Discovery and optimization of therapeutic small molecules targeting alpha-synuclein aggregation

Elpida Tsika, PhD | ADPD™ 2025 | April 2025

AC Immune

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Conflict of interest disclosure

Elpida Tsika is an employee of AC Immune entitled to stock options.

Parkinson’s disease

Pathological deposition of alpha-synuclein

Most common neurodegenerative movement disorder
Affects ~1% of the population over 65 years

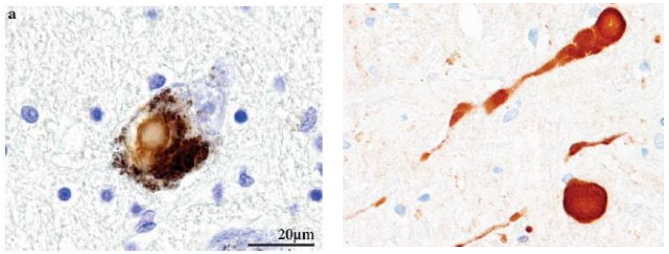
Etiology
5-10% genetic, 90-95% idiopathic, unknown cause

Cardinal motor symptoms
Tremor, rigidity, bradykinesia

Common non-motor symptoms
Sleep disorder, depression, cognitive impairment

Pathological hallmarks
Neuron loss, alpha-synuclein aggregates – Lewy bodies

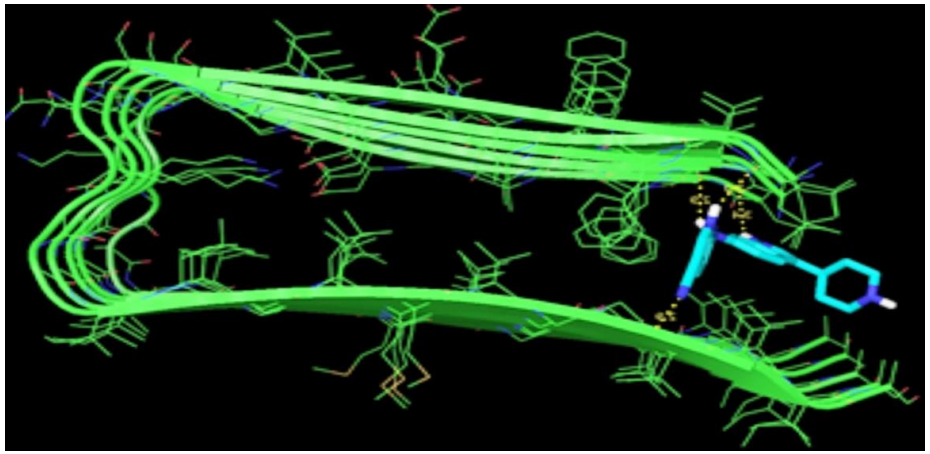
Main component of Lewy bodies: Alpha-synuclein



Halliday *et al.* 2011

Proprietary Morphomer® platform

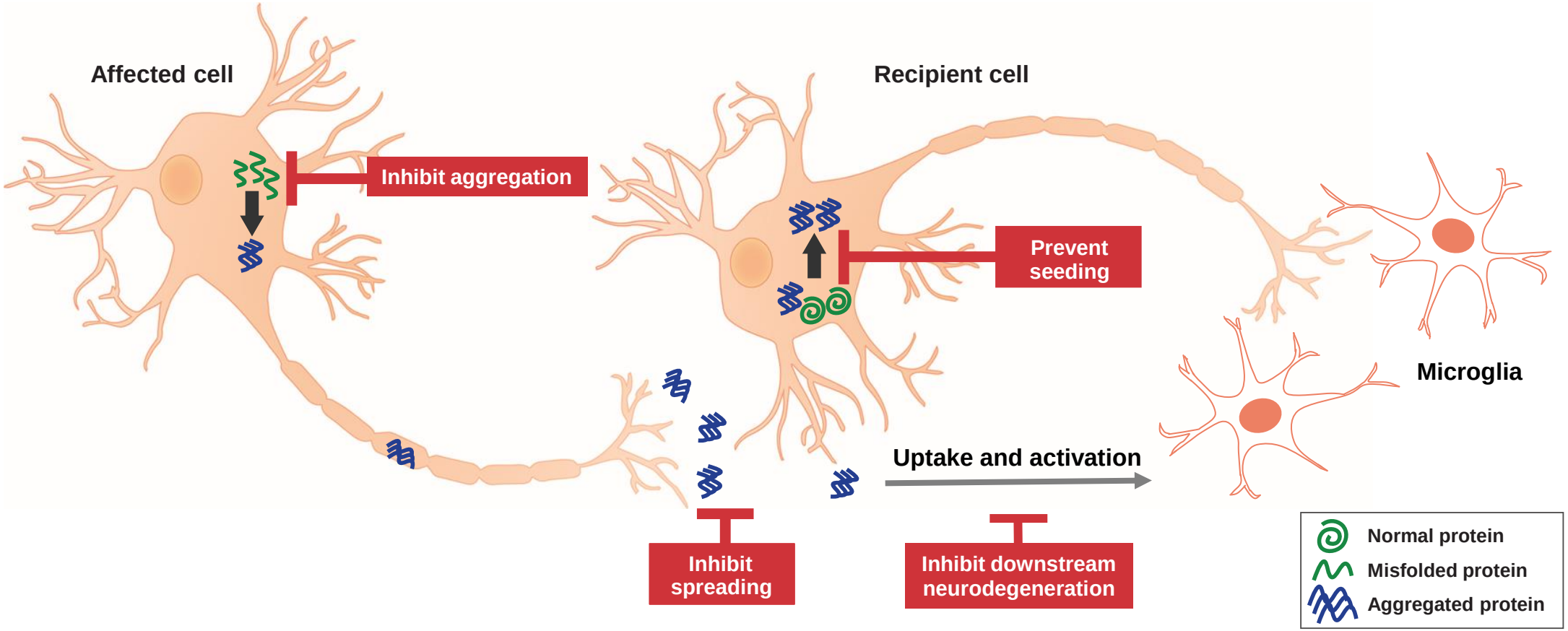
Targeting alpha-synuclein aggregation with small molecules



- Robust library of conformation-specific, non-peptidic small molecules with desirable CNS[1] properties constructed and continuously expanded via rational design over many years
- Comprehensive screening in assays of high translational value to rapidly generate highly specific hits
- Clinically validated platform with two diagnostic PET tracers showing excellent target engagement

(1) Central nervous system

A-syn[1]-targeting Morphomer® designed to stop disease progression

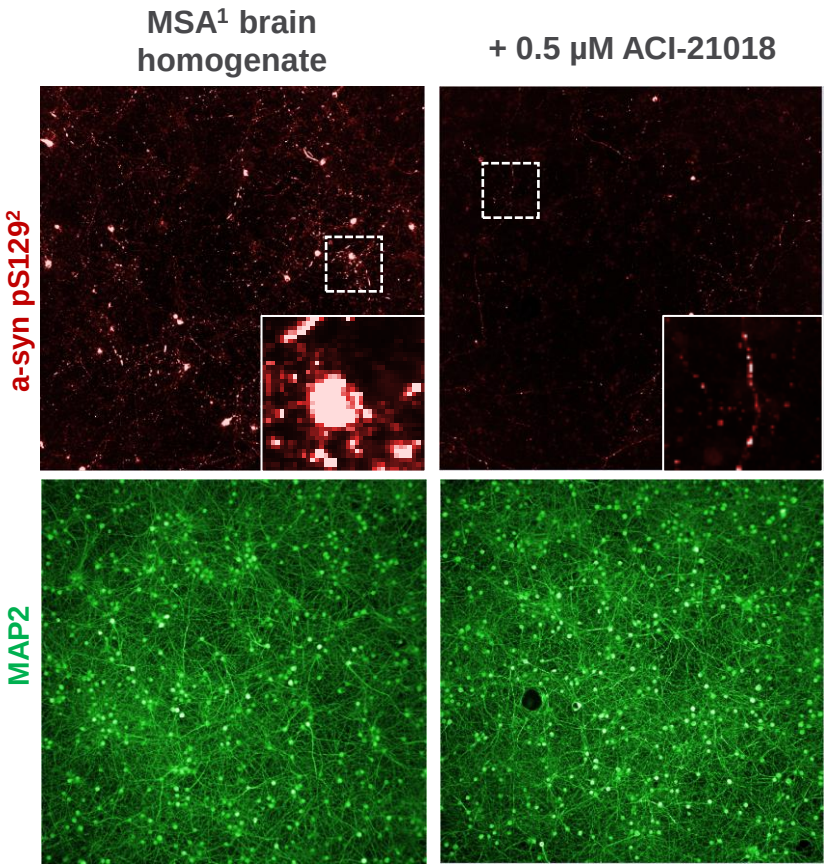


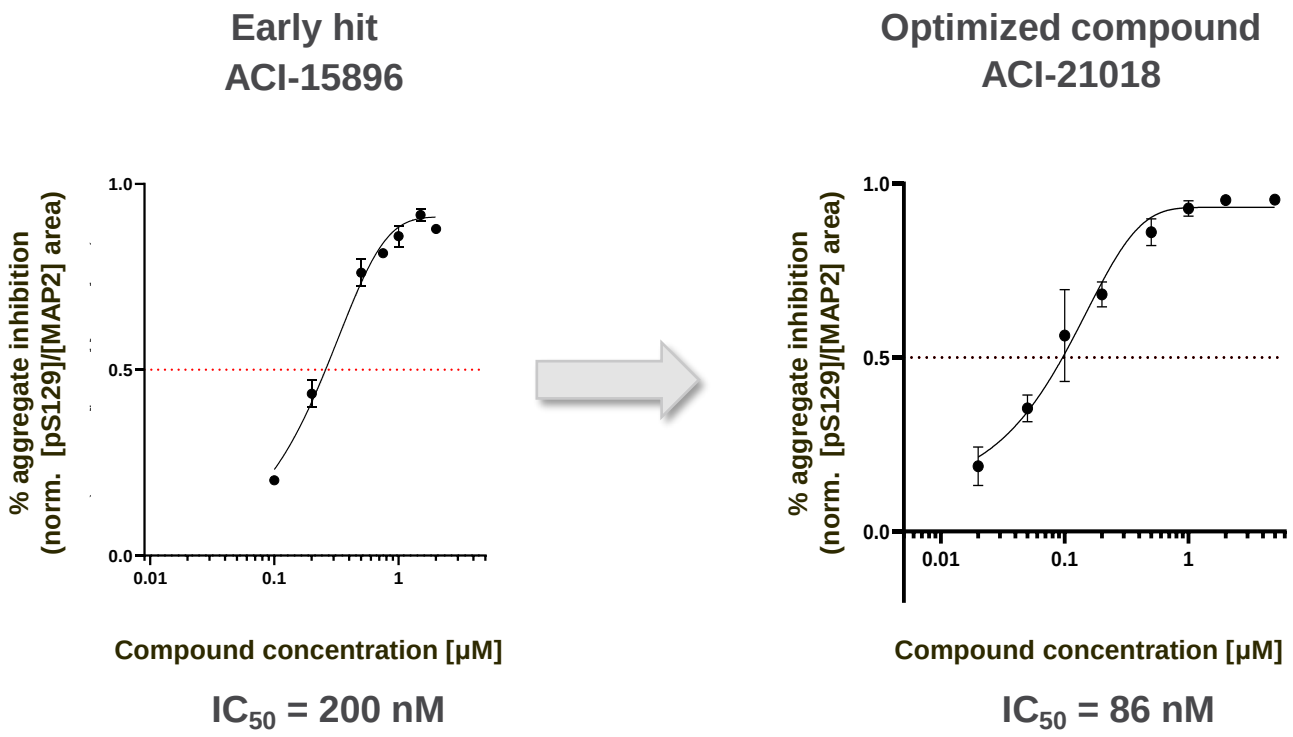
- Targeting aggregation and seeding intracellularly
- Combining with inhibition of extracellular spreading for full control of disease pathology
- Synergizing with AC Immune's a-syn PET tracer program enables our precision medicine approach

(1) Alpha-synuclein

Inhibition of pathological a-syn aggregation in neurons

Potent inhibition using disease brain[1]-derived a-syn aggregates





Ait-Bouziad et al. Synuclein 2022; Tsika et al., ADPD™ 2024

- Treatment reduces intracellular pS129[2] inclusions in rat primary neurons seeded with disease-derived a-syn
- Medicinal chemistry optimization led to ACI-21018 with an improved profile including better potency with IC_{50} in low nM range

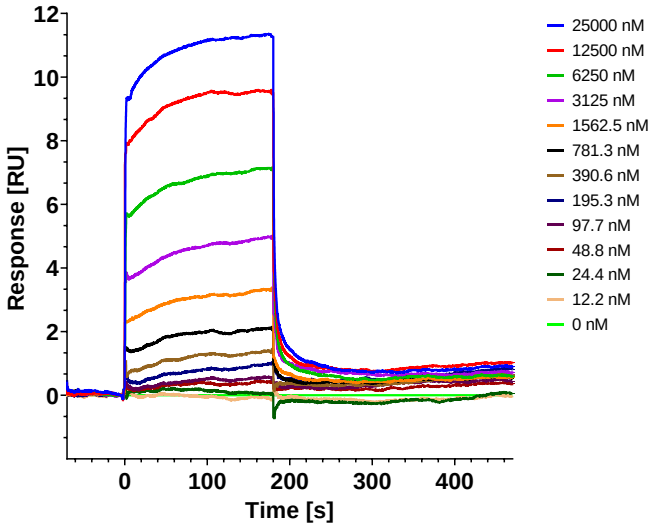
(1) Multiple system atrophy; (2) Phospho-Serine 129

ACI-21018 shows target engagement on disease-derived aggregates

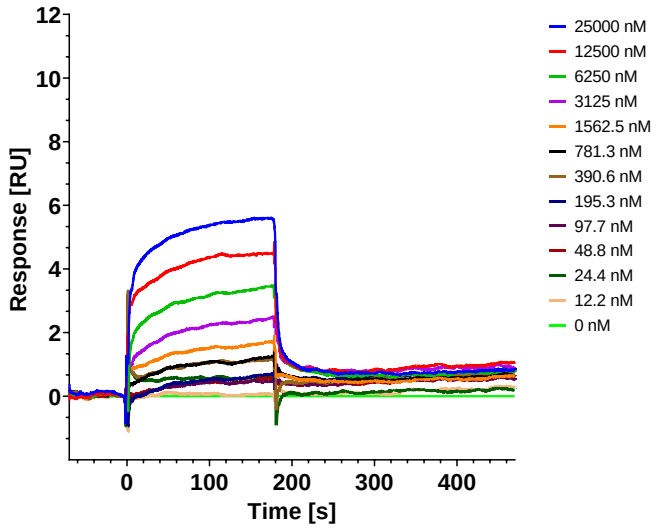
Using Surface Plasmon Resonance and radiobinding assays

Brain-derived homogenates (SPR[1])

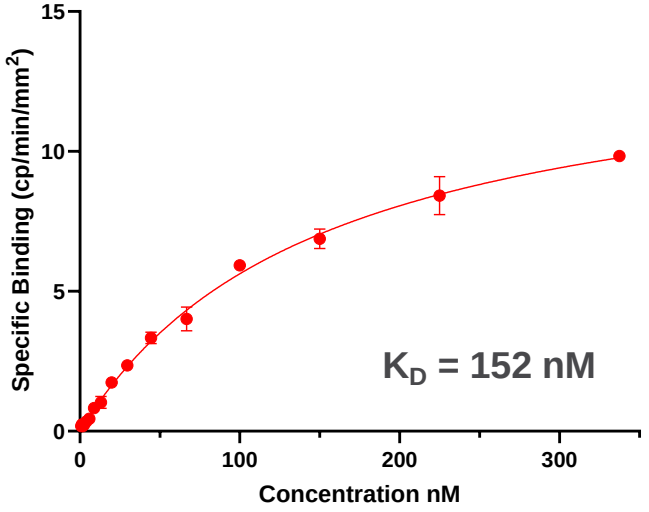
PD[2]



MSA[3]



PD brain-derived a-syn aggregates (Radiobinding)



Tsika et al., ADPD™ 2024; AC Immune unpublished data

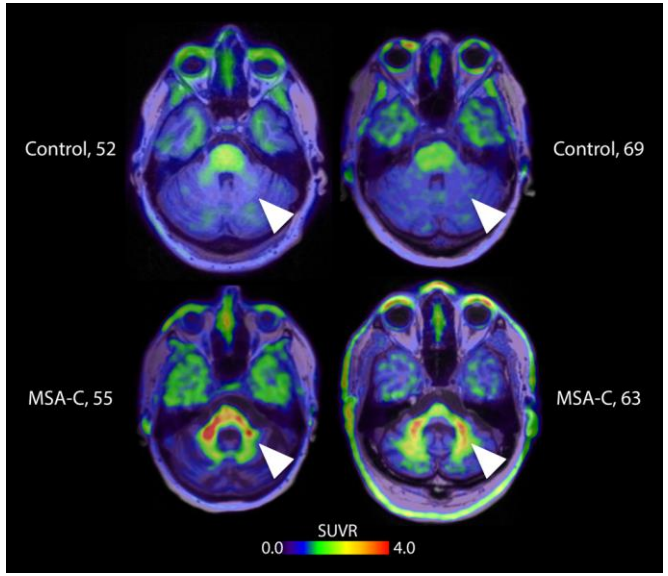
- ACI-21018 demonstrates binding to a-syn aggregates from PD and MSA brain tissues
- Saturation binding studies with [3H]ACI-21018 on PD-derived a-syn aggregates show nM binding affinity in line with its low nM potency observed in the neuronal seeding assay

(1) Surface Plasmon Resonance; (2) Parkinson's disease; (3) Multiple System Atrophy

Common binding site of ACI-21018 and a-syn PET[1] tracer, ACI-12589

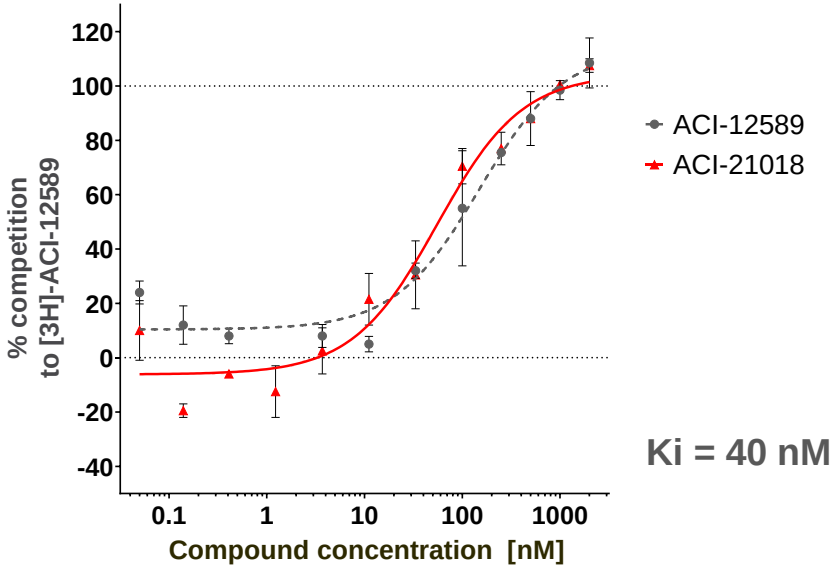
Accelerating and de-risking clinical development in MSA[2]

ACI-12589
PET signal in MSA patients



RR. Smith et al., Nat. Com., 2023

Competition radiobinding on
PD-derived a-syn aggregates



AC Immune ADPD™ 2024

Share binding site(s) with AC Immune's a-syn PET tracer allowing optimized clinical translatability to:

- Assess target engagement in Phase 1b study to inform dose selection
- Provide a pharmacodynamic biomarker to evaluate effect on pathology

(1) Positron emission tomography; (2) Multiple system atrophy

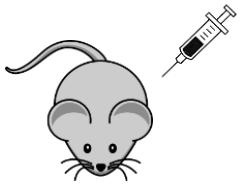
Evaluation of ACI-21018 *in vivo* efficacy in a model of PD[1]

Study design using the a-syn hPFF[2] model

Unilateral **hPFF** injection

Tg M83$^{+/-}$
8-10 weeks

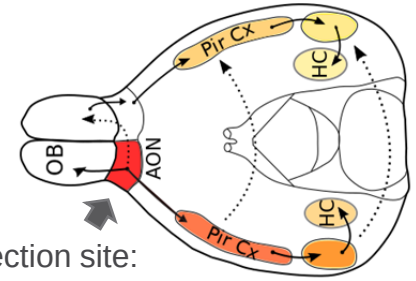
Human A53T a-syn expressed in neurons under the PrP promoter



QD[3] oral gavage for 15 weeks

Start treatments 48h post-hPFF injection

Projections from injection site to interconnected brain areas



Injection site: Anterior Olfactory Nucleus

Group	Inoculum	Treatment
1	PBS	Vehicle
2	hPFF	Vehicle
3	hPFF	ACI-21018 – 50mg/kg
4	hPFF	ACI-21018 – 100mg/kg

Readouts:

- Propagating a-syn aggregates by *ex vivo* seeding of brain lysates in primary neurons
- Neurodegeneration by neuronal marker, NeuN IHC[4]
- Brain regional volume by MRI[5]

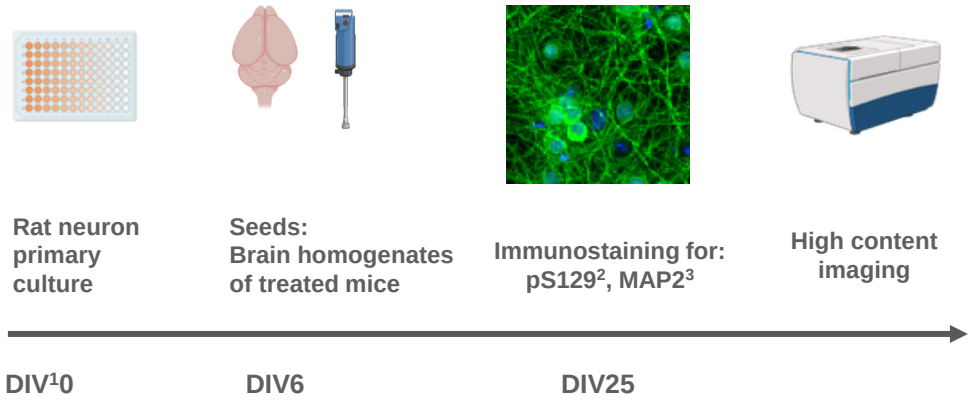
- Therapeutic paradigm used starting treatment 48h post-inoculation of pathological a-syn
- Doses selected to reach unbound brain concentration covering IC_{50} and IC_{80} of the neuronal seeding assay over the dosing interval

(1) Parkinson's disease; (2) human preformed fibrils; (3) Once a day; (4) Immunohistochemistry; (5) Magnetic resonance imaging

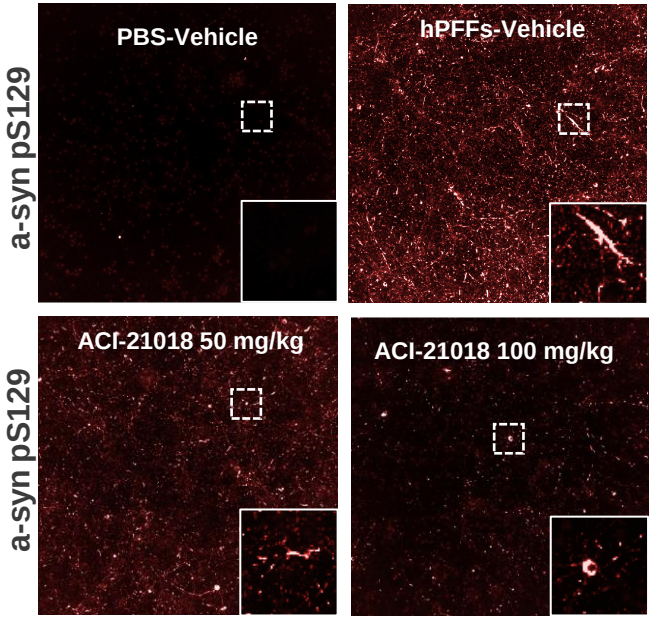
AC Immune unpublished data

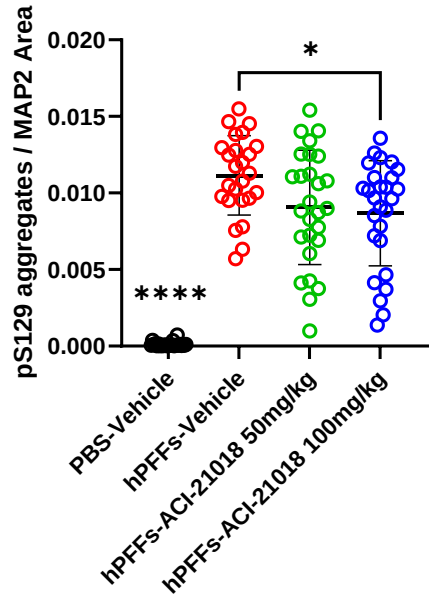
ACI-21018 reduces seeding-competent a-syn species in the brain

Ex vivo seeding with brain homogenates of treated mice



Ex vivo seeding of primary rat neurons with total brain homogenates from treated mice





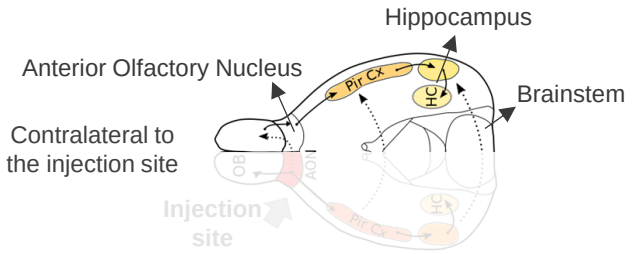
Mean ± SD
One-way ANOVA, Tukey's post-hoc test
*p<0.05; ***p<0.0001

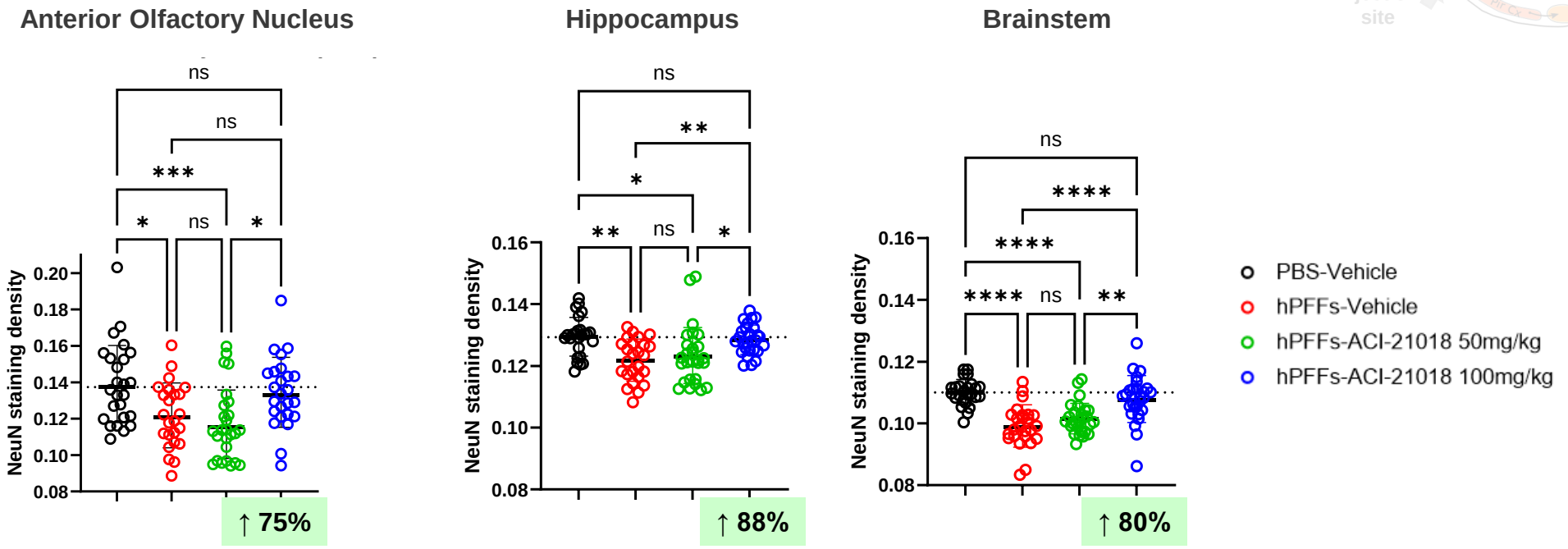
- Brain homogenates of hPFF-a-syn mice are inducing the misfolding of endogenous a-syn acting as seeds
- Seeding potential of brain homogenates measures pathology-propagating a-syn species
- Significant reduction of propagating a-syn seeding species in brains of mice treated with ACI-21018

(1) Days *in vitro;* (2) phosphorylated a-syn at Ser129; (3) Microtubule-associated protein 2 – neuronal marker

ACI-21018 treatment prevents neuronal loss

NeuN (neuronal marker) in the contralateral regions of interest





Geometric means ± geometric SD, One-Way ANOVA; Post-hoc Tukey's test; ns: non-significant, *p<0.05; **p<0.01; ***p<0.001; **** p<0.0001

% change from hPFF-vehicle (relative to PBS-vehicle), group mean values

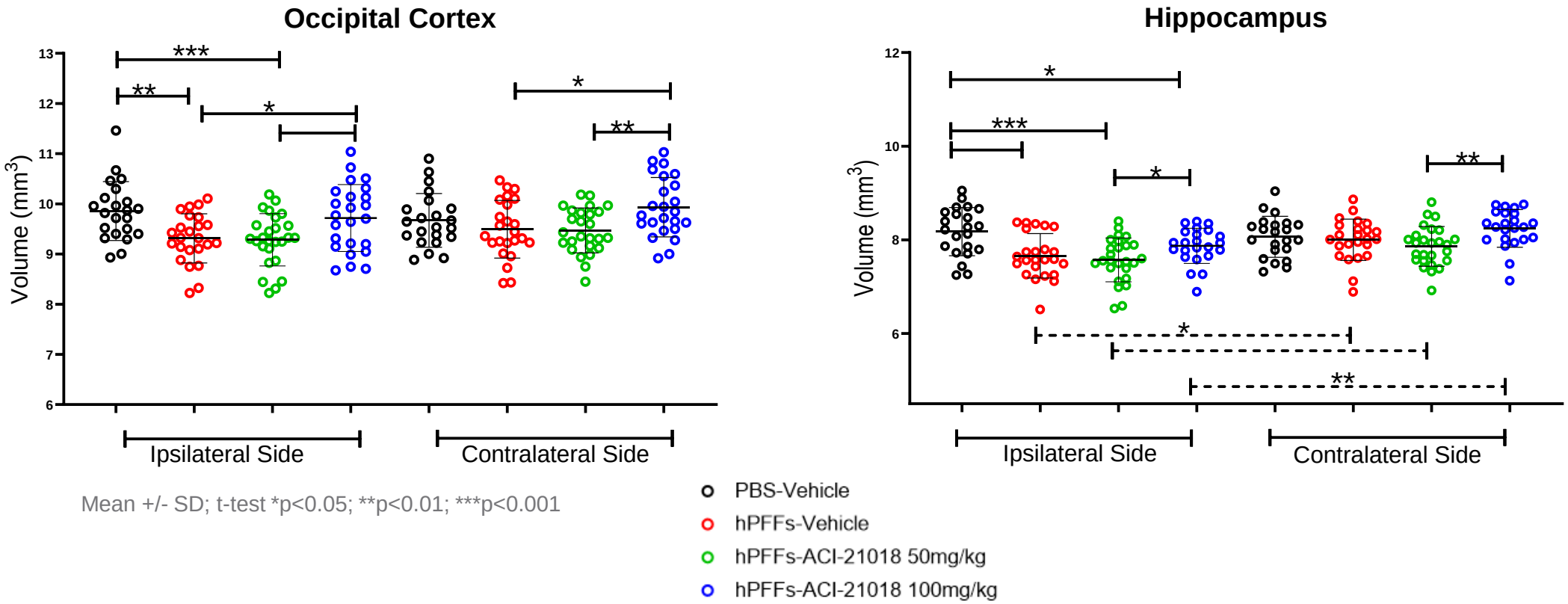
- ACI-21018 treatment prevents neurodegeneration across the brain
- Significant rescue achieved (to the level of healthy mice) in brain regions proximal and distal to the injection site

(1) human preformed fibrils

AC Immune unpublished data

ACI-21018 treatment prevents reduction of regional brain volume

MRI[1] analysis of regional brain volumes ipsilateral and contralateral to the injection site



Mean +/- SD; t-test *p<0.05; **p<0.01; ***p<0.001

- Restore occipital cortex volume to level of healthy mice
- Significant improvement also in hippocampal volume
- ACI-21018 confers broad neuroprotective effects even with treatment starting days after pathology induction

(1) Magnetic resonance imaging

AC Immune unpublished data

Key take away messages

Game changing opportunity for PD and other Synucleinopathies: A-syn Morphomers®

First-in-class

- First-in-class, orally active, CNS-penetrant small molecules that target pathological intracellular a-syn

Precision medicine

A-syn Morphomers® demonstrate:

- Target engagement on PD and MSA brain-derived a-syn aggregates
- Common binding site(s) with AC Immune's a-syn PET tracers for optimized translation and accelerated development

Neuroprotective effects

In vivo efficacy of ACI-21018 exhibits:

- Significant reduction of seeding-competent a-syn species in the brain
- Significant prevention of neuron loss and restoration of brain volume

Therapeutic potential

- A-syn Morphomers® hold promise in providing therapeutic benefit for PD and other Synucleinopathies
- Backup discovery progresses aiming to deliver additional candidates

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AC Immune

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

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