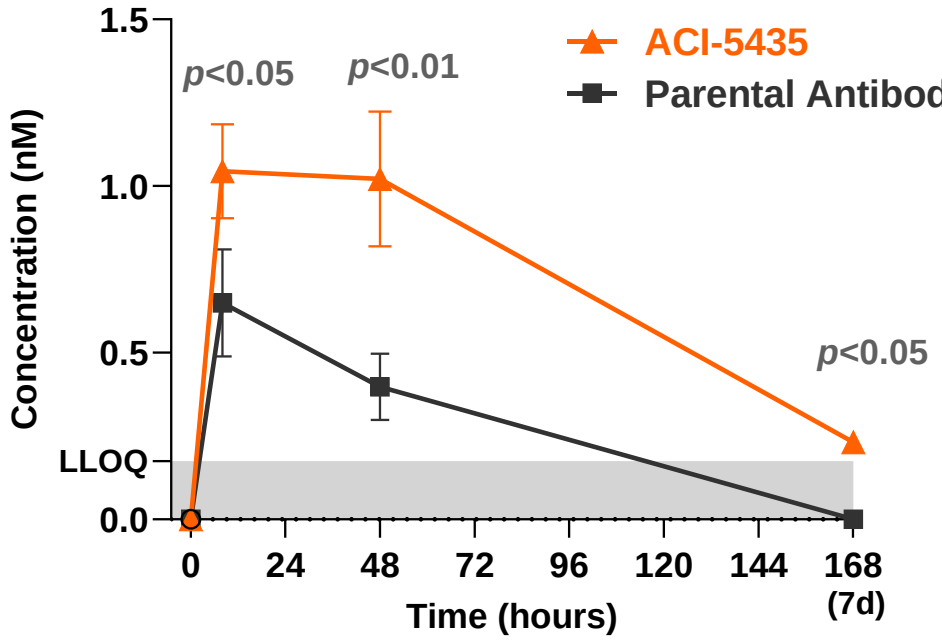
ACI-5435

In vitro BBB permeability



Mean ± SD,
One-way ANOVA, with post-hoc Tukey's multiple comparions

Vessel-free parenchyma exposure Single-dose (50 mg/kg i.v.)



Mean ± SD, with nonparametric Mann-Whitney test

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

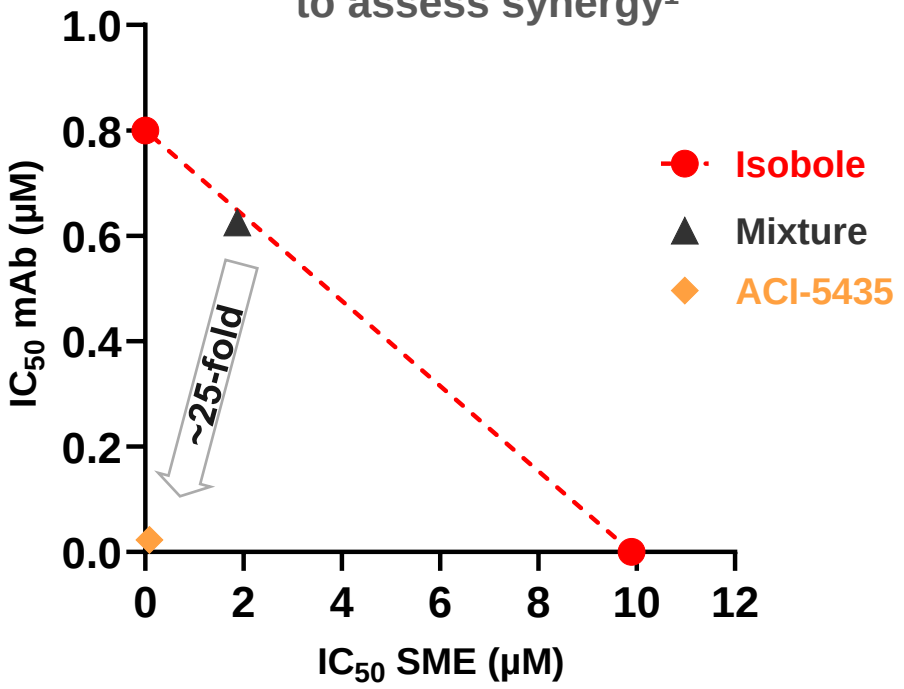
a-syn a-syn

MorADCs display synergistically improved potency

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

Inhibition of aggregation

Analysis of drug combinations to assess synergy[1]



Inhibition of a-syn aggregation (IC_{50})

Parental Antibody	Parental Morphomer	Mixture of parental drugs (1:3 ratio)	morADC ACI-5435-1
800 nM	9926 nM	2528 nM	103 nM

$$Combination\ index\ (C.I.) = \frac{a}{IC50\ A} + \frac{b}{IC50\ B}$$

- 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

AC Immune unpublished data

AC Immune

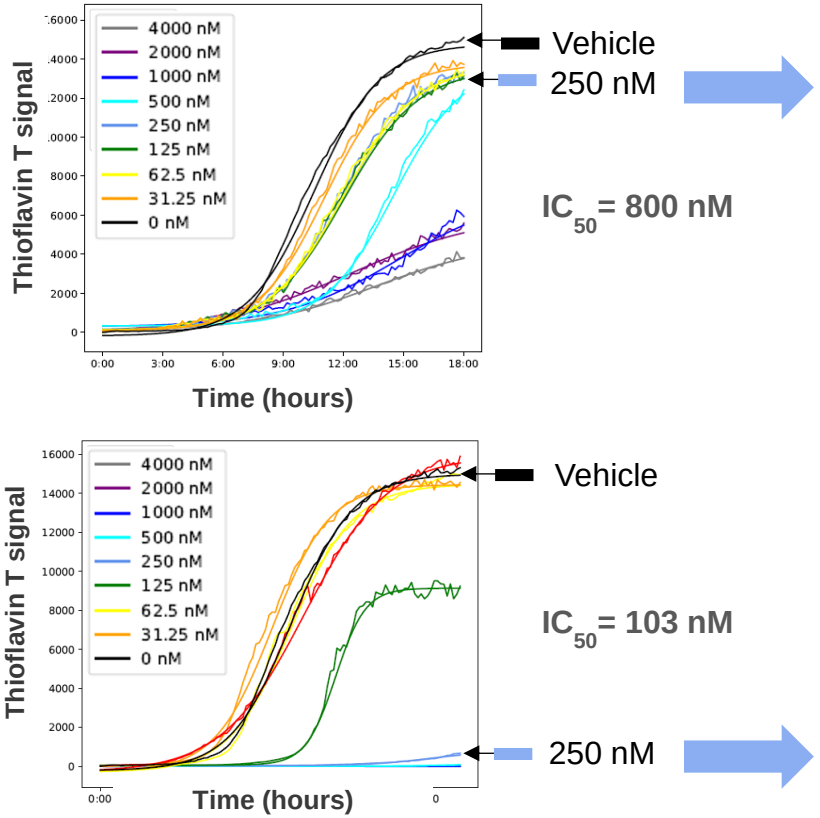
MorADCs are more potent inhibitors *in vitro*

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

Parental Antibody

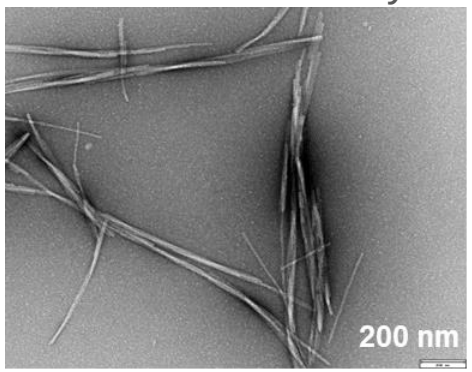
ACI-5435

ThT[1] assay

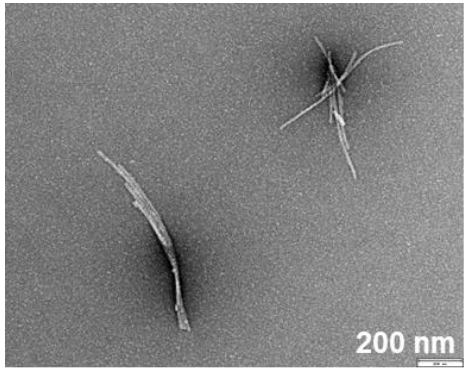


Filament formation[2]

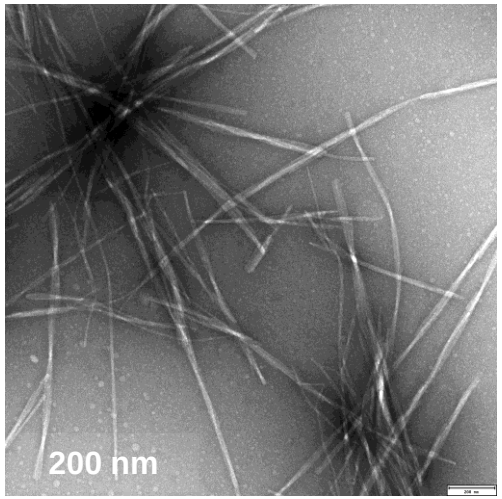
Parental antibody



ACI-5435



Vehicle control

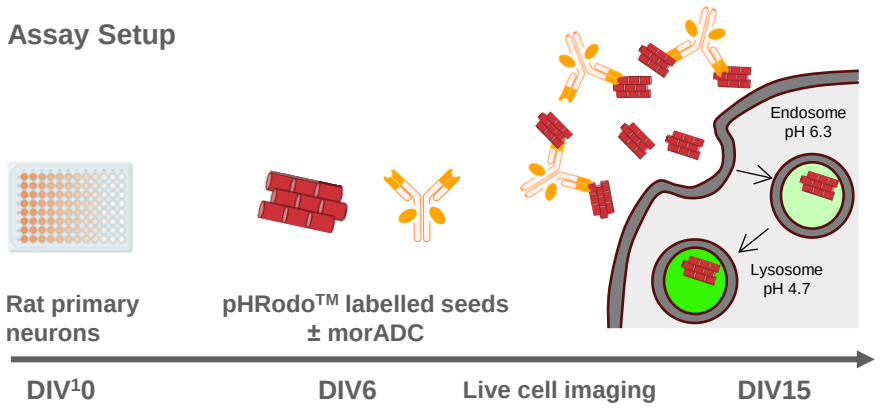


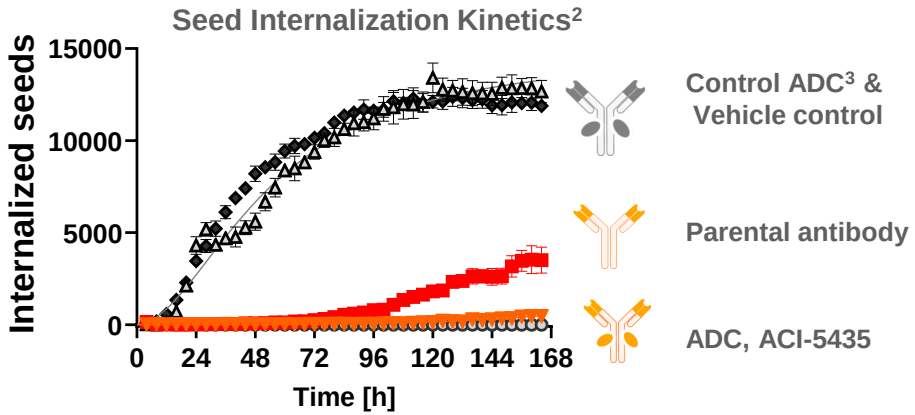
- MorADCs are highly potent as able to completely inhibit a-syn aggregation formation confirming the synergism when combined as one therapeutic molecule

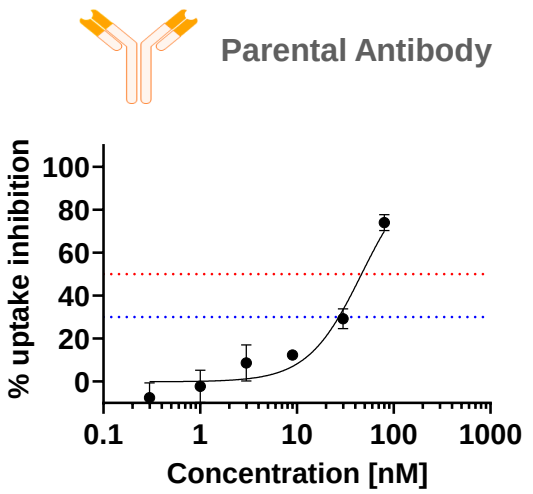
(1) Thioflavin T; (2) images generated by electron microscopy

MorADCs inhibit a-syn seed internalization into neurons

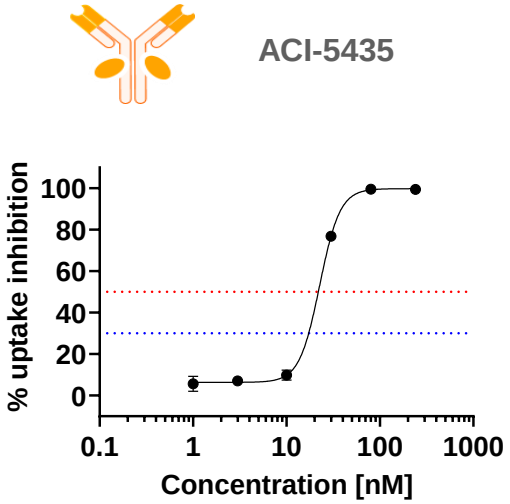
Kinetics of seed uptake in neurons







IC_{50} = 46 nM



IC_{50} = 23 nM

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

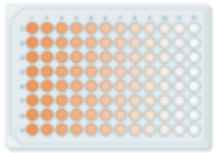
(1) Days *in vitro*; (2) Test articles used at 80nM; (3) Non-a-syn binding antibody conjugated to non-a-syn binding small molecule

AC Immune unpublished data

MorADCs inhibit intracellular pS129 a-syn accumulation

Treatment effects on *de novo* aggregates formed at endpoint

Assay Setup

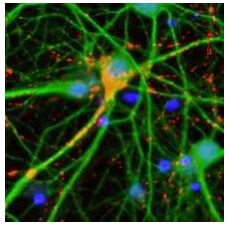


DIV[1]0

Rat primary neurons

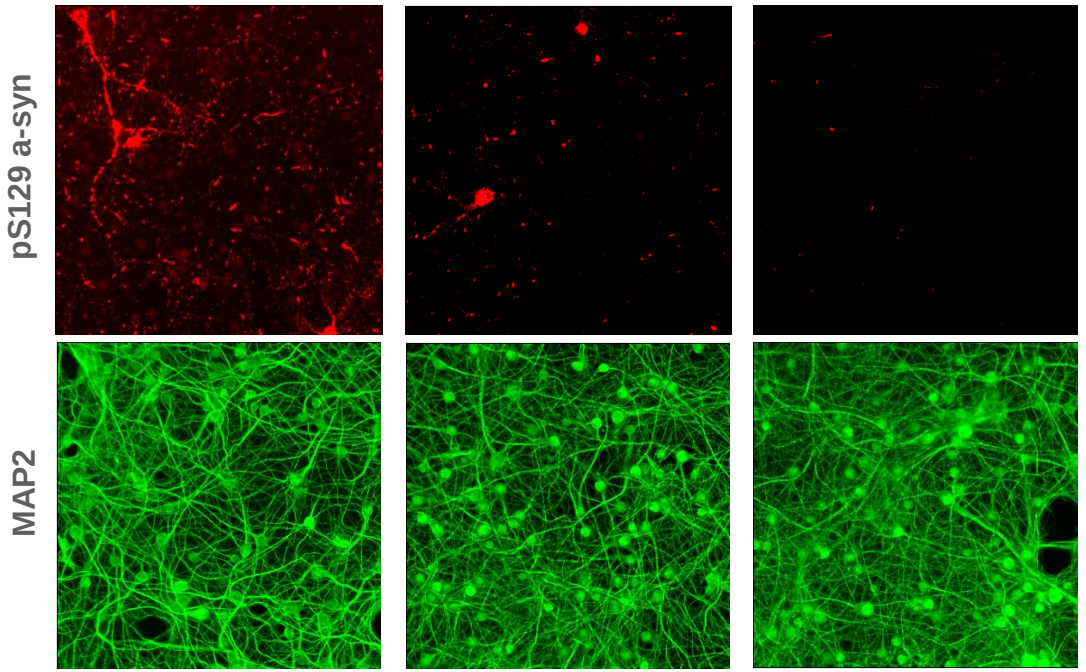
DIV6

a-syn seeds ± morADC

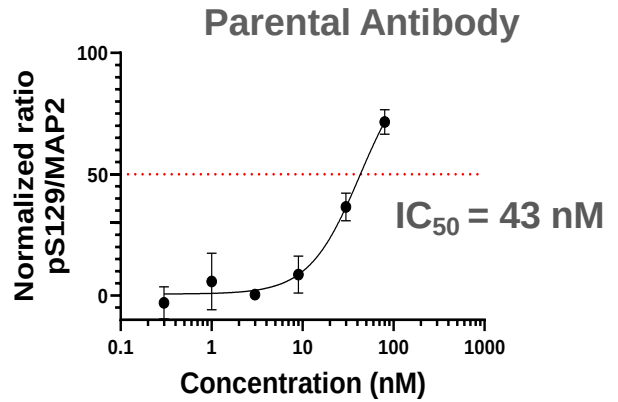


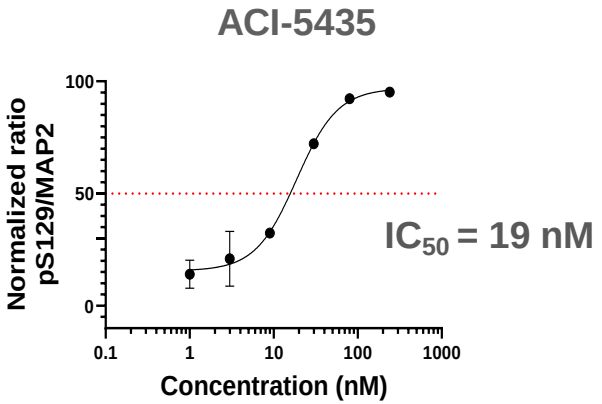
DIV15

pS129[2], MAP2[3] immunostaining



Representative images on neurons treated with 80 nM of compound





- 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[1] 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

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AC Immune

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