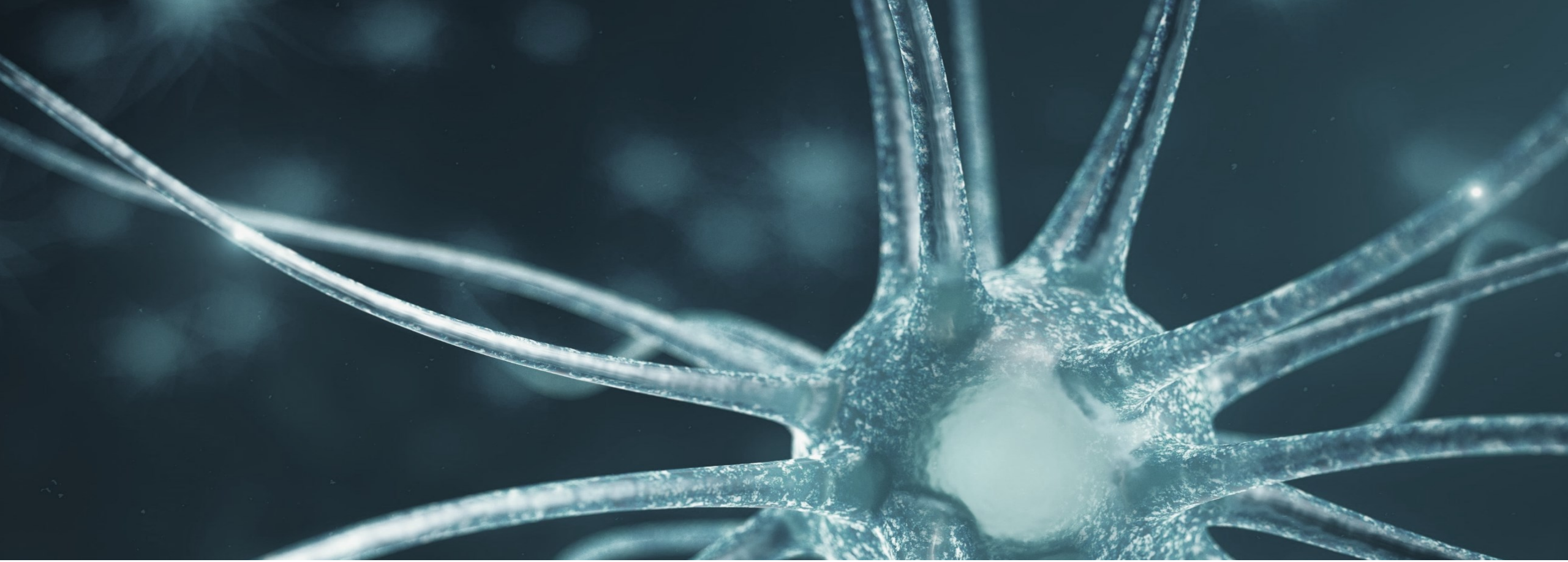

# Discovery and initial clinical evaluation [18F]ACI-12589, a novel and promising PET-tracer for a-synuclein

Francesca Capotosti, PhD | AD/PD™ 2023 | March 30th

AC Immune

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# Disclosures

*Francesca Capotosti is an employee of AC Immune entitled to stock options*

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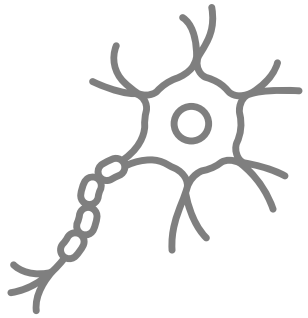
# A-syn[1] PET[2] tracers can improve the diagnosis and treatment of NDD[3]

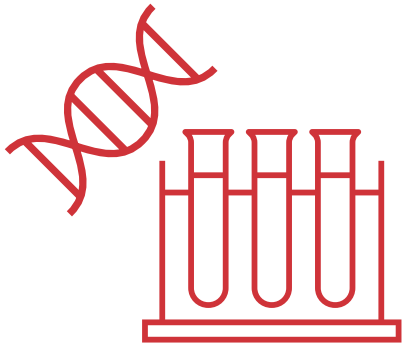
## Needed to best enable precision medicine for a-synucleinopathies

### Early Diagnosis and Treatment is Key in NDD



- Once neurons are damaged, they cannot be repaired or replaced with current therapies

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



- Dopaminergic imaging correlates poorly with disease severity
- Genetic testing is ineffective in most cases
- Low abundance of a-syn limits utility of fluid biomarkers

### Benefits of PET tracers for imaging have been validated

- Patient stratification
- Better clinical trials when focused 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





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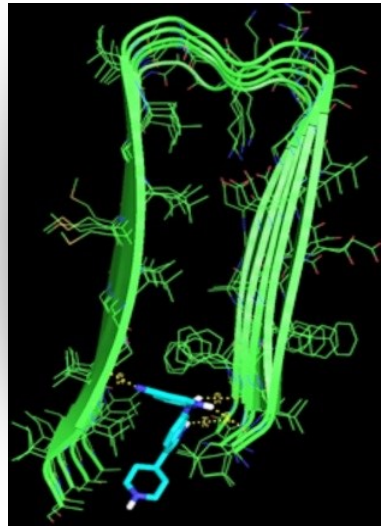
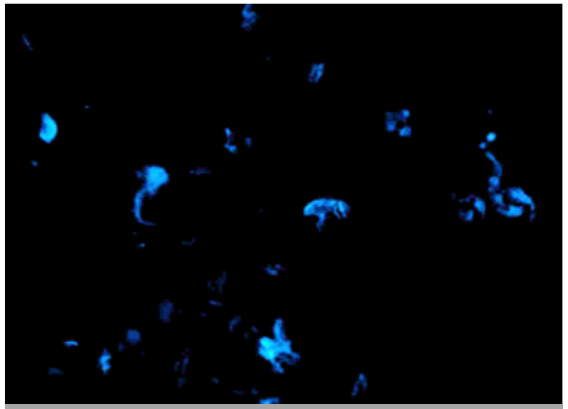
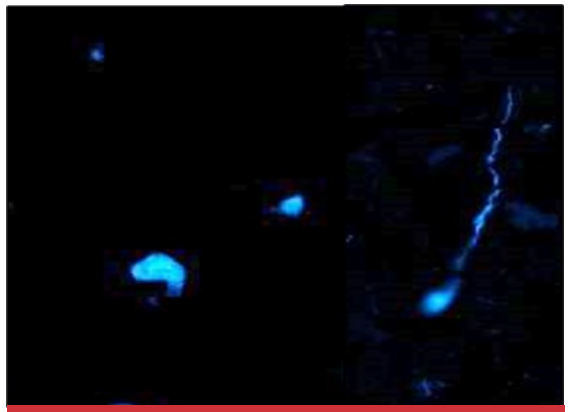
# Precision medicine approach enabled by the Morphomer® platform

## Developing a suite of PET[1] tracers against emerging targets in NDD[2]

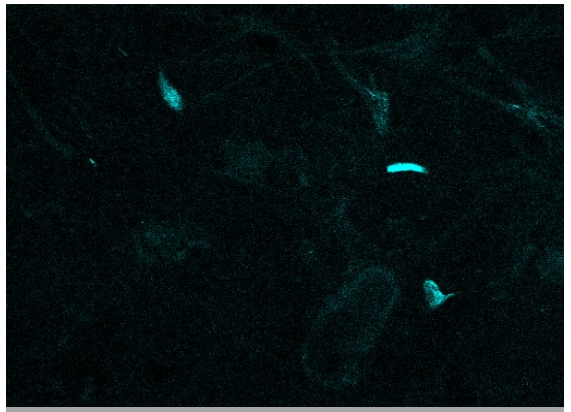




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

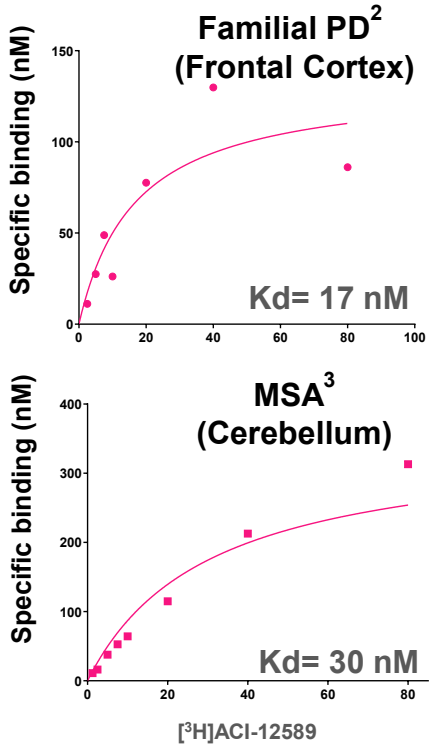
**Leverage the Morphomer® small molecule platform:**

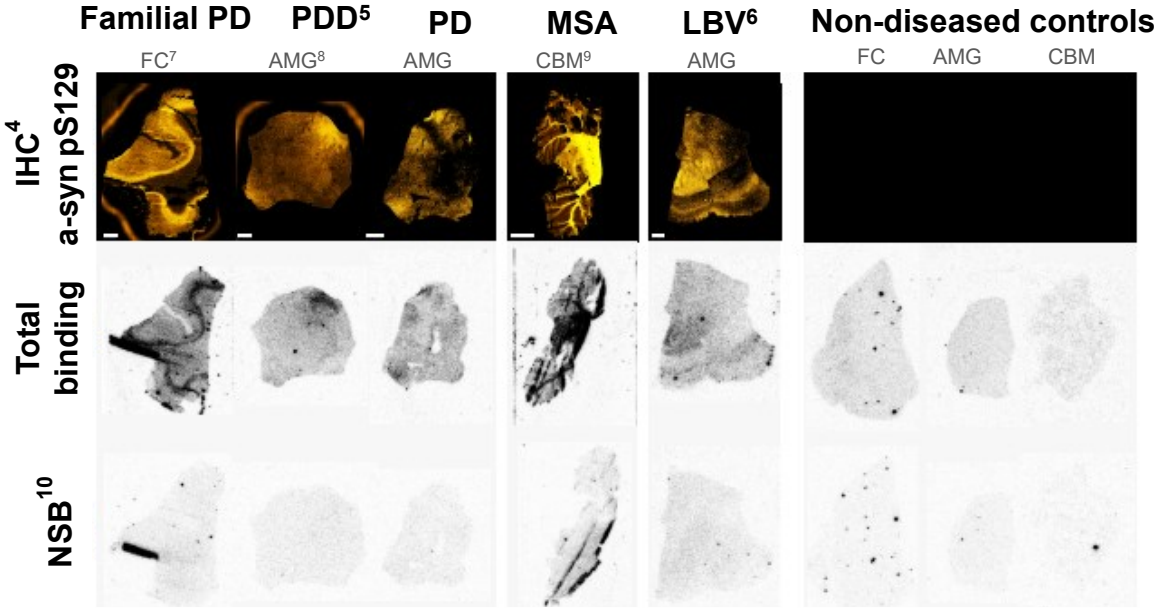
- Non-peptidic, small molecules with CNS-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, TDP-43)
- Pharmacokinetics suitable for brain PET imaging

(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) Alpha synuclein; (5) TAR DNA binding protein-43

# ACI-12589 binds specifically a-syn[1] pathology in human tissues

## From different a-synucleinopathy cases




Ref.: Capotosti et al., ADPD 2022

- ACI-12589 displays a clear autoradiography signal across different synucleinopathy cases which correlates with the presence of pathological a-syn
- Binding affinities are measured in the range of 8-30 nM with Bmax/Kd ratios of ~ 5-10

(1) alpha-synuclein; (2) Parkinson's disease with G51D SNCA mutation; (3) Multiple system atrophy; (4) Immunohistochemistry; (5) Parkinson's disease with dementia; (6) Lewy Body variant of Alzheimer's disease; (7) Frontal cortex; (8) Amygdala; (9) Cerebellum; (10) Non-specific binding

# [18F]ACI-12589: the first PET[1] tracer to image a-syn[2] in humans

## Demographics of FiH[3] study

| | Control | PD[4] | MSA[5] | DLB[6] | AD[7] | PSP[8] | Ataxias |
|---|---|---|---|---|---|---|---|
| **n (43)** | 8 | 8 | 13 | 2 | 5 | 3 | 3 |
| **Sex (M/F)** | 5/3 | 7/1 | 7/6 | 2/0 | 4/1 | 3/0 | 2/1 |
| **Age (± SD)** | 63±11 | 68±6 | 61±8 | 81±1 | 69±4 | 72±9 | 54±14 |
| **Inj Dose (MBq)** | 314±39 | 308±56 | 297±13 | 289±1 | 296±5 | 298±8 | 267±67 |
| **UMSARS I + II** | N/A | N/A | 53±23 | N/A | N/A | N/A | N/A |
| **UPDRS-III** | N/A | 65±16 | N/A | N/A | N/A | N/A | N/A |

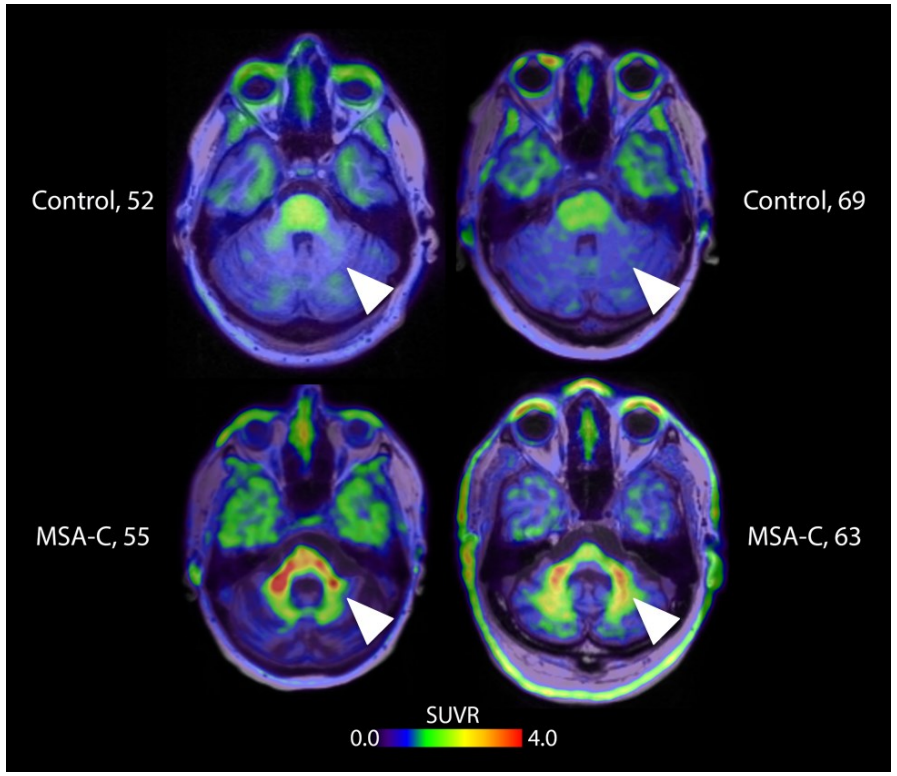
In collaboration with Prof. O. Hansson

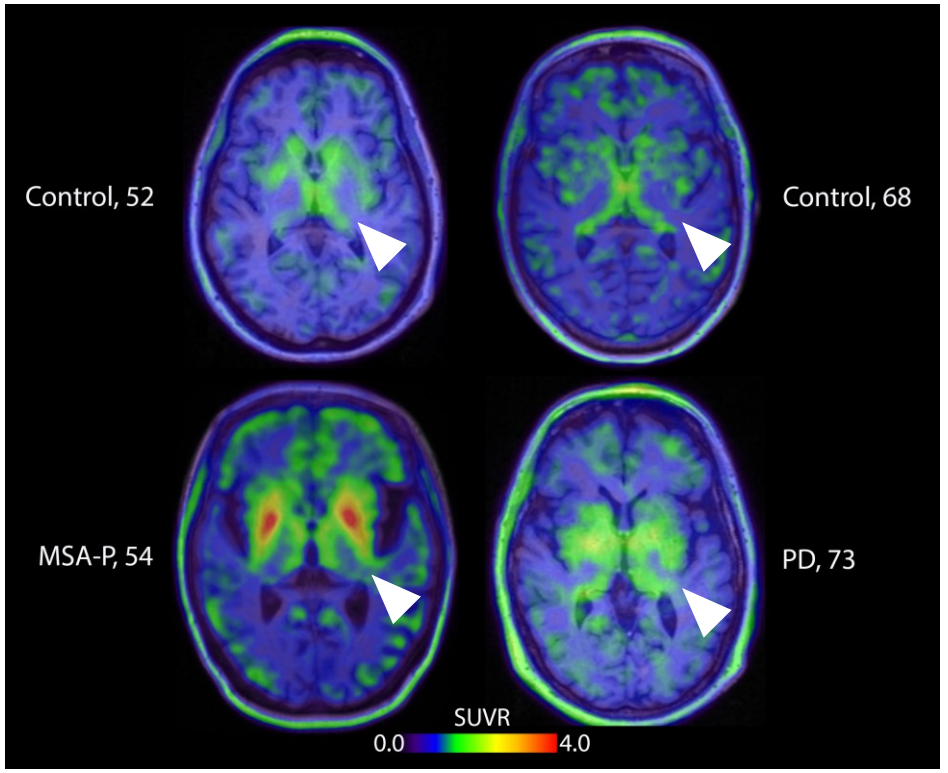
- [18F]ACI-12589 was evaluated in a total of 54 participants; 23 with a-syn-related disorders of which 13 MSA cases
- The initial 25 subjects underwent dynamic 0-90 min scans and the vast majority had arterial blood sampling while following scans were performed with shorted scan time

(1) Positron emission tomography; (2) alpha-synucleini; (3) First in Human; (4) Idiopathic Parkinson's disease; (5) Multiple system atrophy; (6) Dementia with Lewy Bodies; (7) Alzheimer's disease; (8) Progressive supranuclear palsy

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

## SUVR 60-90 min using occipital cortex as reference region



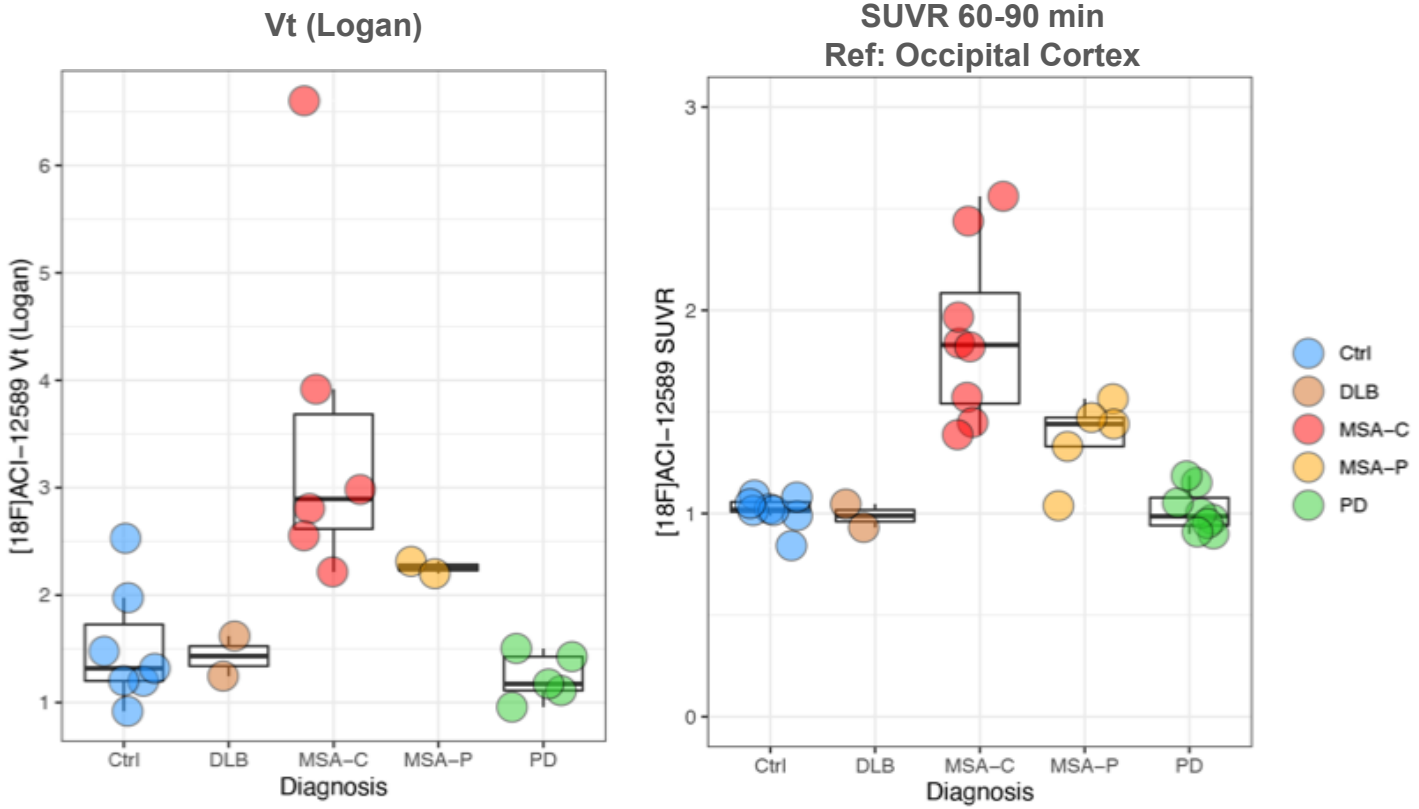



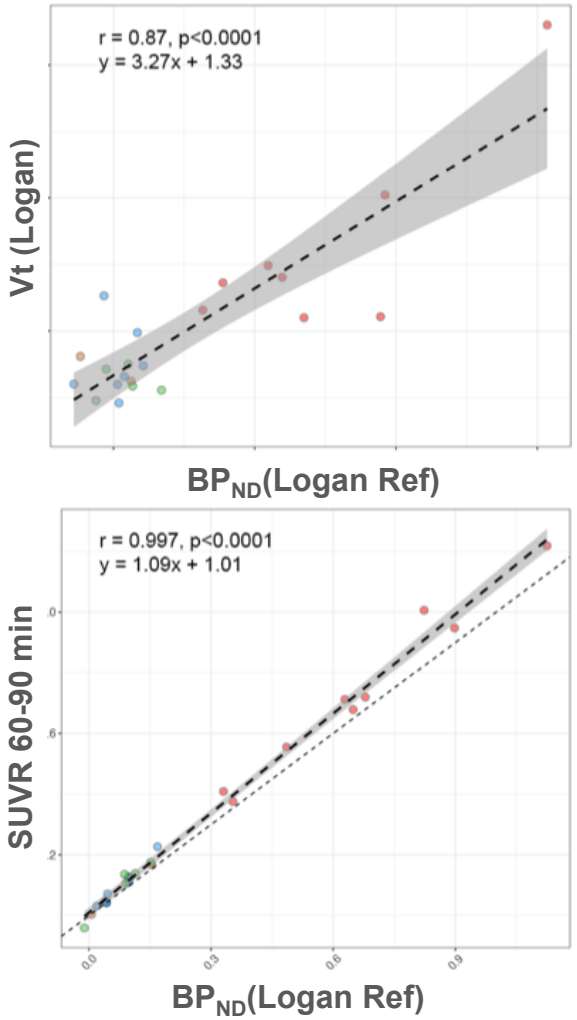

Ref.: Smith et al., ADPD 2022

- 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
- Overall, good correspondence between PET signal and the expected pathological a-syn distribution based on clinical presentation

# [18F]ACI-12589 uptake discriminate MSA from other synucleinopathies

## Signal quantification in the cerebellar white matter



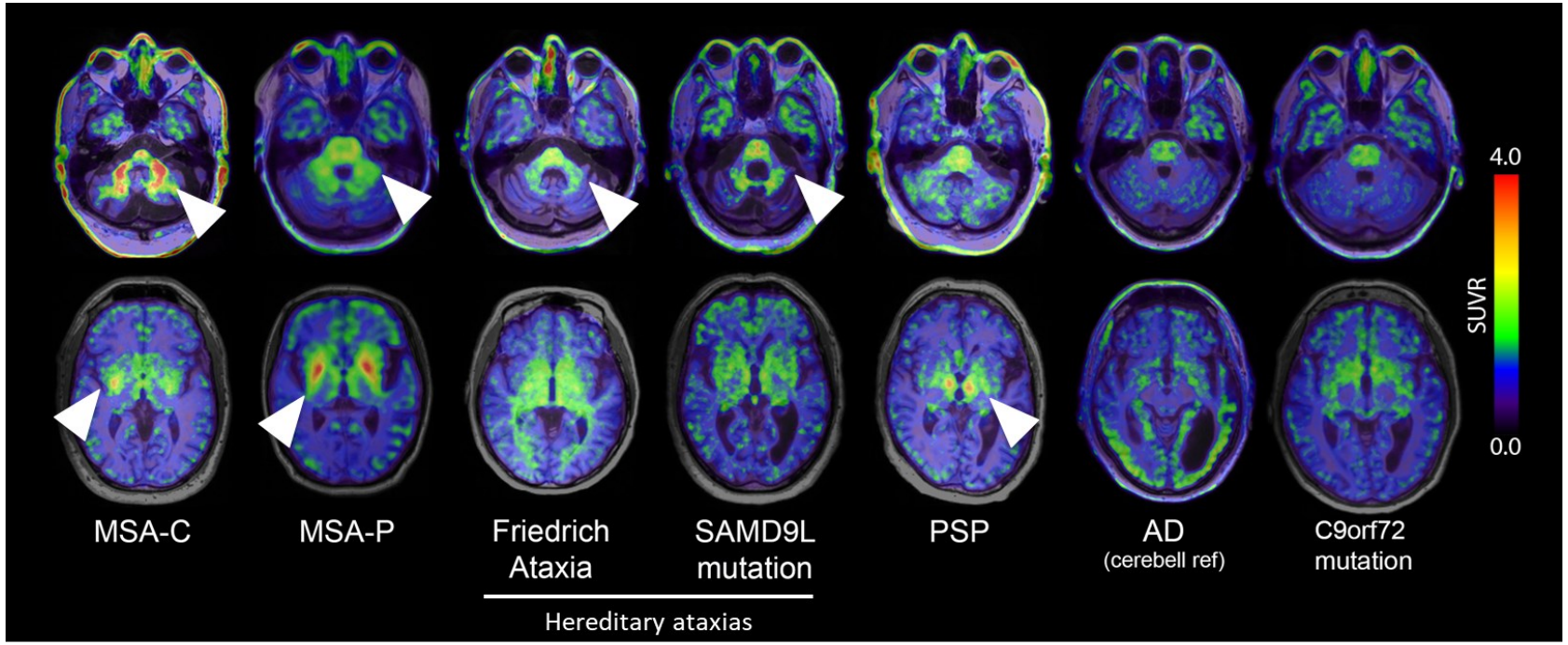



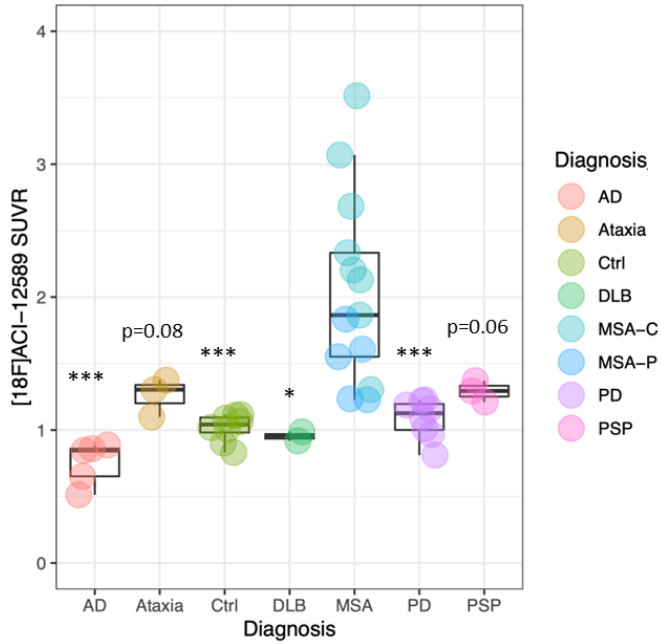

Ref.: Adapted from Smith et al., ADPD 2022

- Cerebellar uptake clearly discriminate MSA cases from controls and other synucleinopathy cases with an excellent correlation between different quantification methods, allowing short scan windows

# [18F]ACI-12589 differentiates MSA[1] from different NDDs[2]

## SUVR 60-90 min using occipital cortex as reference region



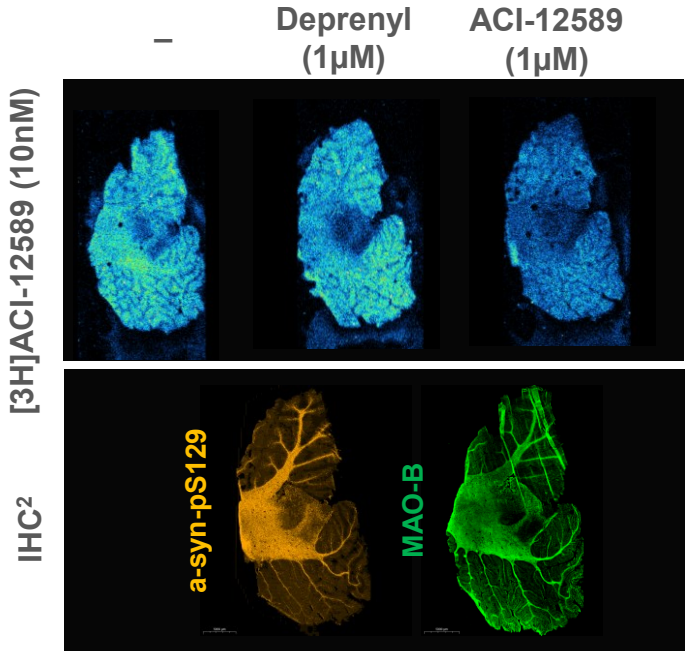

- [18F]-ACI-12589 retention in cerebellar peduncles can clearly differentiate MSA cases from other NDDs
- The weaker signal retention observed in certain NDDs could be due to off-target binding or syn co-pathology
- A recent scan in a C9orf72 case with expected neurodegeneration in the frontal lobes does not show any relevant uptake

(1) Multiple System Atrophy; (2) Neurodegenerative disease

# [18F]ACI-12589: Clean off-target binding

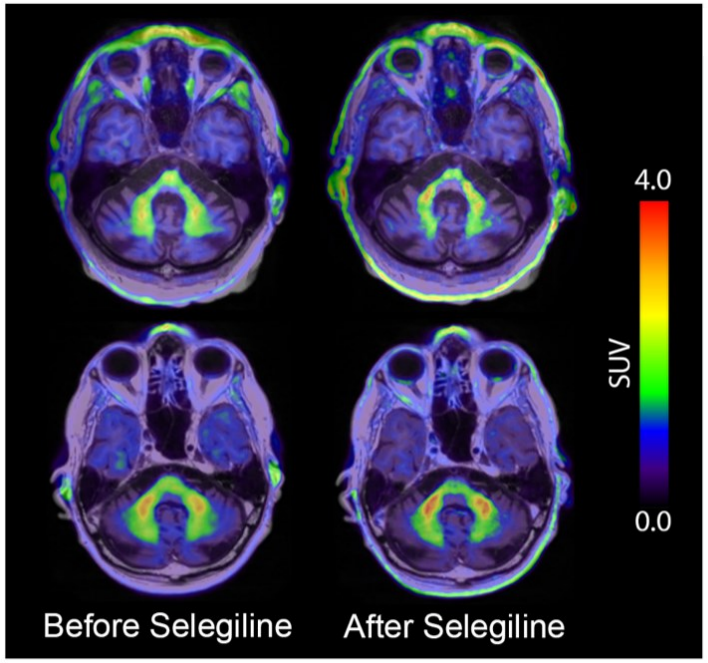
## [18F]ACI-12589 signal in MSA[1] is not due to MAO-B[2] binding

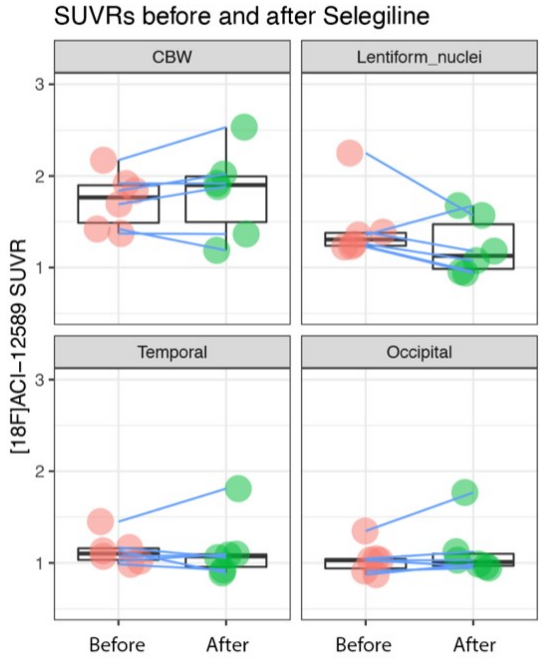
### Ex-vivo MAO-B blocking




MSA tissue, cerebellum

### MAO-B blocking study in MSA cases



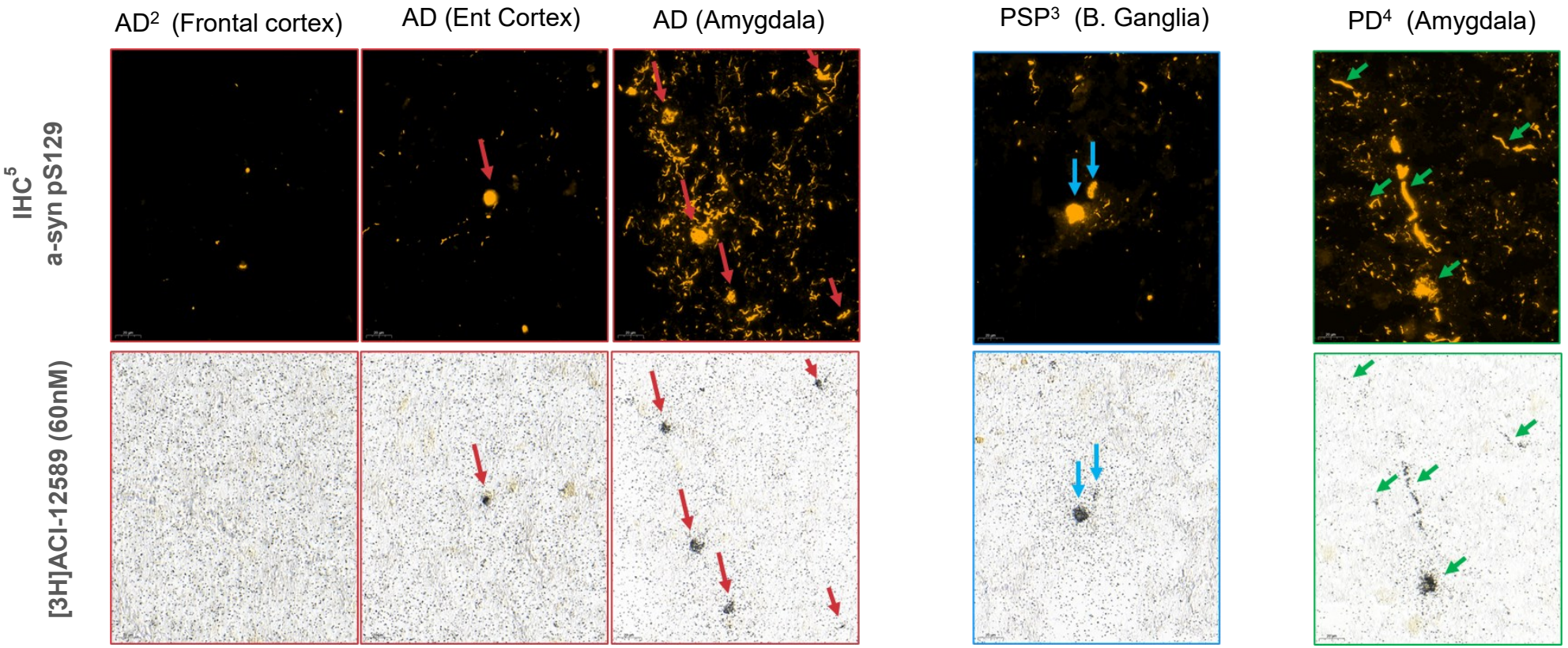




Ref.: Capotosti et al., AD/PD 2022; Smith et al., AAIC 2022

- Pharmacological blocking of MAO-B with Selegiline did not change tracer retention in MSA cases
- Similarly, Deprenyl does not displace ACI-12589 binding ex-vivo
- These data strongly indicate the signal specificity of ACI-12589 for a-syn in the MSA cases

(1) Multiple System Atrophy; (2) Monoamino-oxidase-B

# ACI-12589 binds to a-syn[1] in different neurodegenerative diseases




Ref: Capotosti et al., AAIC 2022

- In the presence of a-syn co-pathology, [3H]ACI-12589 binds to a-syn inclusions in AD and PSP tissues similarly to what observed in PD tissue

(1) alpha-synuclein ; (2) Alzheimer's disease; (3) Progressive Supranuclear Palsy; (4) Parkinson's disease; (5) Immunohistochemistry





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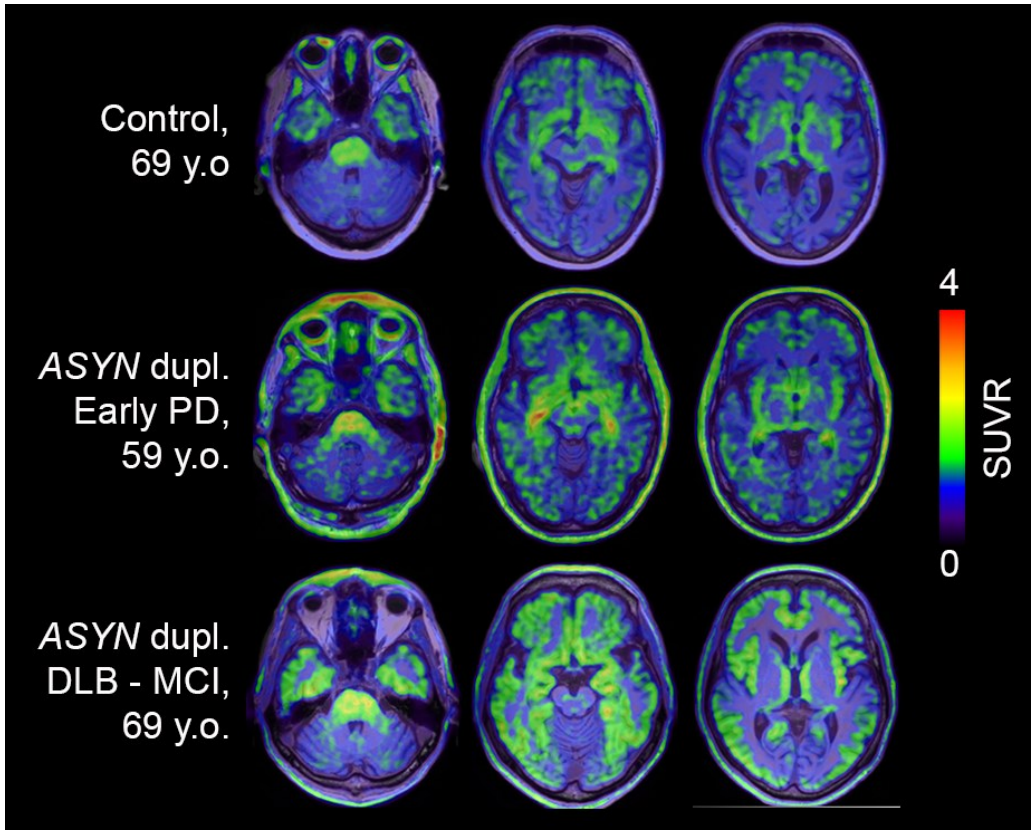
# [18F]ACI-12589 uptake in genetic PD[1] cases

## SUVr 60-90 minutes using cerebellar grey as reference region



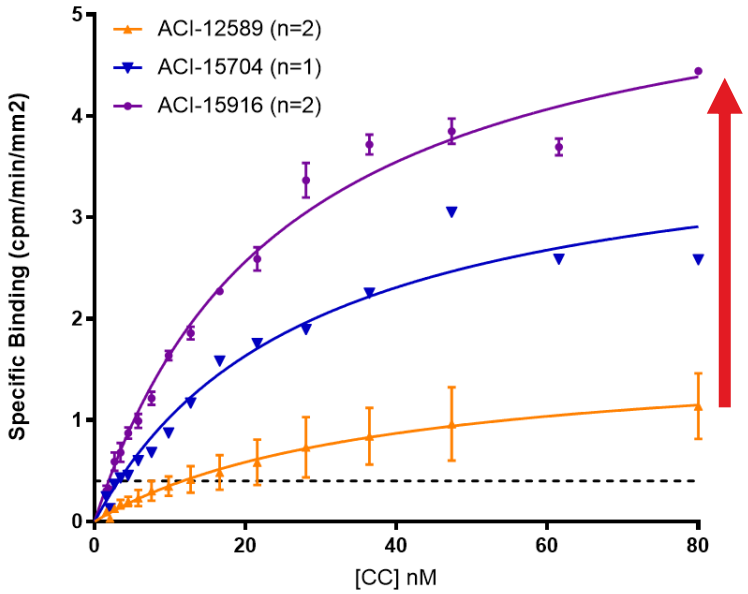

- Signal retention is observed in disease-relevant brain regions in genetic PD cases (SNCA duplication carriers)
- The retention is higher in the more advanced symptomatic case
- Signal distribution pattern is compatible with specificity of the signal for pathological a-syn

(1) Parkinson's disease

Ref.: Smith et al., AAIC 2022

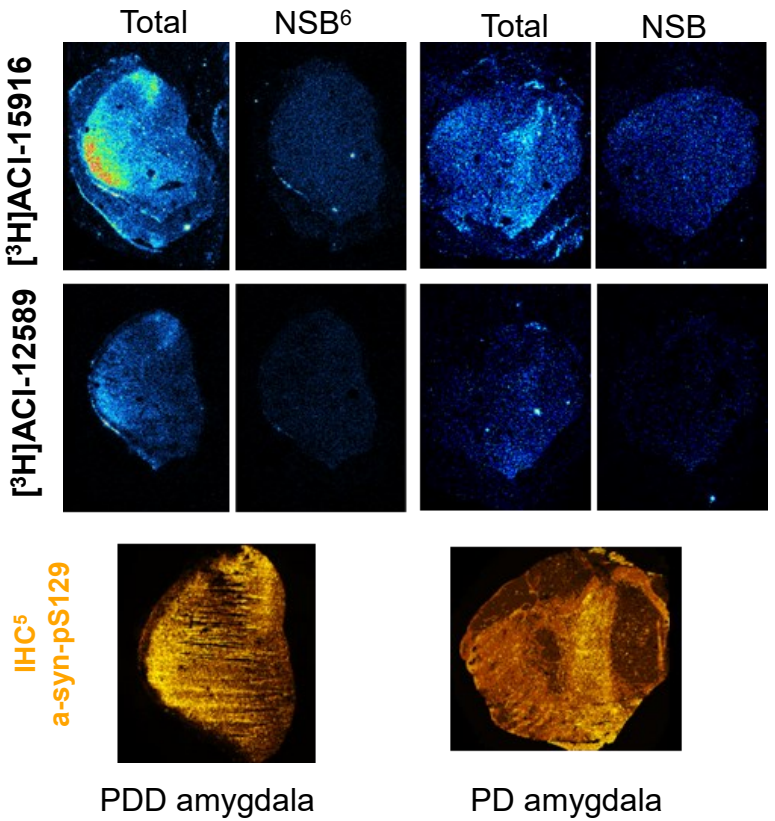
# Next generation a-syn[1] PET[2] tracers for patients with PD[3]

**Saturation binding on total PD brain homogenates**

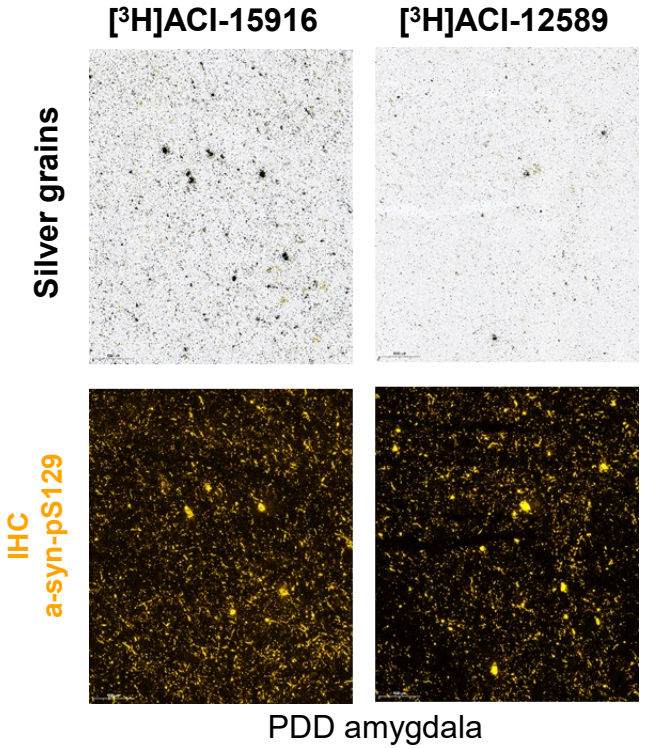



**5x improvement in Bmax/Kd**

**Autoradiography on PD/PDD[4] tissues**




**High-resolution Autoradiography on PDD tissue**




Ref: AC Immune unpublished data

- Newly identified candidates show significantly improved a-syn binding while maintaining good selectivity, clean off-target profile and brain PET ligand-like pharmacokinetic properties

(1) alpha-synuclein ; (2) Positron emission tomography; (3) Parkinson's disease; (4) Parkinson's disease with dementia; (5) Immunohistochemistry; (6) Nonspecific binding





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# [18F]ACI-12589 will improve MSA[1] diagnosis and support Precision Medicine

- *Ex-vivo* ACI-12589 binds specifically and selectively to a-synuclein inclusions:
  - ✓ in different synucleinopathies
  - ✓ In NDDs[2] when present as co-pathology

- [18F]ACI-12589 is the first tracer detecting pathologic a-synuclein in patients
  - ✓ differentiates MSA cases from other synucleinopathies and NDDs,

- [18F]ACI-12589 will:
  - ✓ significantly improve the diagnosis of MSA
  - ✓ enable our Precision Medicine approach and biomarker-based development in MSA

- Newly identified candidates show significantly improved binding properties with potential to detect synucleinopathies including in PD[4]

(1) Multiple system atrophy; (2) Neurodegenerative disease; (3) Positron emission tomography; (4) Parkinson's disease

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