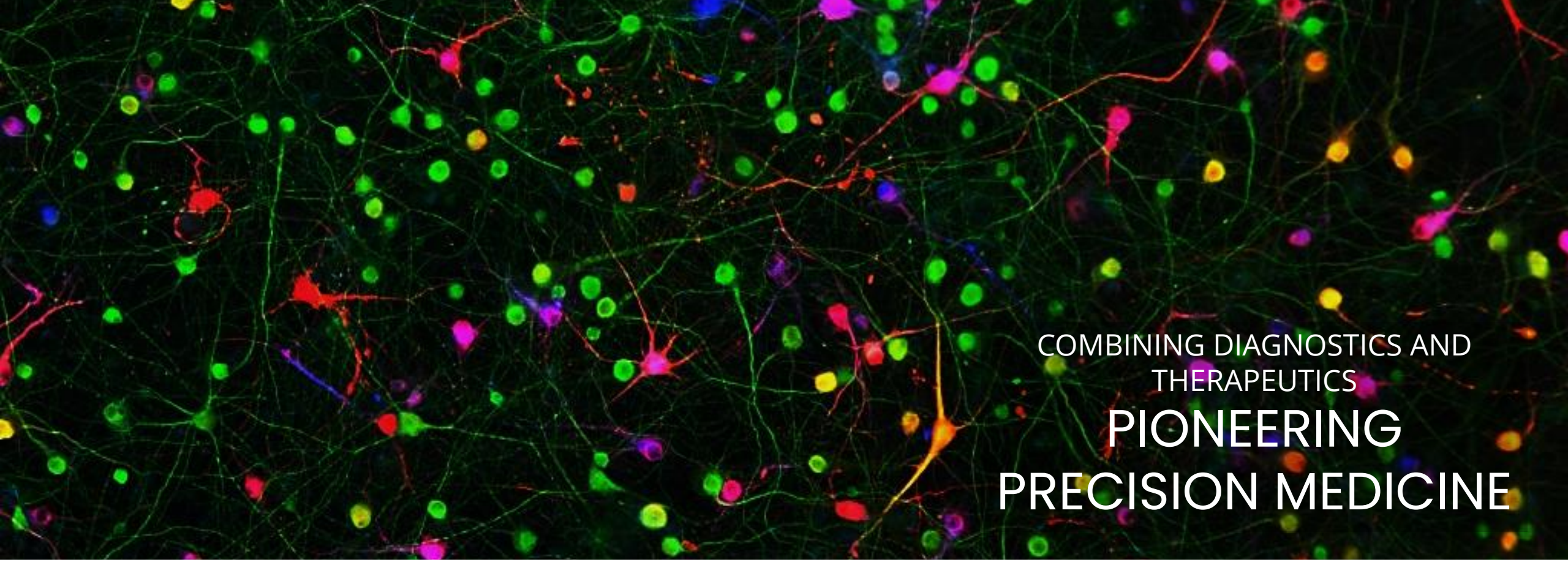
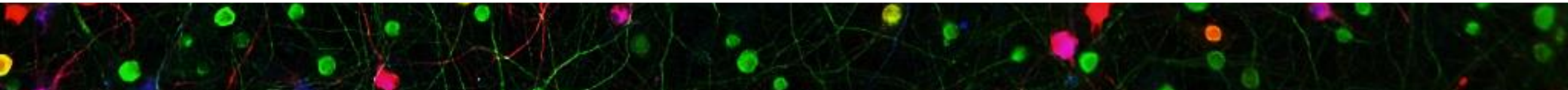


An integrated approach to target Parkinson's disease and other Synucleinopathies

Elpida Tsika, PhD I October 28th, 2025

AC Immune



Outline

- Why alpha-synuclein
- Active immunotherapy
- Targeting intracellular aggregates
- Diagnostic PET tracer

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Parkinson’s disease (PD)

An unmet clinical need

Most common neurodegenerative movement disorder
Fastest growing prevalence and disability neurological disease[1]

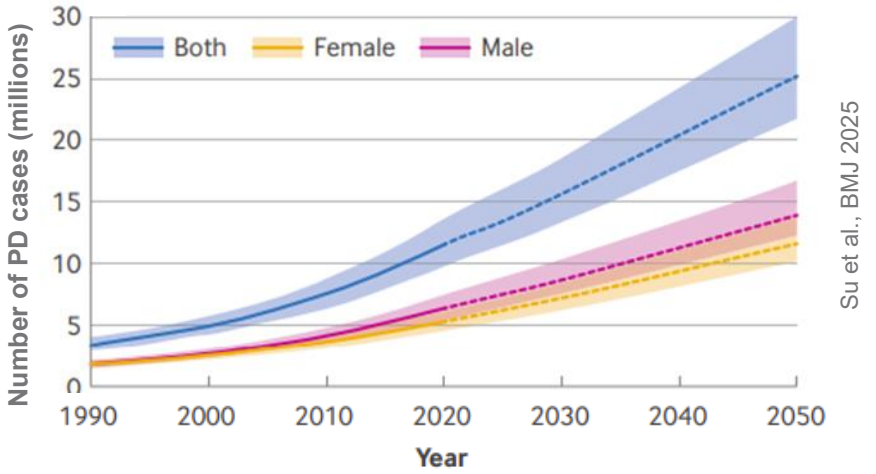
Etiology
5-10% genetic, 90-95% idiopathic, unknown cause

Cardinal motor symptoms
Tremor, rigidity, bradykinesia

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

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

Estimated trends in number of PD cases globally



(1) GBD 2015 Neurological Disorders Collaborator Group. Lancet Neurol 2017

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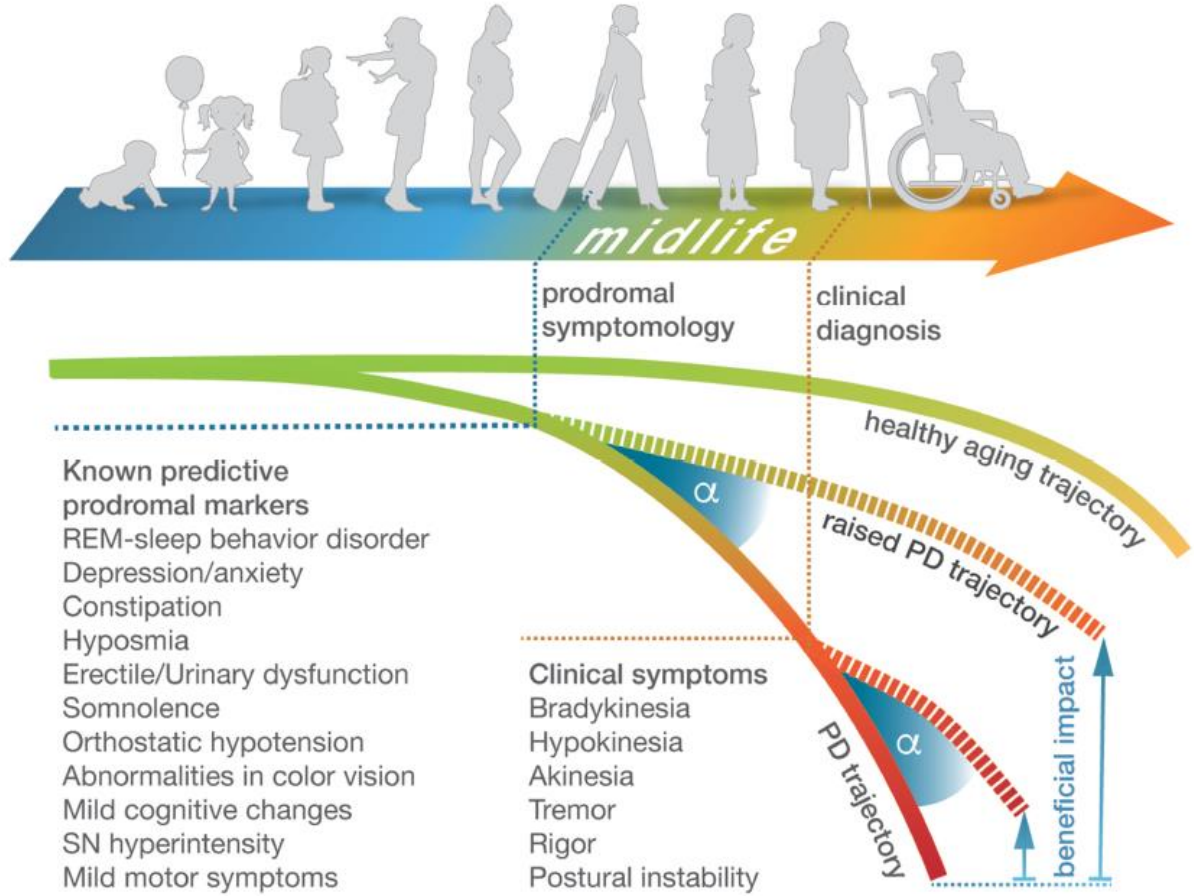
Parkinson’s disease prodromal and clinical symptoms

Earlier diagnosis for greater beneficial impact of disease-modifying therapies



Kilzheimer, et al., Front Neurol 2019

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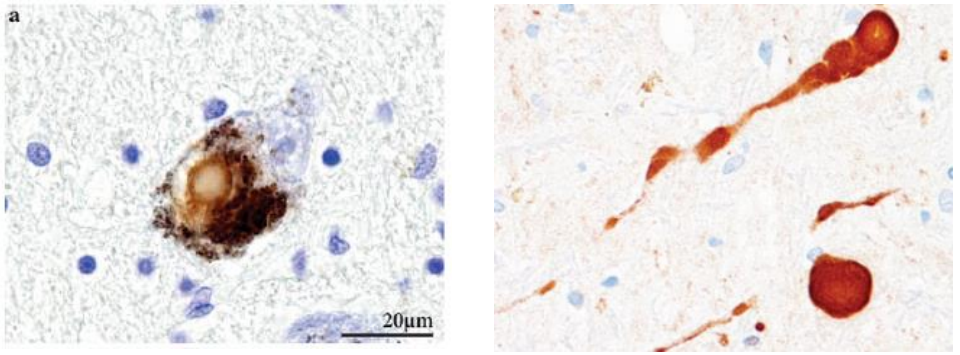
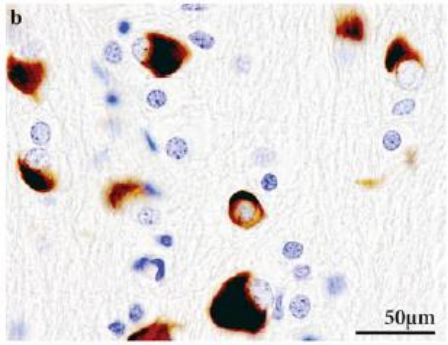
Synucleinopathies

Alpha-synuclein pathology across neurodegenerative diseases

Lewy body and Lewy neurites
Parkinson's disease (PD)

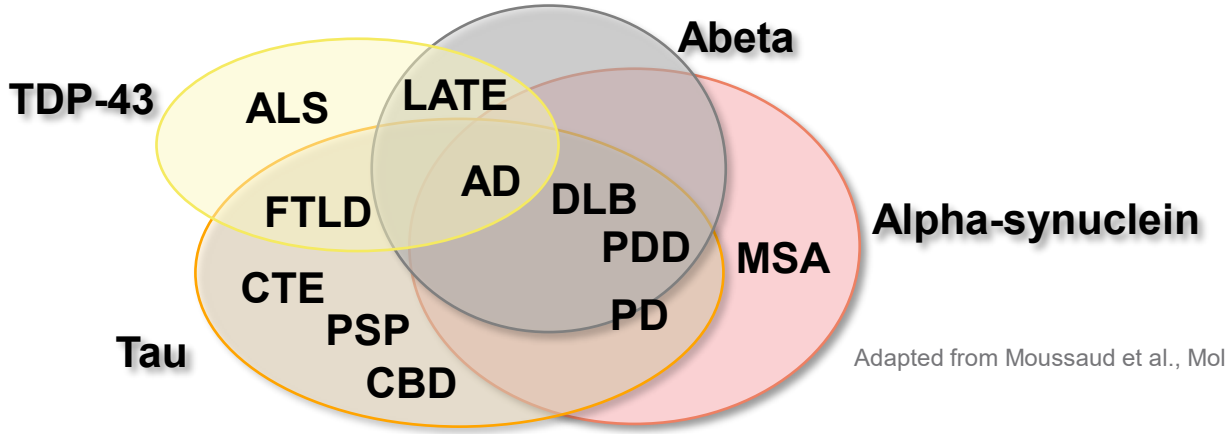


Glial cytoplasmic inclusions
Multiple System Atrophy (MSA)



Halliday et al., Acta Neuropathol 2011

Pathologies overlap in neurodegenerative diseases



Adapted from Moussaud et al., Mol Neurodegen 2014

AD: Alzheimer's disease; ALS: Amyotrophic Lateral Sclerosis; CBD: Corticobasal Degeneration; CTE: Chronic Tramautic Encephalopathy; DLB: Dementia with Lewy bodies; FTLD: Frontotemporal Dementia; LATE: Limbic-predominant Age-related TDP-43 Encephalopathy; MSA: Multiple System Atrophy PD: Parkinson's disease; PDD: Parkinson's disease with Dementia; PSP: Progressive Supranuclear Palsy

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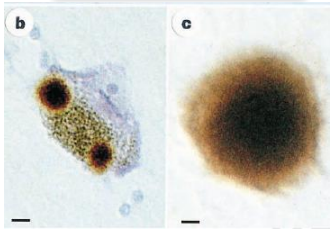
Alpha-synuclein research highlights

From its discovery to defining the disease

1988 — Discovered in the nerve terminals of electric ray (a fish)

1997 — Genetic mutations in SNCA gene cause Parkinson's disease

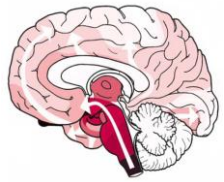
- Alpha-synuclein in Lewy bodies



Spillantini et al., Nature

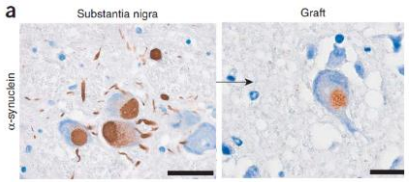
2000 — Transgenic & knock out mouse models

2003 — Staging of alpha-synuclein pathology



Braak et al., Neurobiol Aging

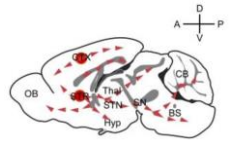
2008 — Alpha-synuclein pathology in embryonic transplants



Li et al., Nat Med

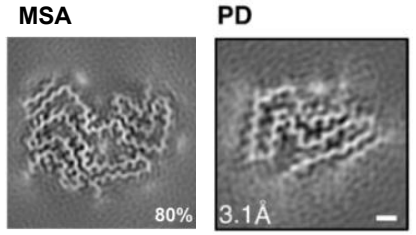
2010 — Physiological function in regulating synaptic vesicle release

2012 — Alpha-synuclein seeding in mice



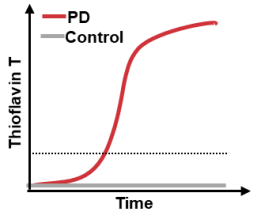
Luk et al., J Exp Med

2016 — Structures of alpha-synuclein filaments in MSA and PD



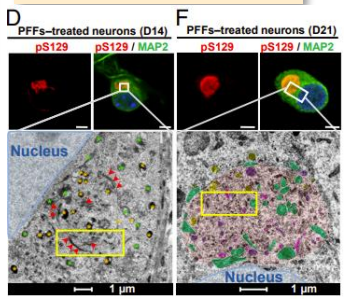
Schweighauser et al., Nature — Yang et al., Nature

- Seed amplification to detect alpha-synuclein in brain and CSF



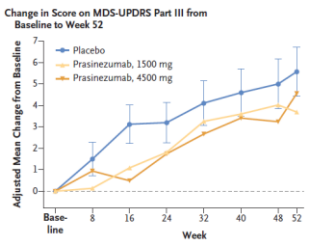
Fairfoul et al., Ann Clin Transl Neurol

2019 — Lewy pathology formation in neurons



Mahul-Mellier et al., PNAs

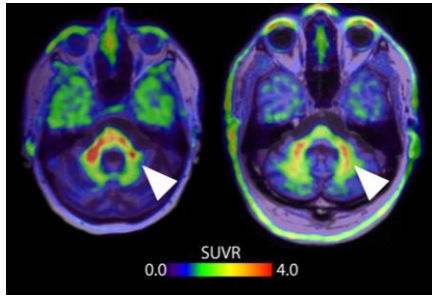
2020 — Phase 2 trial in PD targeting alpha-synuclein



Pagano et al. NEJM

2021 — Biological classification of PD / Biological definition of neuronal alpha-synuclein disease

2022 — 1st diagnostic agent to image alpha-synuclein pathology in living patients



Smith, Capotosti et al., Nat Commun

2024

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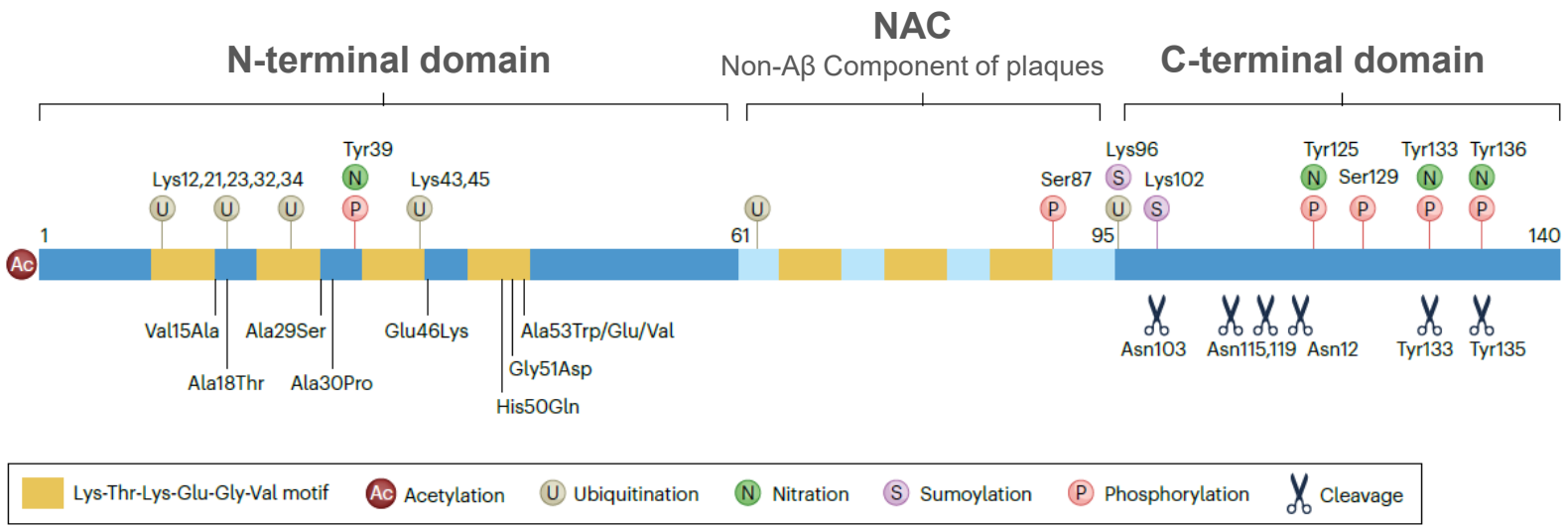
Alpha-synuclein structure

Post-translational modifications and genetic mutations



Park et al., Nat Rev Neurol 2025

- Point-mutations in N-terminus and multiplications of its gene cause autosomal dominant Parkinson's disease
- Undergoes several post-translational modifications, their physiological or pathological roles are being debated; aggregates found in synucleinopathies contain nitrated, truncated, and phosphorylated alpha-synuclein (e.g., phosphoserine 129)
- Expressed in CNS, localized in presynaptic terminals, but also in other tissues
- Intrinsically disordered, adopts helical structure upon association with membranes, binds to synaptic vesicles
- Propensity to aggregate and form β-sheet-rich amyloid fibrils through the central NAC region (non-Aβ component of amyloid plaques)

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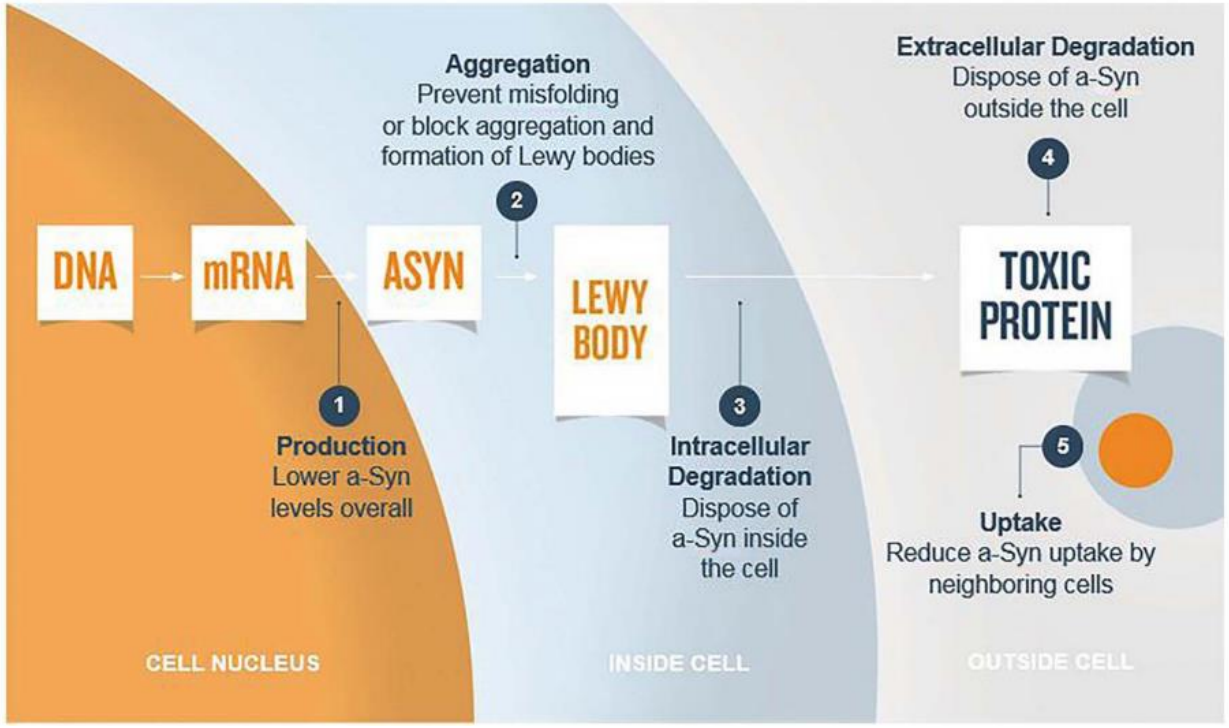
Therapeutic approaches targeting alpha-synuclein pathology

Intervention at different stages of the pathological pathway



Brundin et al., Exp Neurol. 2017

Examples of strategies:

1. **Lowering alpha-synuclein protein synthesis**
   siRNA, anti-sense nucleotides
2. **Inhibiting aggregation intracellularly**
   Small molecule inhibitors
3. **Degrading aggregates**
   Targeted protein degraders such as PROTAC[1], LYTAC[2]
4. **Inhibiting propagation**
   Active & Passive immunotherapy

(1) Proteolysis-targeting chimera; (2) Lysosome-targeting chimera

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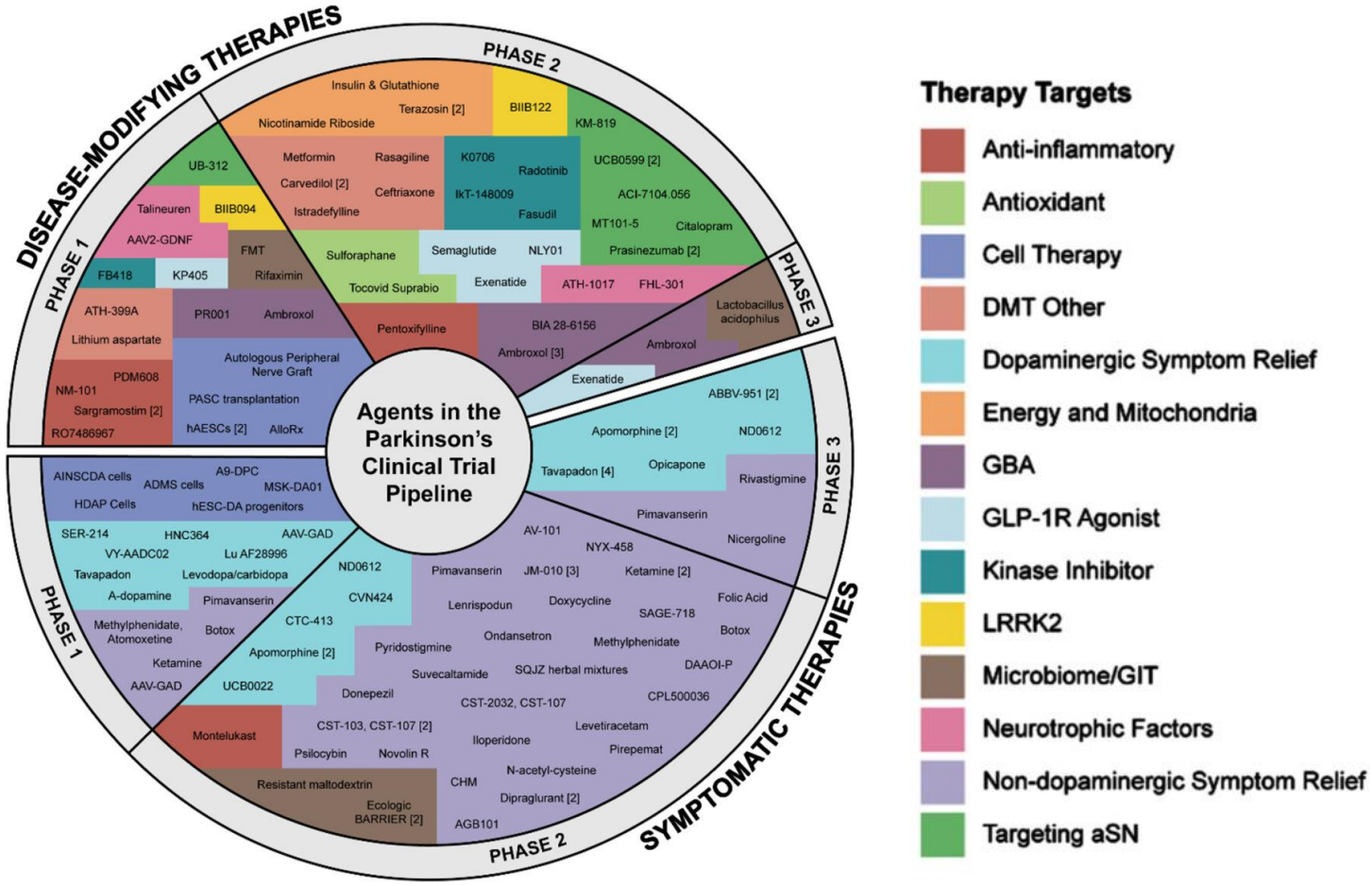
Parkinson’s disease clinical trials

All active clinical trials as of January 2024



McFarthing et al., Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update. J Parkinsons Dis. 2024;14(5):899-912. doi: 10.3233/JPD-240272

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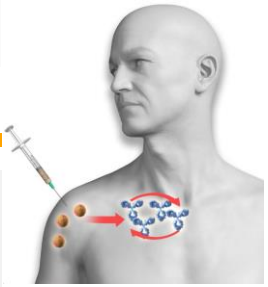
Active immunotherapy: clear advantages for long-term use

Provides opportunity to prevent AND treat neurodegenerative diseases globally

ACTIVE Immune Therapy

- Long-lasting specific immunity for pathological target, consistent, boostable, durable
- Limited annual dosing (once or twice) after priming year
- Safety profile well suited to long-term use
- Cost-effective (attractive healthcare economics across global populations)
- Improved access (ease of administration, simple logistics)

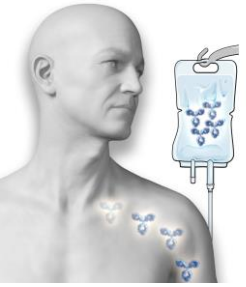


Active immunotherapy

Vaccines stimulate the patient's immune system to produce antibodies

Passive immunotherapy

Externally generated monoclonal antibodies require administration every two to four weeks



- Active immunotherapy is potentially the only option for global prevention of neurodegenerative diseases

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Immunological potential of ACI-7104

The optimized alpha-synuclein peptide-conjugate formulation

ACTIVE Immune Therapy

Generates target-specific antibody response

Safely engages target-unrelated T-cells to enhance & maintain response

Key outcomes

Immunogenicity	✓
Target specificity	✓
Selective for aggregated α-syn	✓
Sustained antibody response	✓
Boosting	✓
Evidence of memory B cells	✓
Preclude activation of T cells specific for α-syn	✓

- ACI-7104: optimized formulation delivers the clinical validated PD01A peptide[1] which provided:
  - Robust alpha-synuclein immunogenicity with a well tolerated profile in PD patients
  - Long lasting antibody responses supporting a disease prevention approach

(1) Volc et al., Lancet Neurol. 2020;

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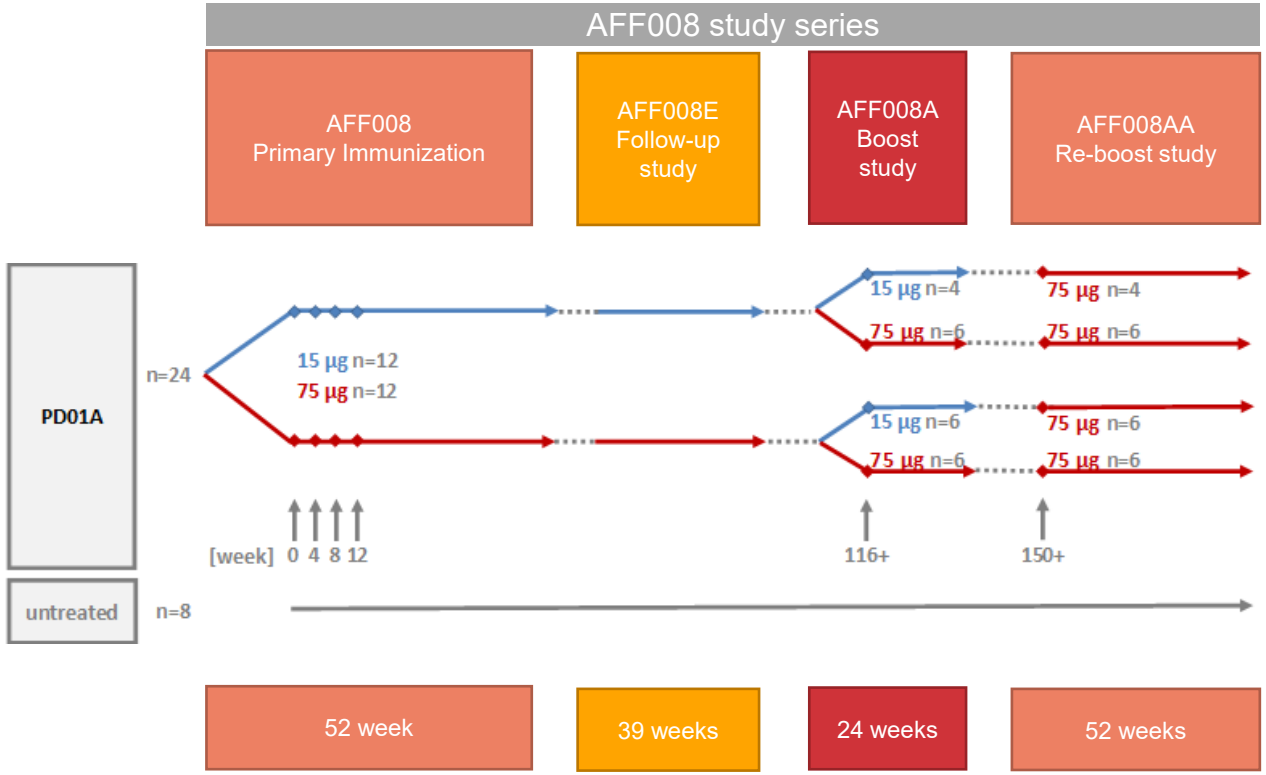
Phase 1 study series outline

Early PD patients were followed for over 3.5 years



THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Volc et al., Lancet Neurol. 2020

- A randomized, controlled, parallel group, patient-blinded, single-center, Phase I pilot study to assess tolerability and safety of repeated subcutaneous administration of two doses of PD01 vaccine, ACI-7104 predecessor, to patients with early PD

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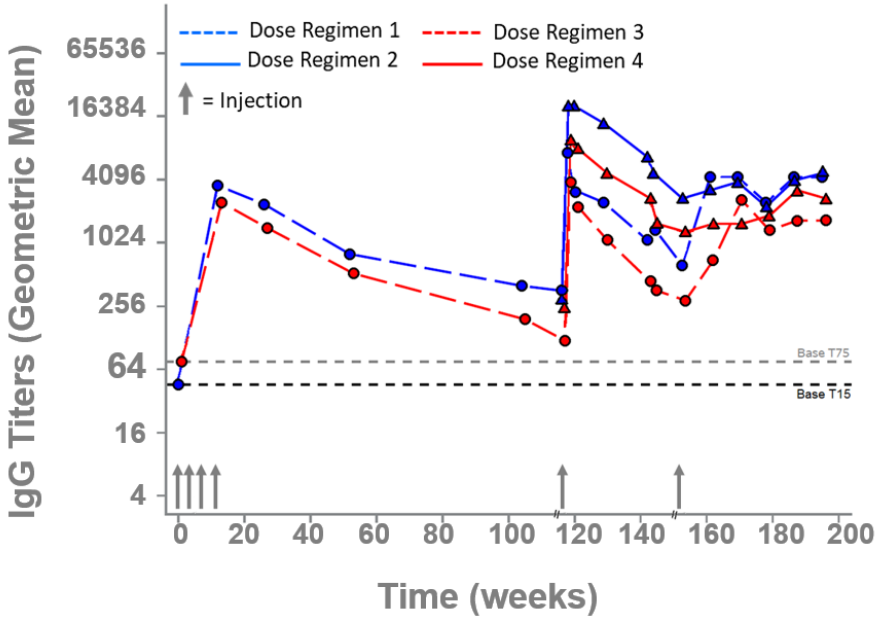
AC Immune

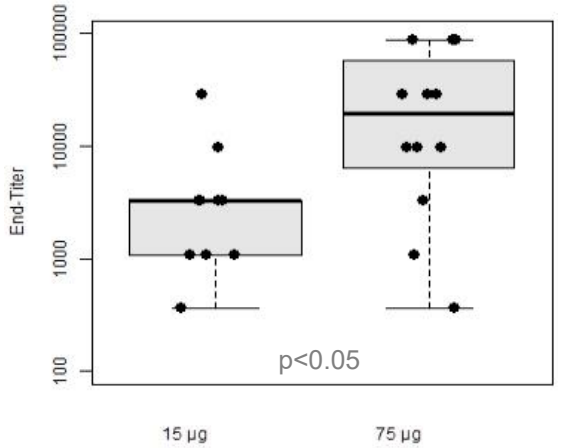
Phase 1 results in Parkinson's disease

Good safety, potent immunogenicity, evidence of target engagement and efficacy

Strong and boostable antibody response



Significant higher titers after the booster application with high dose



Patients were grouped according to the booster dose they received

Volc et al., Lancet Neurol. 2020

- Induced strong and boostable antibody response
- Significantly higher titers after the booster application with the high dose

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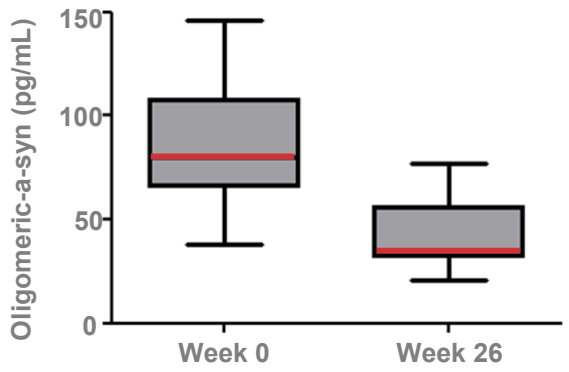
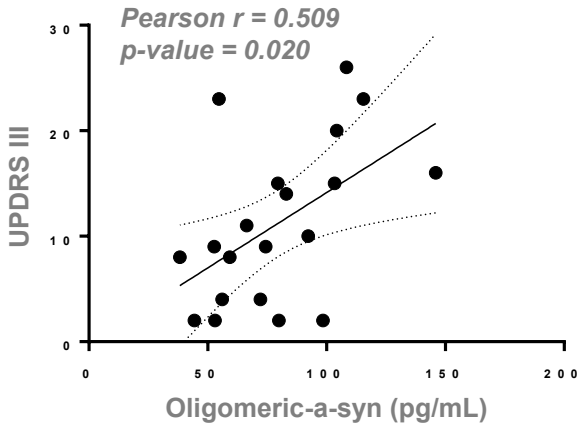
Phase 1 results in Parkinson's disease

Good safety, potent immunogenicity, evidence of target engagement and efficacy

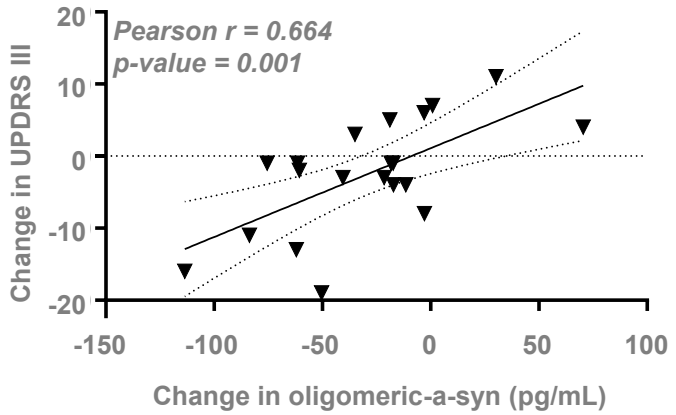
50% reduction[4] of pathological a-syn in CSF



UPDRS III and oligo-a-syn in CSF correlate at baseline



Changes[5] in oligo-a-syn and UPDRS III correlate



Volc et al., Lancet Neurol. 2020

- Evidence of target engagement as shown by a 50% reduction in pathological (oligomeric) a-syn[1] in the CSF[2]
- Signal of clinical efficacy as shown by a correlation between reductions in oligomeric a-syn and stabilization of UPDRS III[3] scores

(1) Alpha-synuclein; (2) Cerebrospinal fluid; (3) Unified Parkinson's Disease Rating Scale; (4) Data from 75 µg dose group; (5) Change in oligomeric a-syn calculated at week 26, change in UPDRS III calculated at week 100

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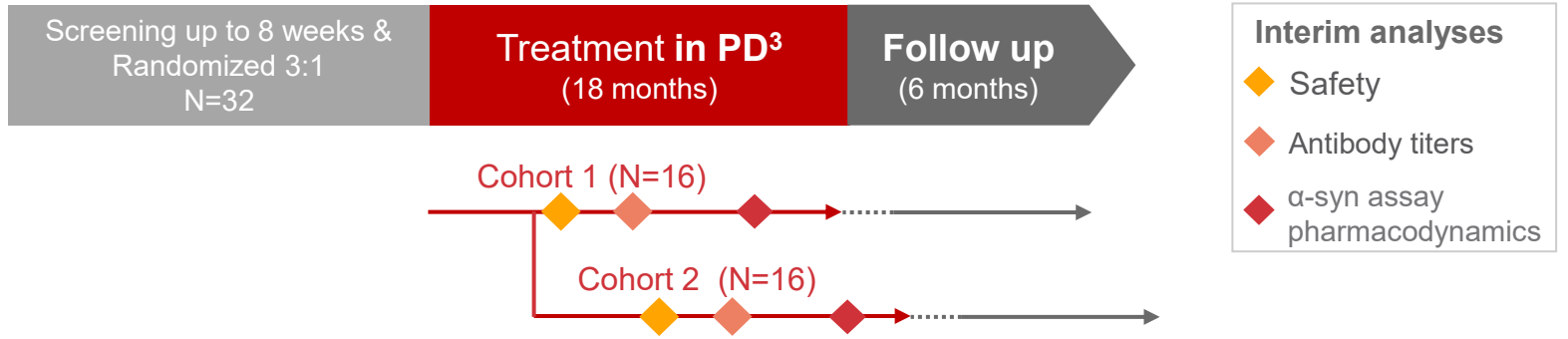
VacSYn: an adaptive biomarker-based Phase 2 study of ACI-7104 in early PD[1]

Placebo-controlled Phase 2 Study Overview (NCT06015841)

Part 1: Safety & PD[2]

- Key immunogenicity measures
- Measures of pathological α-syn[4] (a-syn oligomers and aggregates)



Part 2: Clinical PoC[5]

- Motor and Non-Motor Functioning (UPDRS[6] based)
- Degeneration of dopaminergic terminals (DaT SPECT[7] imaging)
- Advanced MRI (including ASL[8] and DTI[9])
- Digital biomarkers of motor and non-motor function
- Functional and patient reported outcomes

All participants from Part 1 will contribute to final analysis

Kostrica, Staffler et al, ADPD™ 2024

(1) Parkinson's disease; (2) Pharmacodynamics; (3) Participants must have idiopathic PD and be stable on up to 300 mg of L-Dopa treatment and dopaminergic deficit determined by Dopamine Transporter Single Photon Emission Computed Tomography; (4) alpha-synuclein; (5) Proof-of-concept; (6) Unified Parkinson's disease rating scale; (7) Dopamine Transporter Single Photon Emission Computed Tomography; (8) Arterial spin labeling; (9) Diffusion tensor imaging

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Anti-alpha-synuclein active immunotherapy: ACI-7104

Conclusions

Safety & Immunogenicity	▪ Safe and well tolerated with no safety concerns noted in patients ▪ Induced strong and boostable antibody responses
Target engagement	▪ Evidence of target engagement: 50% reduction in pathological (oligomeric) alpha-synuclein in the CSF[1]
Signal of clinical efficacy	▪ Stabilization of UPDRS III[2] scores correlated with reductions in oligomeric alpha-synuclein
Status	▪ Phase 2 study in early PD subjects based on innovative biomarker-based two-part trial design is ongoing

(1) alpha-synuclein; (2) Unified Parkinson's Disease Rating Scale Part III

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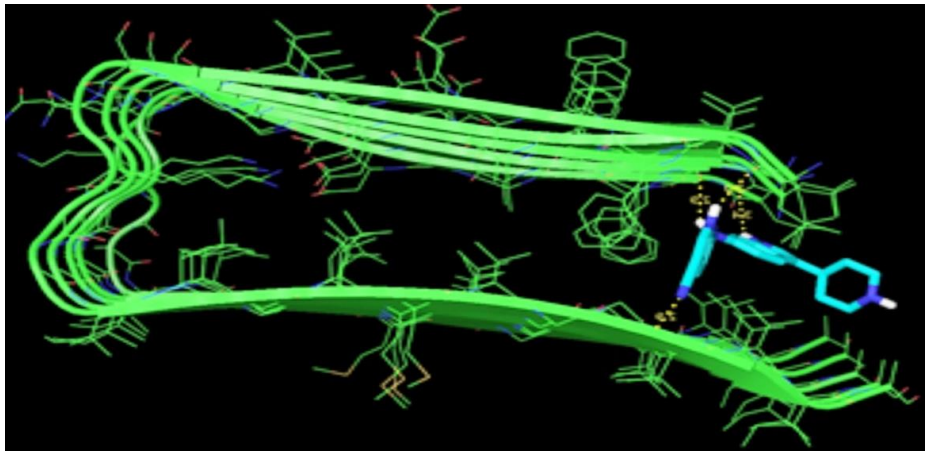
Targeting intracellular a-syn aggregation with small molecules

Proprietary Morphomer® platform



- Robust library of conformation-specific, non-peptidic small molecules with desirable CNS[1] properties constructed and continuously expanded *via* rational design over many years
- Used with comprehensive screening 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

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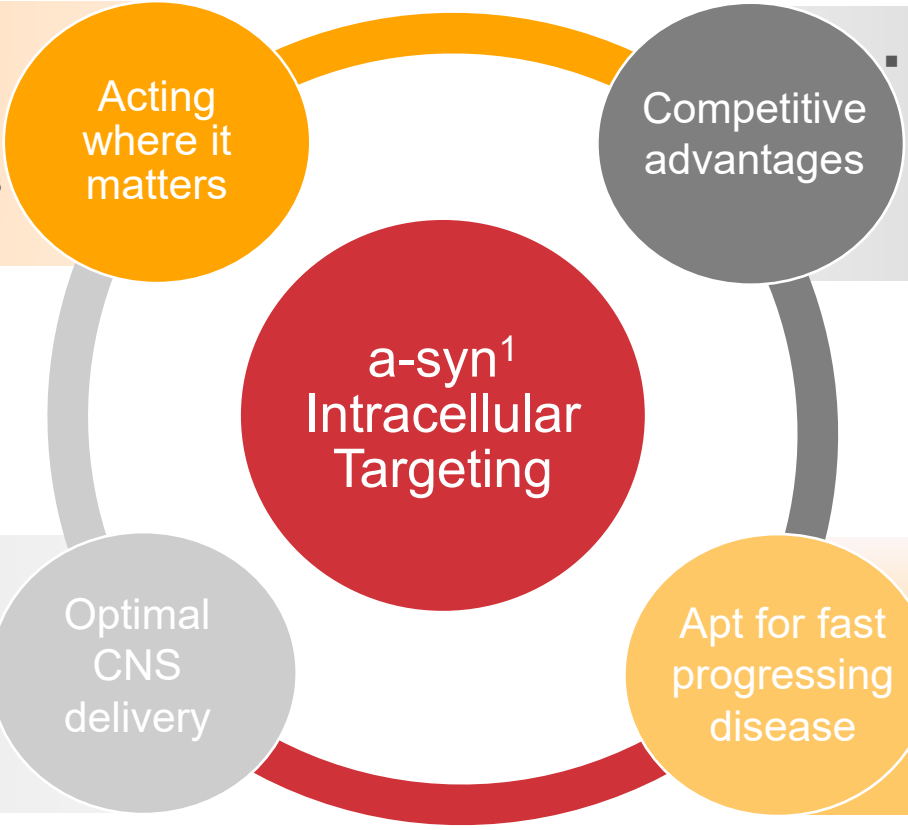
Intracellular targeting of misfolded a-syn[1] with Morphomers®

Key advantages and opportunities

- a-syn[1] pathological aggregates accumulate intracellularly forming:
  - ✓ Lewy bodies within neurons in PD[2]
  - ✓ Glial cytoplasmic inclusions in MSA[3]



- Over gene-silencing / mAbs[6]:
  - ✓ No interference with physiological a-syn
  - ✓ Acting intra- and extra-cellularly
  - ✓ Easy administration as orally available

- a-syn targeting Morphomers® are designed to be:
  - ✓ highly CNS[5] penetrant
  - ✓ plasma membrane permeable

- Full control of pathological processes by inhibiting:
  - ✓ Intracellular aggregation
  - ✓ Seeding within cells
  - ✓ Cell-to-cell spreading

- Potential to halt disease progression by blocking pathogenic pathways leading to aggregation
- Can be used as a stand-alone therapy or in combination with other therapeutic approaches

(1) alpha-synuclein; (2) Parkinson's disease; (3) Multiple System Atrophy; (4) Small molecular entities; (5) Central nervous system; (6) Monoclonal antibodies

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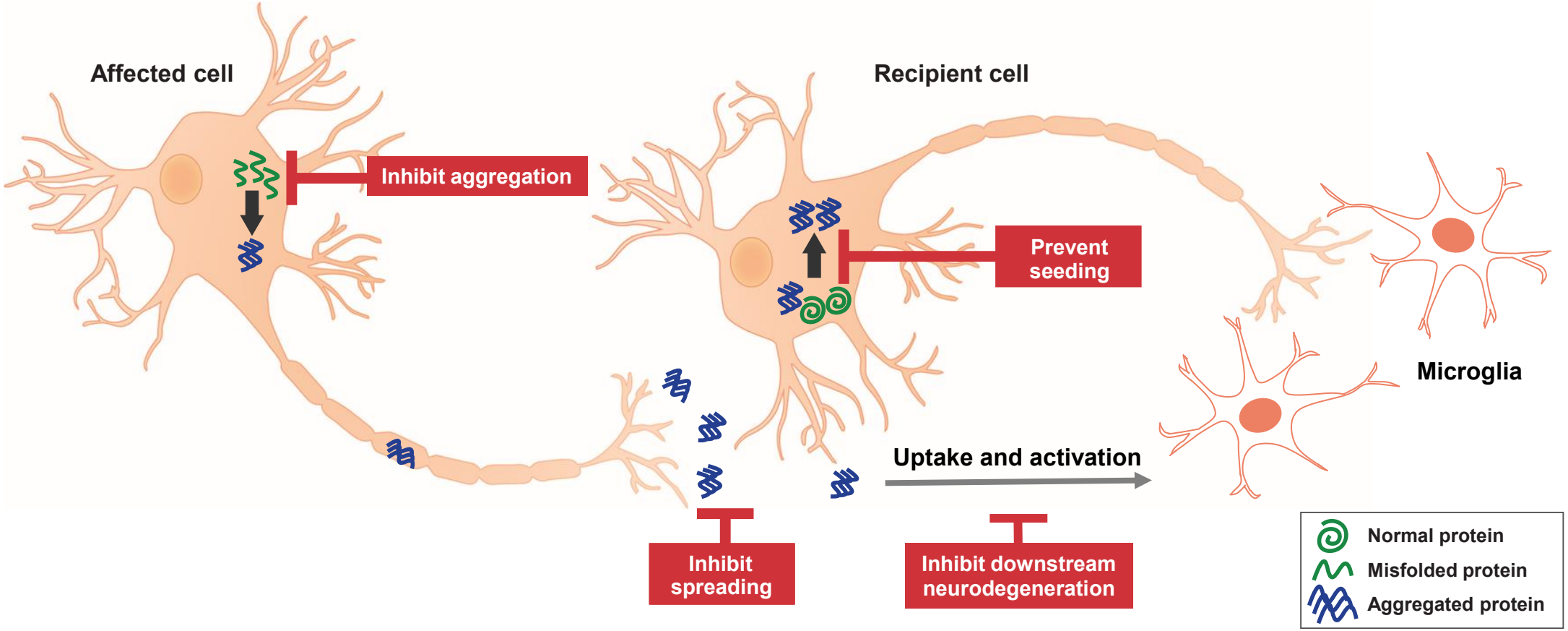
A-syn[1]-targeting Morphomers® may halt pathology at multiple points



- Intracellular targeting of aggregation and seeding
- Combined with inhibition of extracellular spreading offers full control of disease pathology
- Synergy with AC Immune's a-syn PET tracer program enables our precision medicine approach

(1) Alpha-synuclein

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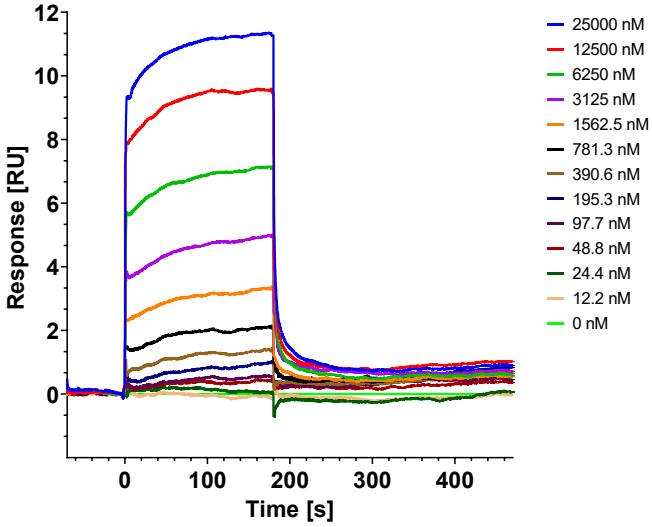
Specific binding of Morphomers® to a-syn aggregates over monomers

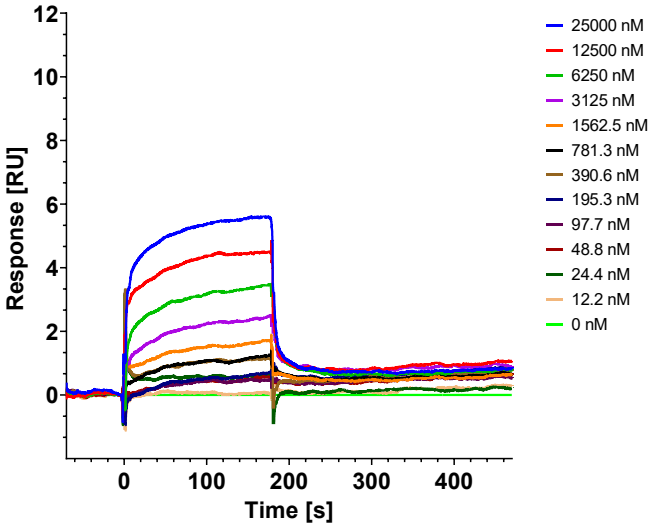
Demonstrated target engagement to PD and MSA derived a-syn aggregates by SPR[1]

Brain-derived homogenates[2]

PD[3]

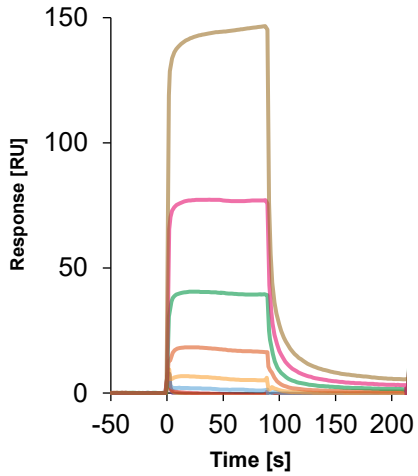


MSA[4]

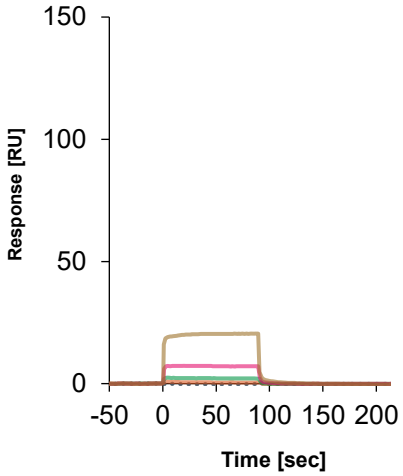


Recombinant a-syn[5]

Fibrils



Monomer



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

- Morphomers® bind pathological a-syn forms from different diseases with specificity for aggregates over monomers
- Strongly suggesting that Morphomers® will not interfere with the physiological functions of a-syn

(1) Surface Plasmon Resonance; (2) ACI-21018; (3) Parkinson's disease; (4) Multiple System Atrophy; (5) ACI-15896

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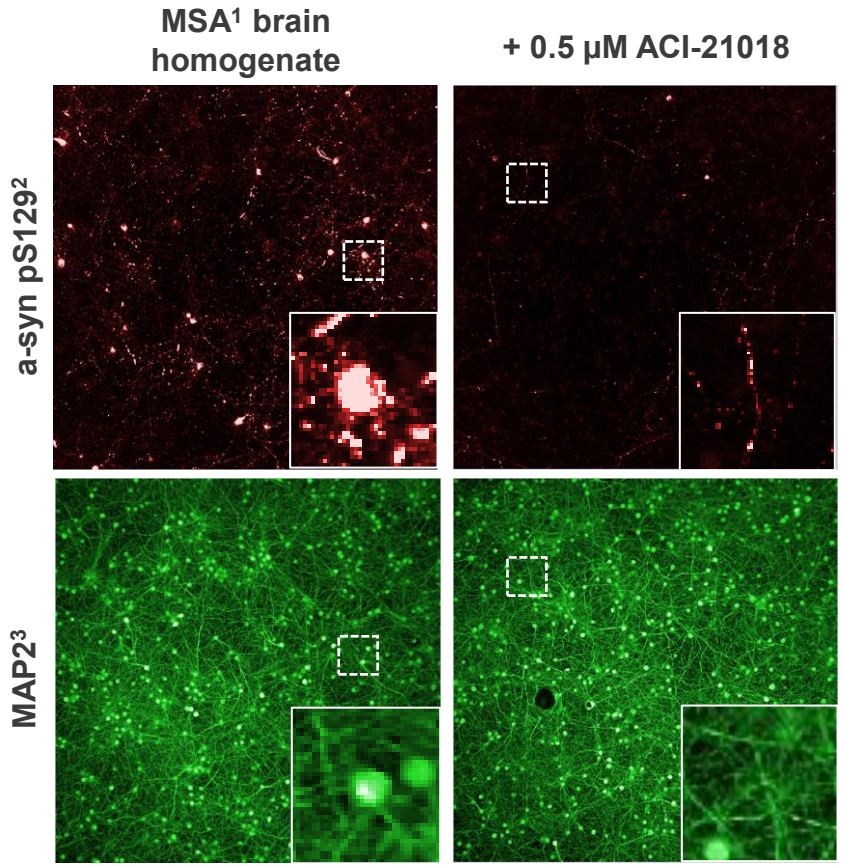
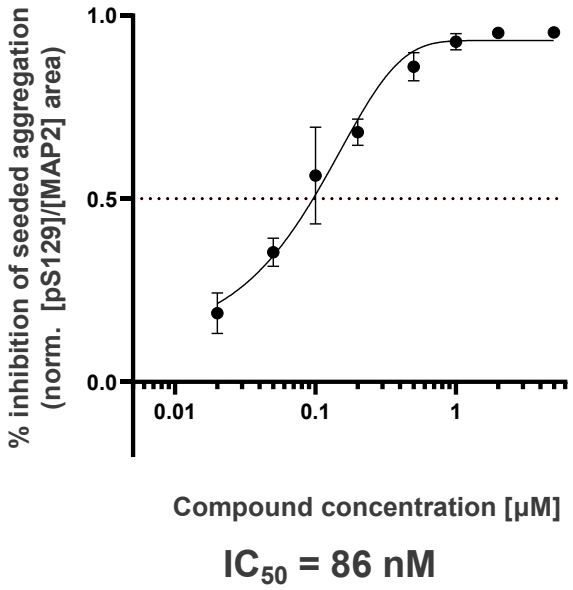
Morphomers® halt a-syn aggregation

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





IC_{50} = 86 nM

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

- Morphomers® reduce intracellular a-syn[2] inclusions, indicating a potent effect at blocking seeding and therefore spreading of the a-syn pathology

(1) Multiple system atrophy; (2) Phospho-Serine 129; (3) Microtubule associated protein 2

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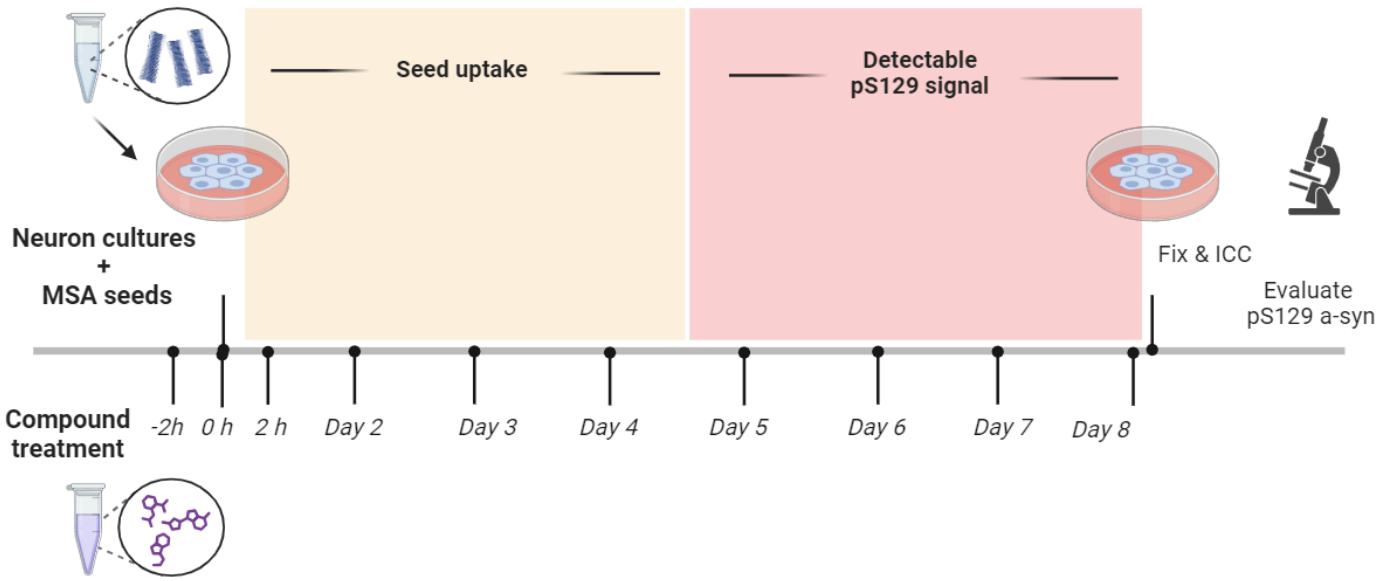
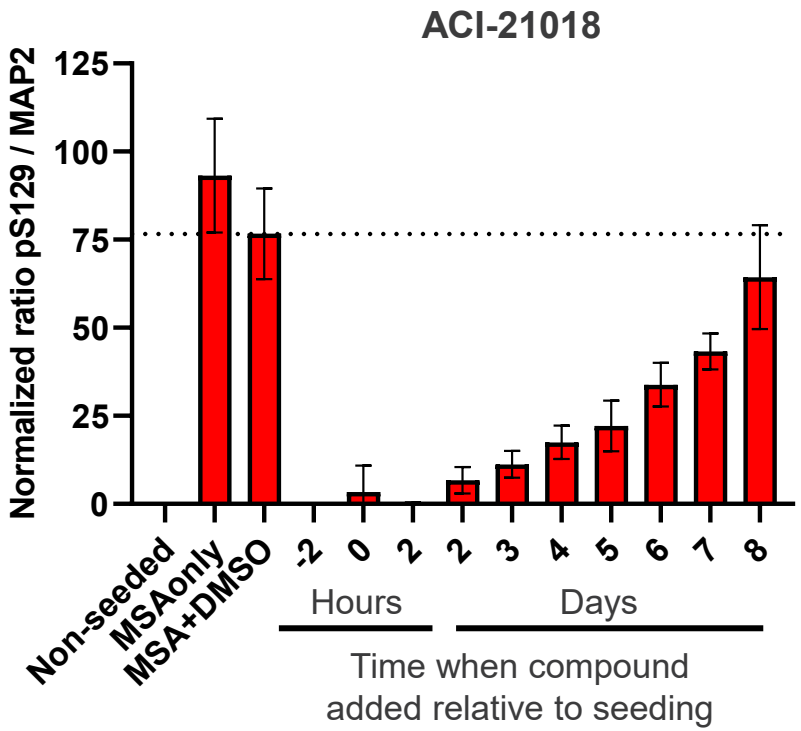
Assessing intracellular aggregation mediated by MSA[1]-derived seeds

Delayed treatment effect in primary neurons

Experimental timeline





Tsika et al., ADPD™ 2024

- Reduction of aggregate burden even when compound treatment delayed by several days after seeding
- Demonstrates compound treatment prevents *de novo* aggregation intracellularly

(1) Multiple system atrophy

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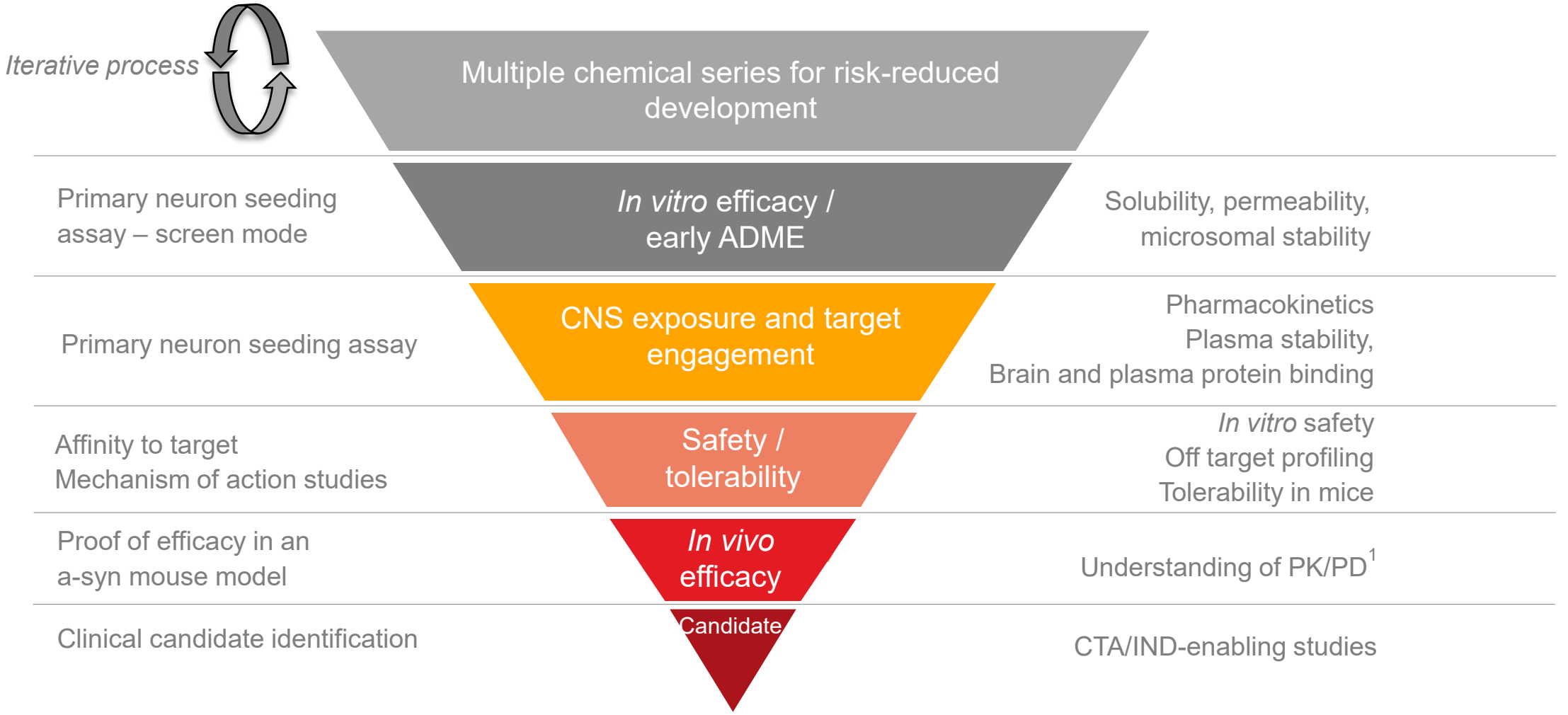
Comprehensive screening to identify a-syn aggregation inhibitors

Compound flow progression



(1) Pharmacokinetic / Pharmacodynamic

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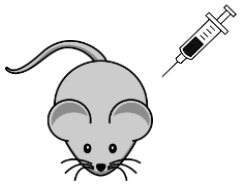
Evaluation of ACI-21018 *in vivo* efficacy in a model of PD[1]

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

Unilateral **hPFF** injection

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

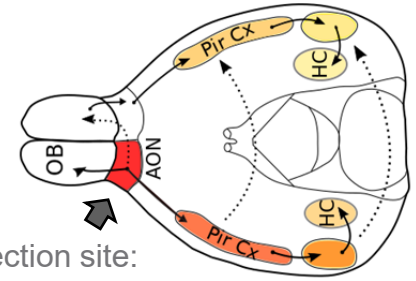
Human A53T a-syn expressed in neurons under the PrP promoter



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

Tsika *et al.*, ADPD™ 2025

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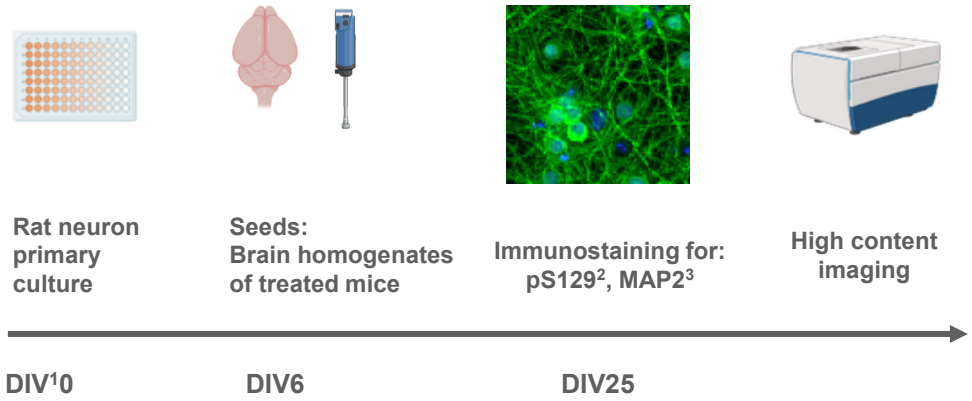
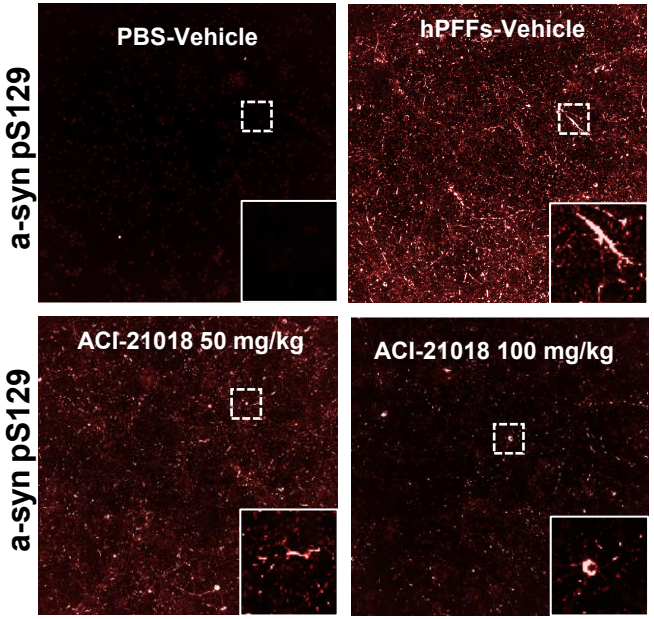
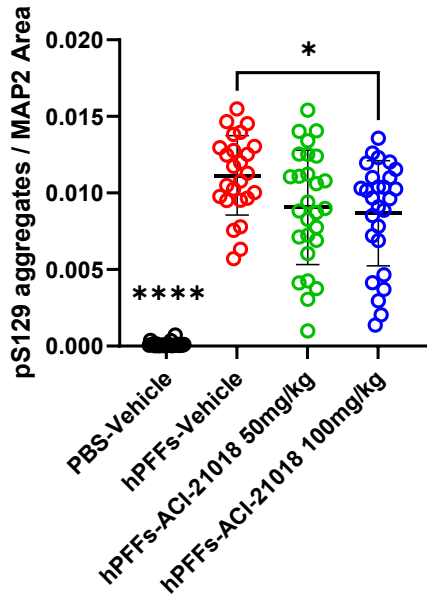
ACI-21018 reduces seeding-competent a-syn species in the brain

Ex vivo seeding with brain homogenates of treated mice



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





Tsika *et al.*, ADPD™ 2025

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

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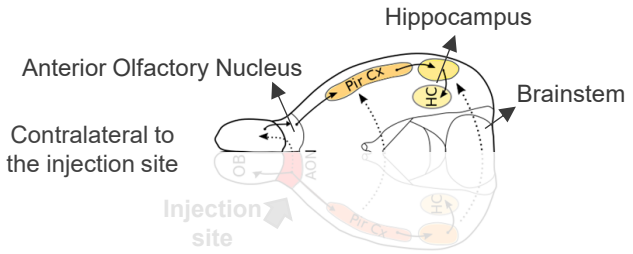
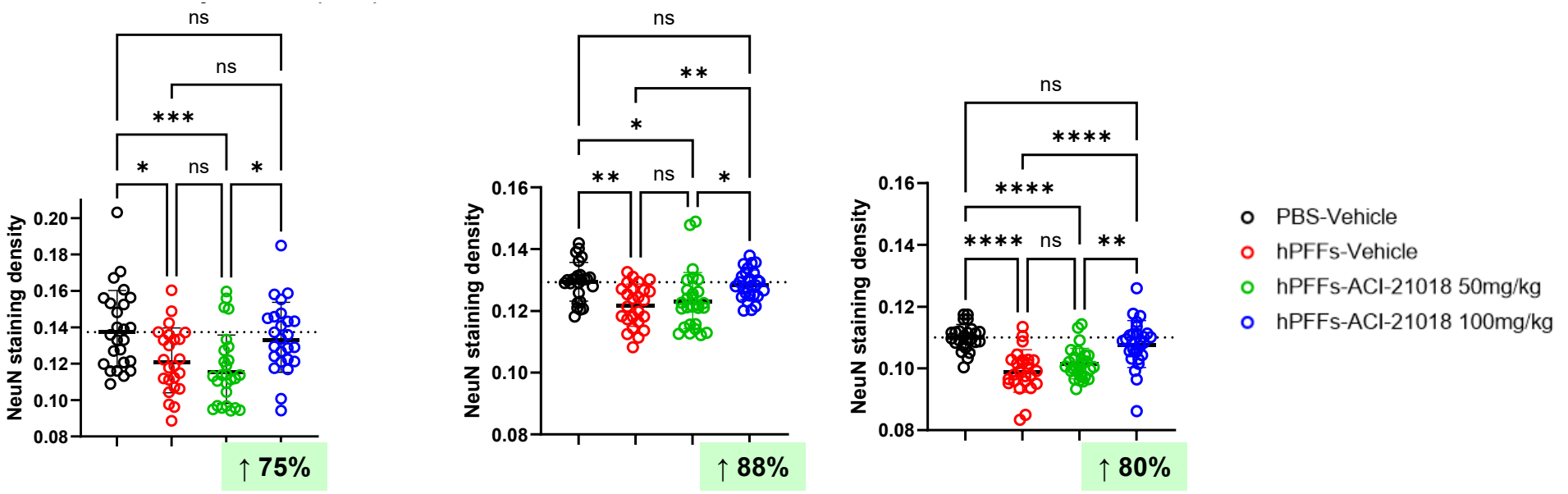
ACI-21018 treatment prevents neuronal loss

NeuN (neuronal marker) in the contralateral regions of interest





Tsika *et al.*, ADPD™ 2025

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

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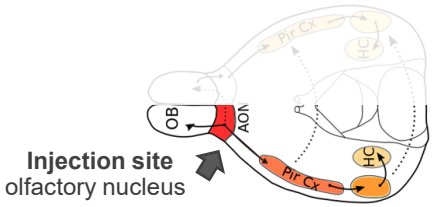
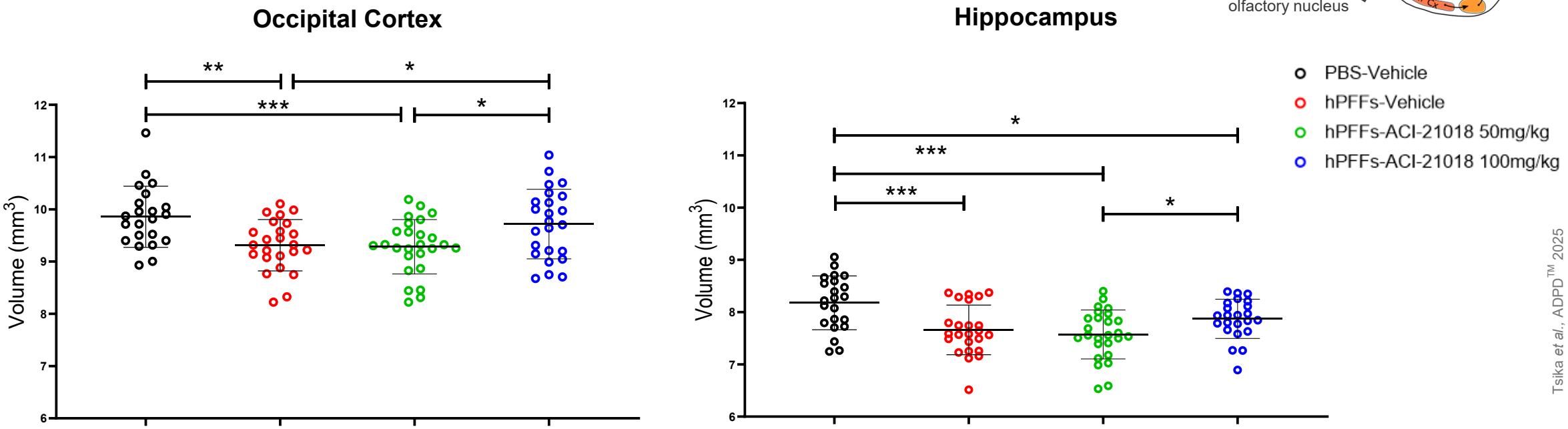
ACI-21018 prevents regional brain atrophy

MRI[1] analysis of regional brain volumes ipsilateral to the injection site[2]



Injection site
olfactory nucleus



Tsika *et al.*, ADPD™ 2025

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

- ACI-21018 treatment resulted in broad neuroprotective effects, close to the levels of healthy mice
- This neuroprotective effect can be measured by MRI, ensuring high translational value of these results

(1) Magnetic resonance imaging; (2) human a-syn preformed fibrils injected in olfactory nucleus

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Targeting intracellular a-syn aggregation with small molecules

Conclusions

First-in-class	▪ First-in-class, orally available, CNS[3]-penetrant small molecules that target pathological a-syn intracellularly
Intracellular targeting	▪ Excellent CNS and cell permeability enabling the drug to reach the sites of pathology ▪ Inhibition of a-syn aggregation and seeding with potential to halt the disease ▪ No expected interference with the physiological functions of a-syn
Precision medicine	▪ Common binding site(s) with AC Immune's a-syn PET[4] tracer offers a unique opportunity for a derisked and accelerated development
Therapeutic potential	▪ Broad recognition of a-syn pathological forms across multiple synucleinopathies ▪ Preclinical therapeutic efficacy demonstrated with translationally relevant biomarkers ▪ a-syn Morphomers® potential therapeutic benefit even in fast progressing diseases, e.g. MSA

(1) alpha-synuclein; (2) Multiple system atrophy; (3) Central nervous system; (4) Positron emission tomography

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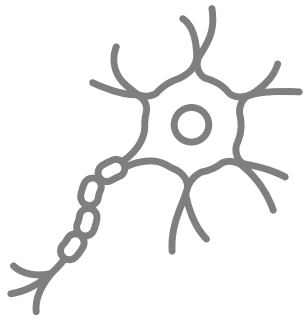
A-syn[1] PET[2] tracers can improve the diagnosis and treatment of NDD[3]

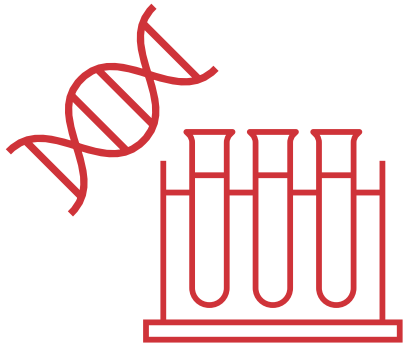
Needed to enable precision medicine for synucleinopathies

Early diagnosis and treatment is key in NDD



- Neuronal damage/death is presently an irreversible event
- Approved disease-modifying agents for NDD showed improved efficacy in early disease stages

Early diagnosis of a-syn-opathies[4] is not possible with current techniques



- DaTscan does not support early diagnosis
- Genetic testing is ineffective in idiopathic cases
- Fluid biomarkers, including SAA[5] , are not yet quantitative

Benefits of PET tracers for imaging have been validated

- Better designed clinical trials using PET tracer for recruitment and monitoring
- May enable combination treatment of co-pathologies

(1) Alpha-synuclein; (2) Positron emission tomography; (3) Neurodegenerative disease; (4) Alpha-synucleinopathies; (5) Seed amplification assay

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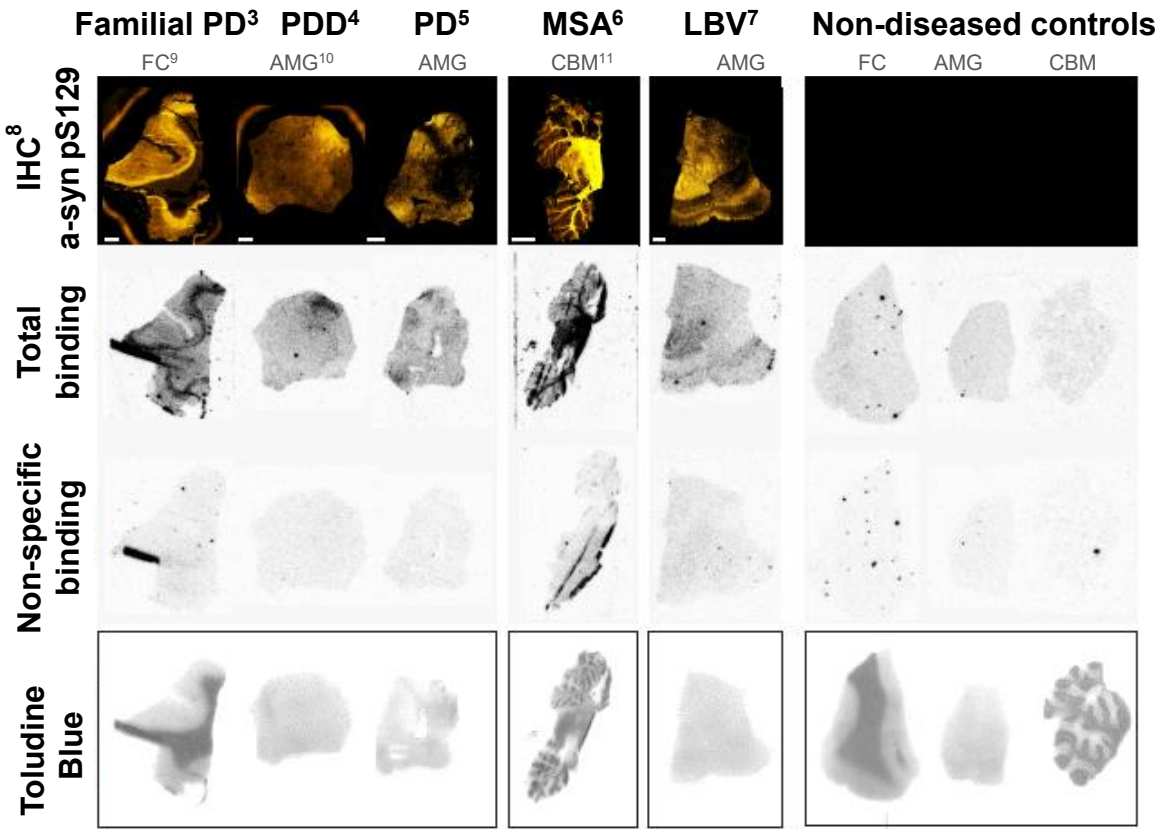
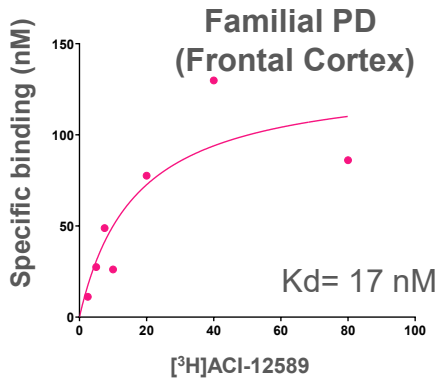
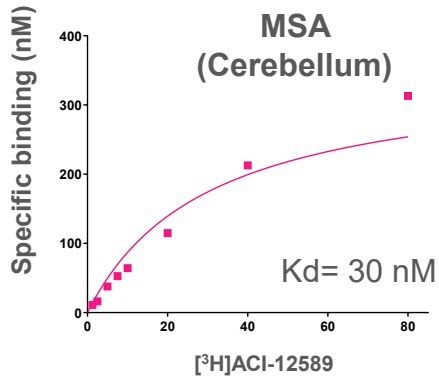
ACI-12589: a promising a-syn[1] PET[2] tracer

[3H]ACI-12589 specific binding on brain tissue from different synucleinopathy cases







Binding / Disease	MSA	Familial PD	PD#1	PD#2
Target density (nM)	~350	133	80	14
Affinity (nM)	28	17	65	38
Target occupancy	13	8	1	0.4

In collaboration with Prof. A. Varrone
Smith, Capotosti, et al., Nature Communications 2023

- ACI-12589 displays a clear autoradiography signal across different synucleinopathy cases which correlates with the presence of pathological a-syn
- Target occupancy depends on the levels of pathological a-syn and varies from ≤ 1 in idiopathic PD to ≥ 10 in MSA

(1) Alpha-synuclein; (2) Positron emission tomography; (3) Parkinson's disease with G51D SNCA mutation; (4) Parkinson's disease with dementia; (5) Idiopathic Parkinson's disease; (6) Multiple system atrophy; (7) Lewy Body variant of Alzheimer's disease; (8) Immunohistochemistry; (9) Frontal cortex; (10) Amygdala; (11) Cerebellum

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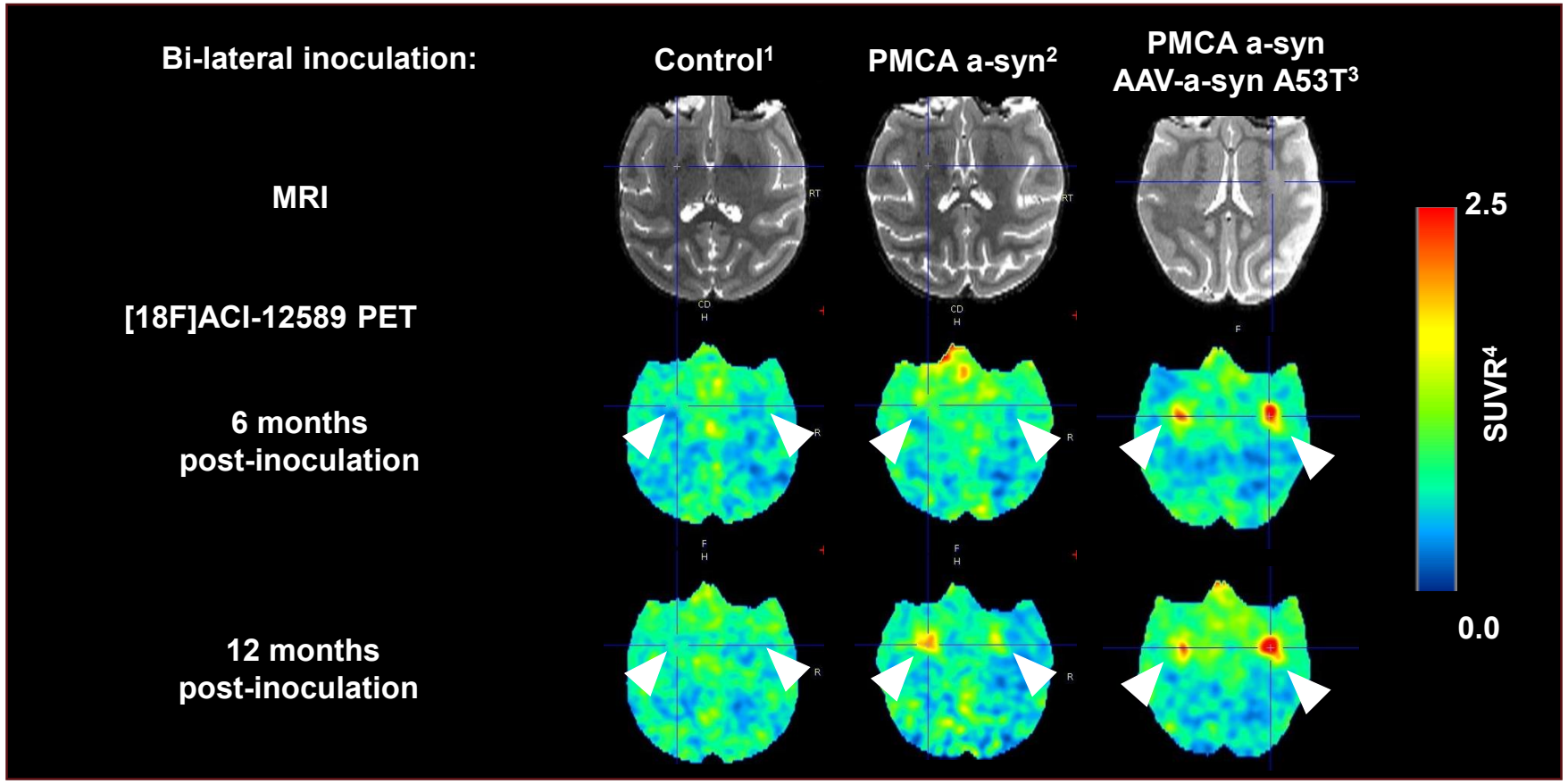
[18F]ACI-12589 uptake in monkey models of a-syn pathology

Longitudinal brain uptake in two different a-syn inoculation models



A-syn models developed by:

In collaboration with CEA / MIRCen
Capotosti et al., ADPD™ 2024

- Higher retention observed in the PMCA-AAV model suggests that the intensity of the PET signal is related to the pathological a-syn load
- A longitudinal increase in [18F]ACI-12589 uptake is observed in two a-syn monkey models

(1) PBS; (2) A-syn amplified by Protein Misfolding Cyclic Amplification from human PD seeds injected in the striatum at baseline and 6 months; (3) Adeno-associated virus expressing human a-syn with the A53T mutation injected in the substantia nigra at baseline; (4) Standardized uptake value ratio with whole cerebellum as reference

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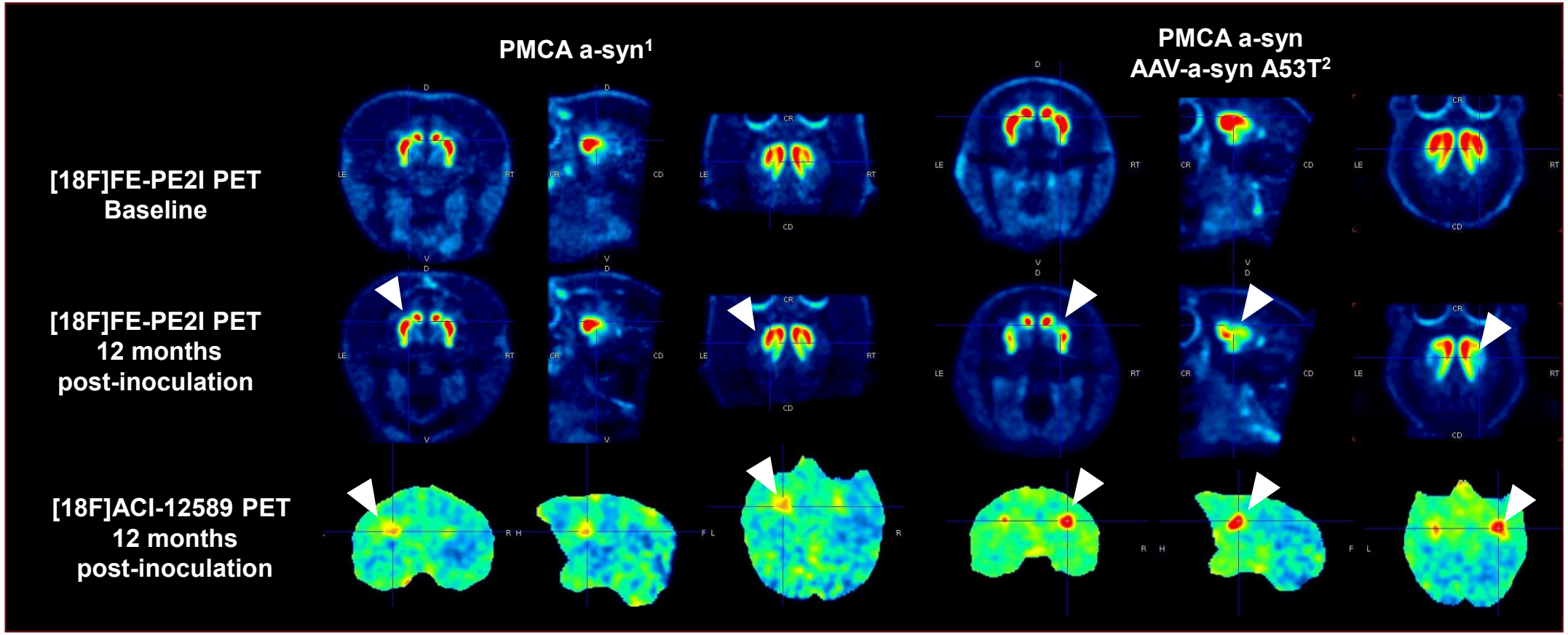
A-syn PET precedes dopaminergic loss

Comparison of [18F]FE-PE2I dopaminergic imaging and [18F]ACI-12589 PET



In collaboration with CEA / MIRCen
Capotosti et al., ADPD™ 2024

- The loss of dopaminergic neurons follows the appearance of a-syn pathology
- The a-syn PET signal increases as the dopaminergic loss progress

(1) A-syn amplified by Protein Misfolding Cyclic Amplification from human PD seeds injected in the striatum; (2) Adeno-associated virus expressing human a-syn with the A53T mutation injected in the substantia nigra

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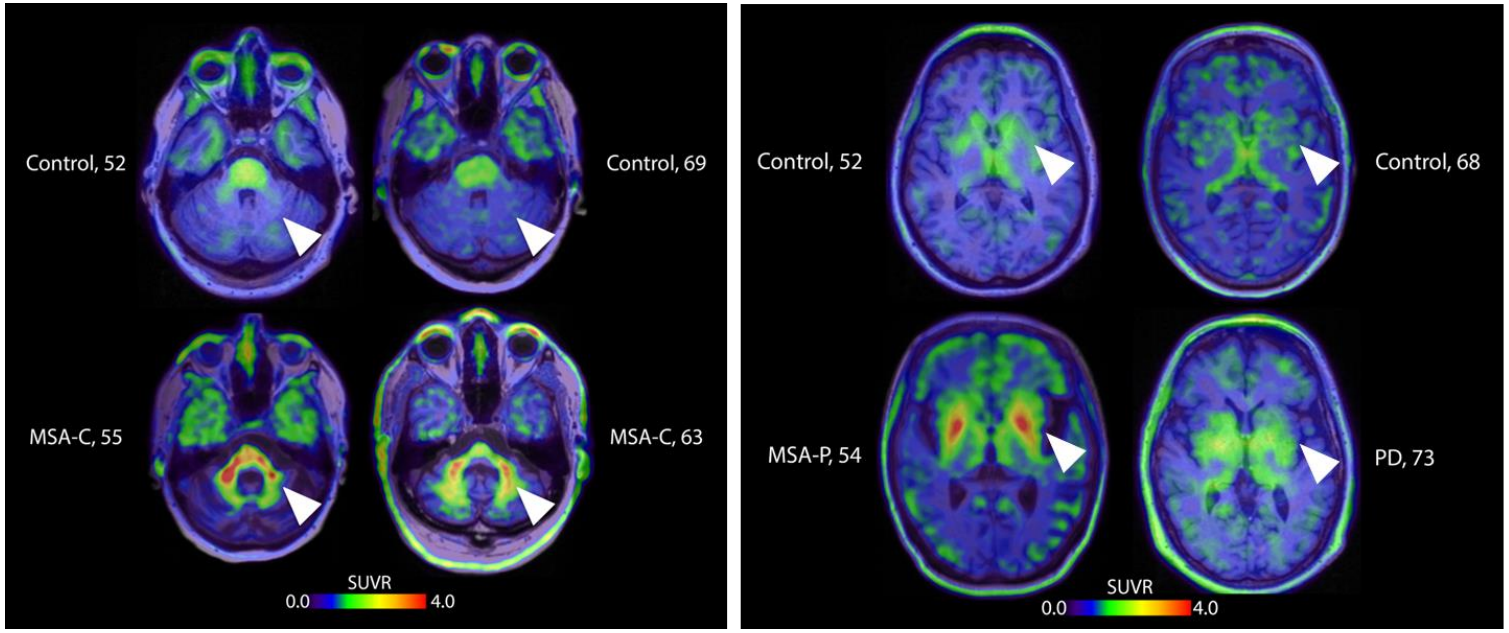
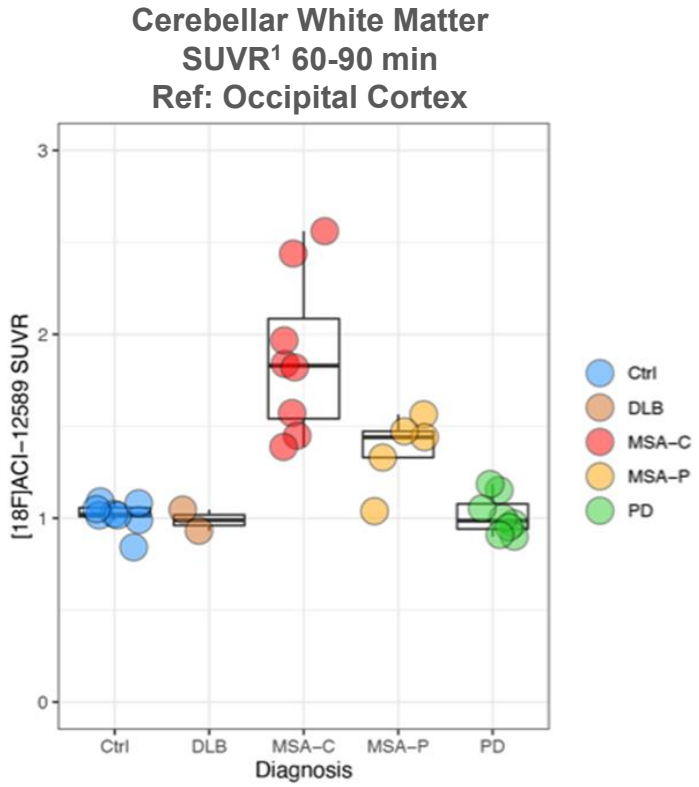
[18F]ACI-12589 uptake in MSA cases compared to controls

SUVR 60-90 min using occipital cortex as reference region





Smith, Capotosti, et al., Nature Communications 2023

- Clear tracer retention in cerebellar white matter and cerebellar peduncles in MSA-C cases
- Increased basal ganglia uptake in MSA-P cases in comparison to controls and PD cases
- Excellent discrimination between MSA cases and controls as well as other synucleinopathies, including Parkinson's' disease and Dementia with Lewy bodies

(1) Standardized uptake value ratio with occipital cortex reference region

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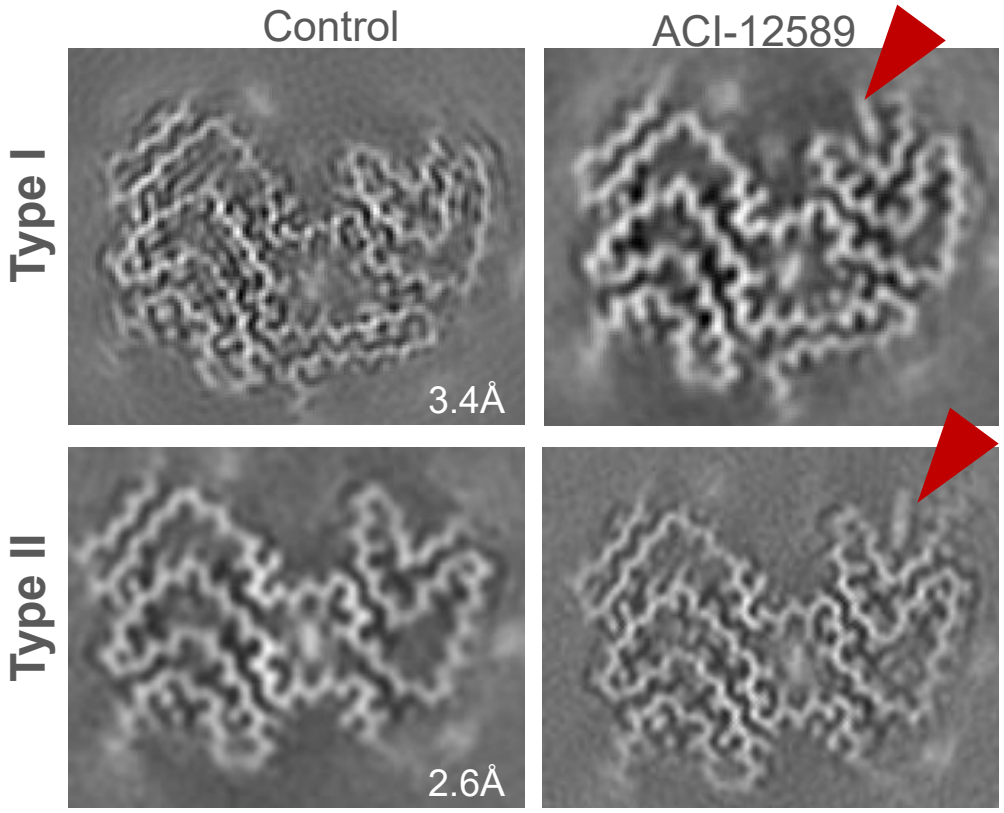
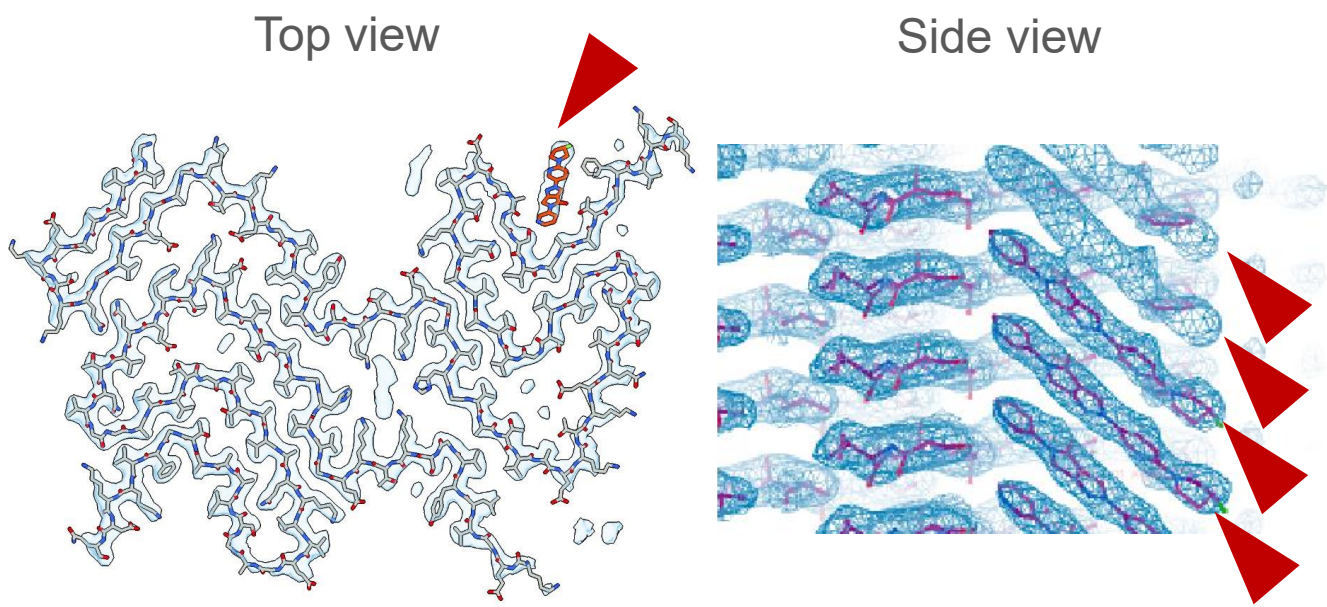
ACI-12589 binding to MSA fibrils by high-resolution cryo-EM

Binding of ACI-12589 across the stack of the Type I and II MSA a-syn filaments

3D reconstruction



MSA type II with ACI-12589



In collaboration with Dr. Yang Yang
Capotosti et al., Grand Challenges in Parkinson's disease 2024

- Mapping of ACI-12589 to MSA filaments by Cryo-EM reveals that it binds:
  - to the C-terminus of the protofilament A of the Type I and II MSA a-syn folds
  - along the stack of the fibrils; one ACI-12589 molecule per rung

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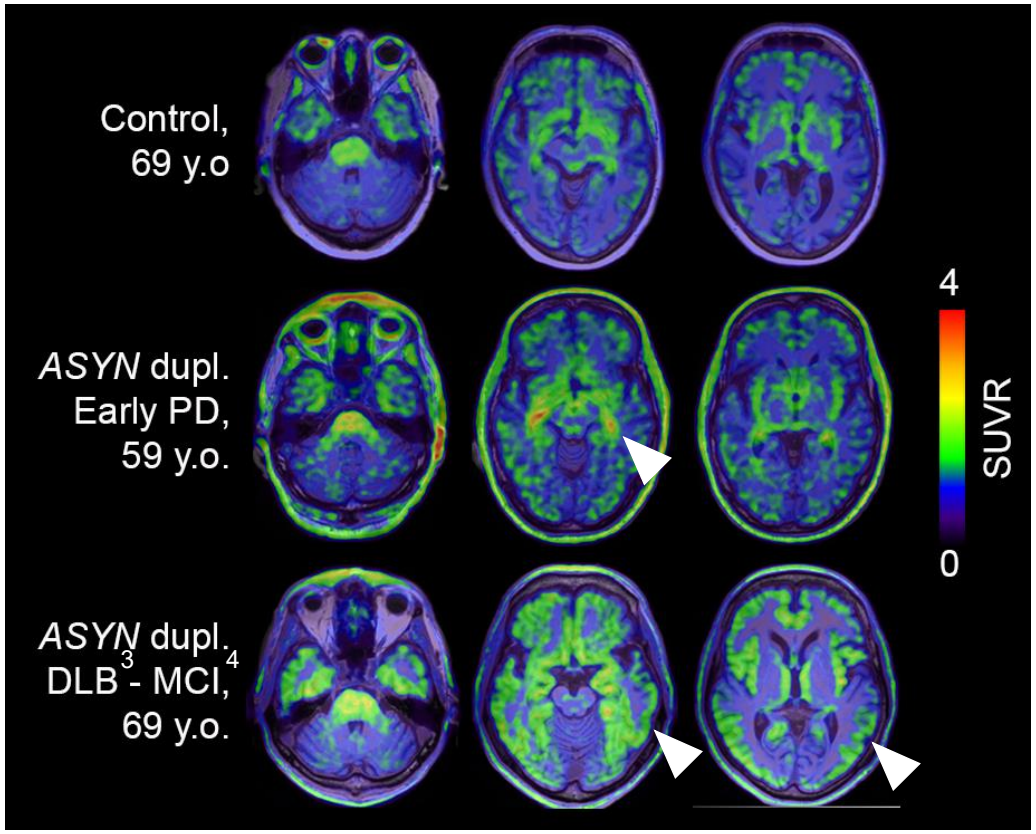
[18F]ACI-12589 uptake in genetic PD[1] cases

SUVR[2] 60-90 minutes using cerebellar grey as reference region



- Signal retention is observed in disease-relevant brain regions in genetic PD cases (SNCA duplication carriers)
- The retention is higher in the more advanced symptomatic case
- Signal distribution pattern is compatible with specificity of the signal for pathological a-syn

(1) Parkinson's disease; (2) Standardized Uptake Value Ratio; (3) Dementia with Lewy Bodies; (4) Mild Cognitive Impairment

Smith, Capotosti, et al., Nature Communications 2023

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Why [18F]ACI-12589 works *in vivo* in MSA but not in idiopathic PD?

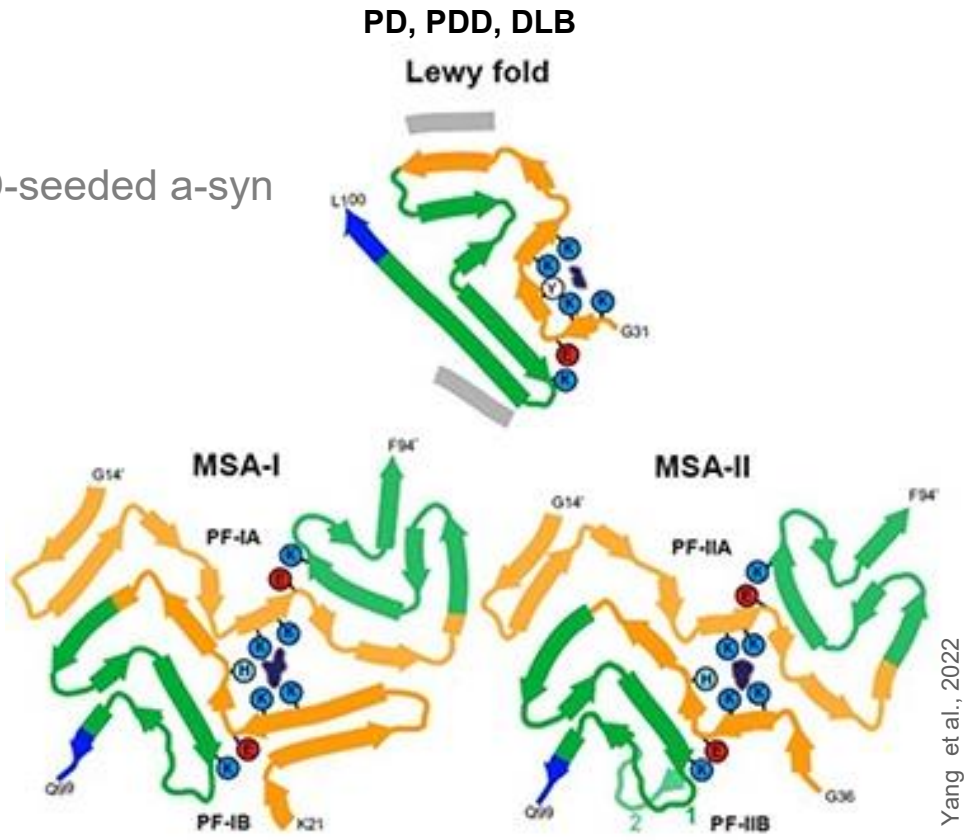
Target density and/or a-syn fibrils folding?

Arguments in favour of the higher target density:

- ACI-12589 binds *in vitro* to a-syn inclusions in PD, PDD[1], and DLB[2]
- [18F]ACI-12589 shows signal retention in SNCA duplication carriers
- [18F]ACI-12589 shows signal retention in a NHP model injected with PD-seeded a-syn

However:

- A-syn fibril fold is very different in MSA from PD:
  - Glial Cytoplasmic Inclusions are more densely packed than Lewy Bodies and contain two protofilaments
- This difference in folding could impact the binding



Yang et al., 2022

(1) Parkinson's disease with dementia; (2) Dementia with Lewy Bodies

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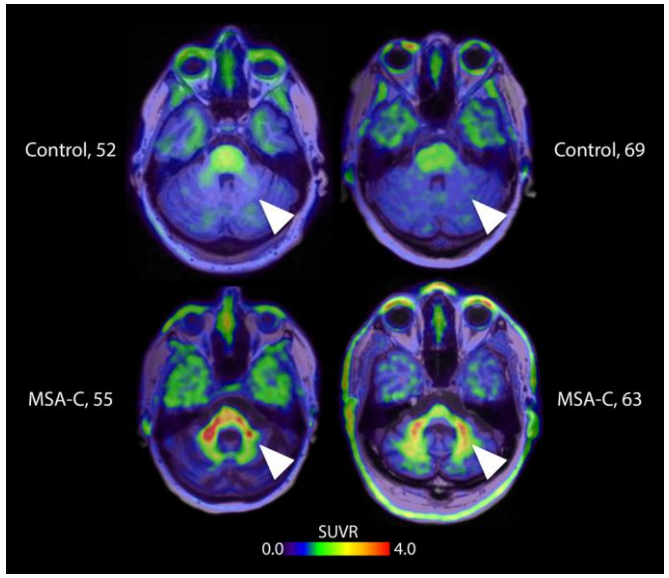
Accelerating and derisking clinical development in MSA[1]

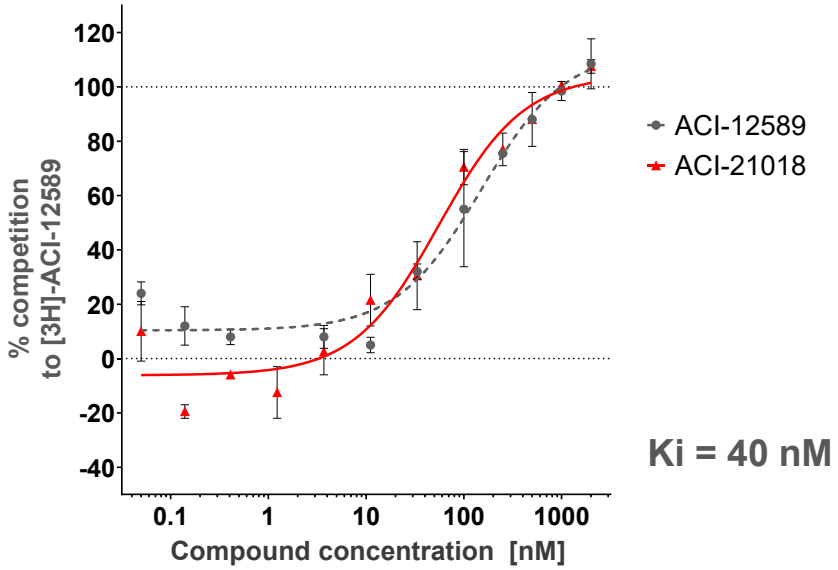
Unique opportunity to combine AC Immune's a-syn PET[2] tracer and therapeutic Morphomers®

a-syn PET ligand ACI-12589 is clinically validated in MSA



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

a-syn PET and therapeutic Morphomers® share a common binding site



Tsika et al., ADPD™ 2024

Shared 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 intracellular a-syn pathology

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

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[18F]ACI-12589 a clinically validated PET tracer for MSA[1]

Conclusions

First-in-class	▪ The first tracer detecting pathologic a-synuclein in patients differentiating MSA cases from other synucleinopathies and neurodegenerative diseases
Specificity and selectivity	▪ Binds specifically and selectively to alpha-synuclein pathology across NDDs[2] ▪ Longitudinally increased uptake in a-syn[3] NHP[4] models and appearance of PET[5] signal prior dopaminergic loss
Precision medicine	▪ Significantly improves the diagnosis of MSA ▪ Enables Precision Medicine and biomarker-based development in MSA
Status	▪ Currently being evaluated in longitudinal clinical studies

(1) Multiple system atrophy; (2) Neurodegenerative diseases; (3) Alpha-synuclein; (4) Non-human primate; (5) Positron emission tomography

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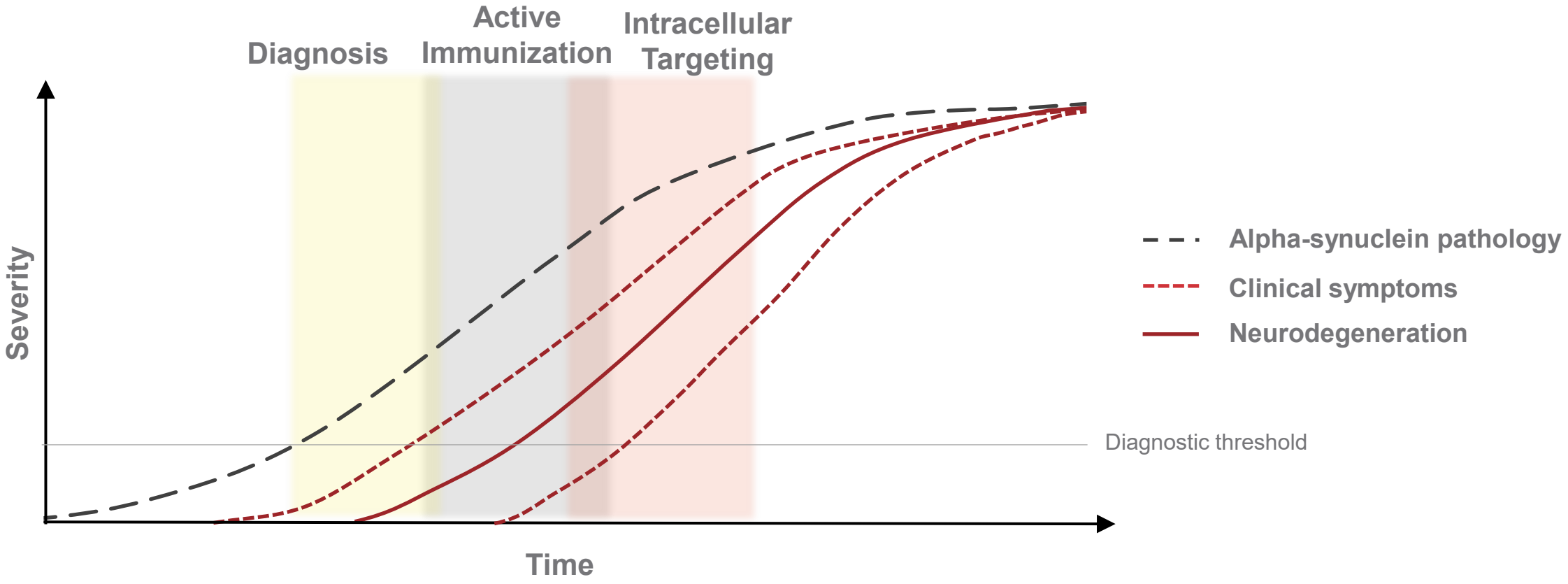
An integrated approach to target alpha-synuclein pathology

Earlier diagnosis for higher beneficial impact of disease-modifying therapies



Adapted from Simuni et al., Lancet Neurol 2024

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All the donors and their families for their indispensable contributions to research

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AC Immune: Pioneering science and precision medicine

Shifting the treatment paradigm for neurodegenerative disease towards precision medicine and disease prevention

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