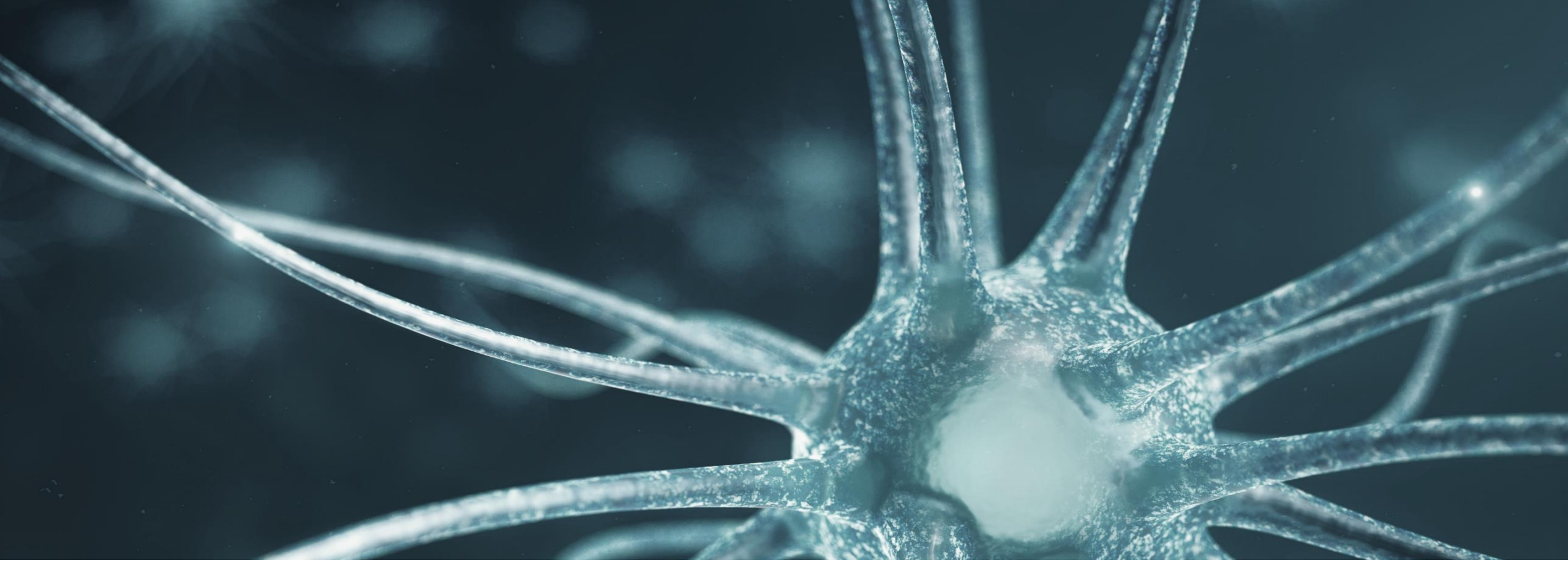

DISCOVERY OF [18F]ACI-12589: A NOVEL AND PROMISING PET-TRACER FOR ALPHA-SYNUCLEIN

Francesca Capotosti, PhD | AD/PD™ 2022 | 18 March

AC Immune

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Disclosures

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

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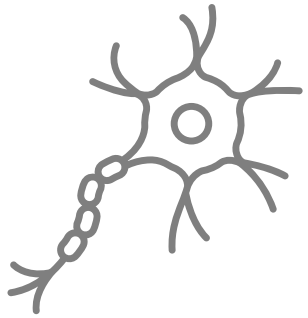
A-syn[1] PET[2] tracers can improve the diagnosis and treatment of NDD[3]

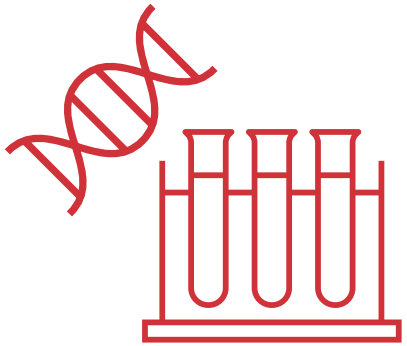
An effective PET tracer is needed to best enable precision medicine for a-synucleinopathies

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

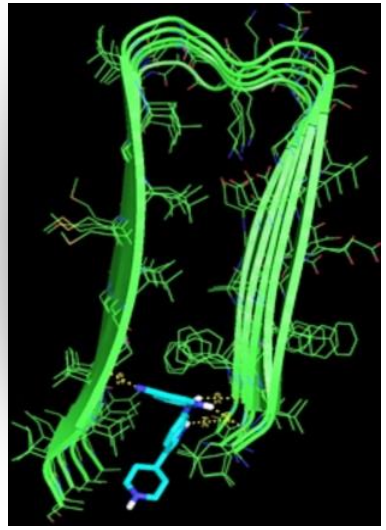
Benefits of PET tracers for imaging have been validated

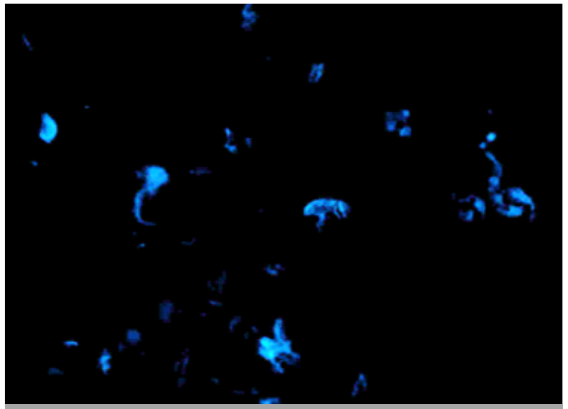
- Patient stratification
- Better clinical trials when focused using PET tracer for recruitment and monitoring
- May enable combination treatment of co-pathologies

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

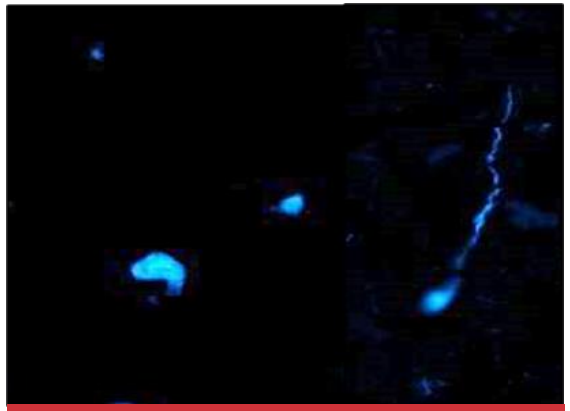
Precision medicine approach enabled by the Morphomer® platform

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

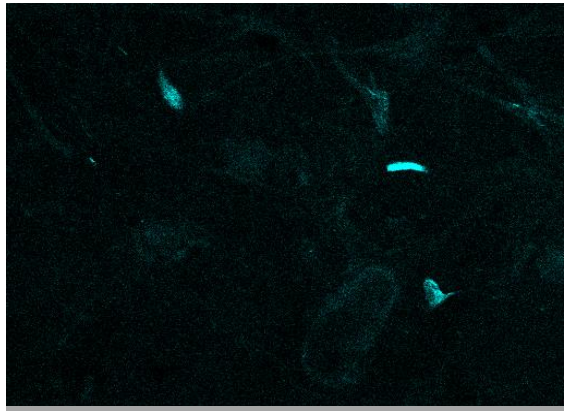




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

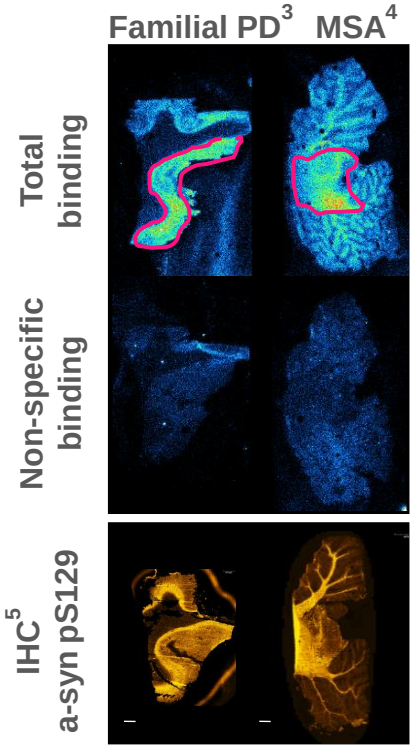
Leverage the Morphomer® small molecule platform:

- 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

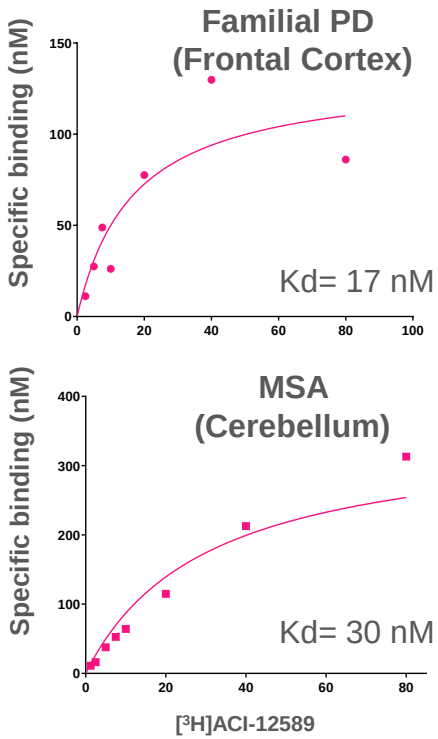
(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) Alpha synuclein; (5) TAR DNA binding protein-43

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

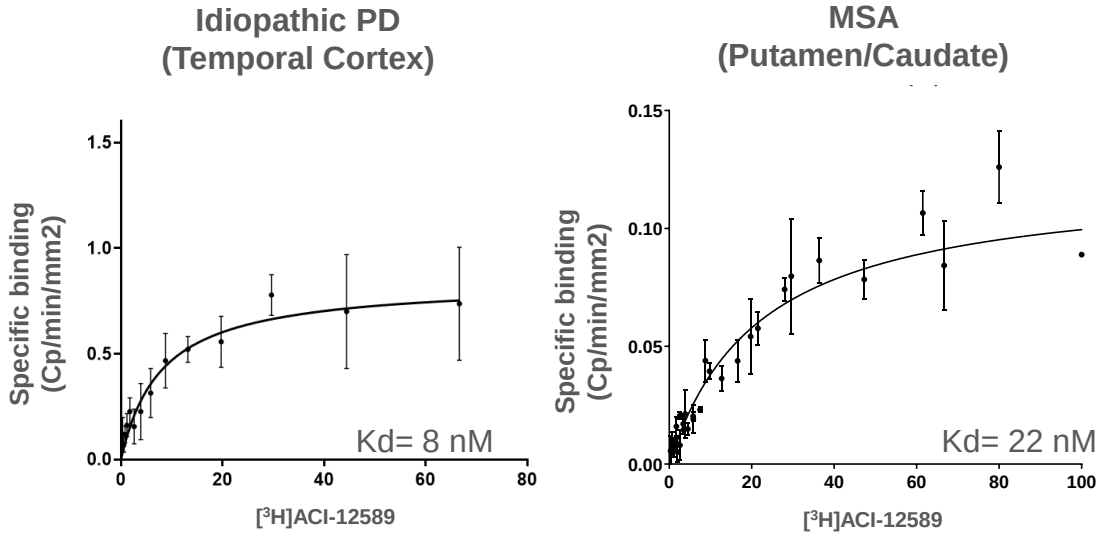
[3H]ACI-12589 specific binding on brain tissue from different a-synucleinopathy cases



Tissue slices



Tissue homogenates



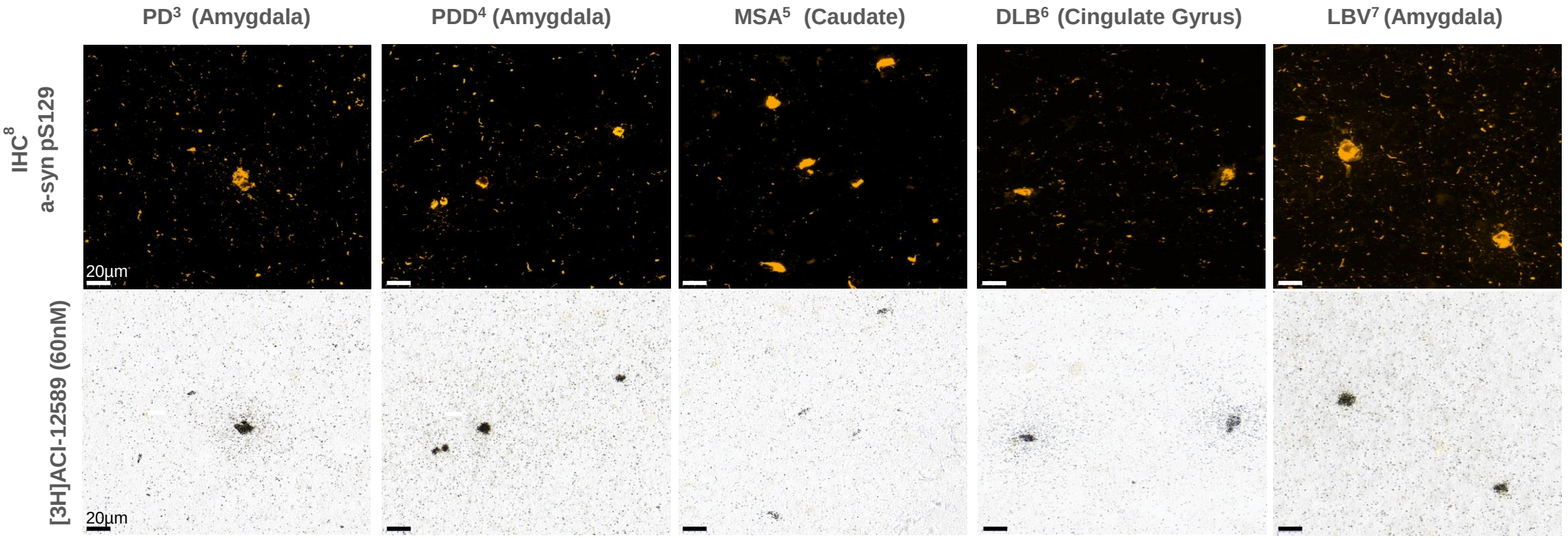
Ref.: AC Immune unpublished data

- ACI-12589 displays a clear autoradiography signal 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) Positron emission tomography; (3) Parkinson's disease with G51D SNCA mutation; (4) Multiple system atrophy; (5) Immunohistochemistry

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

[3H]ACI-12589 target engagement on a range of different a-syn inclusions



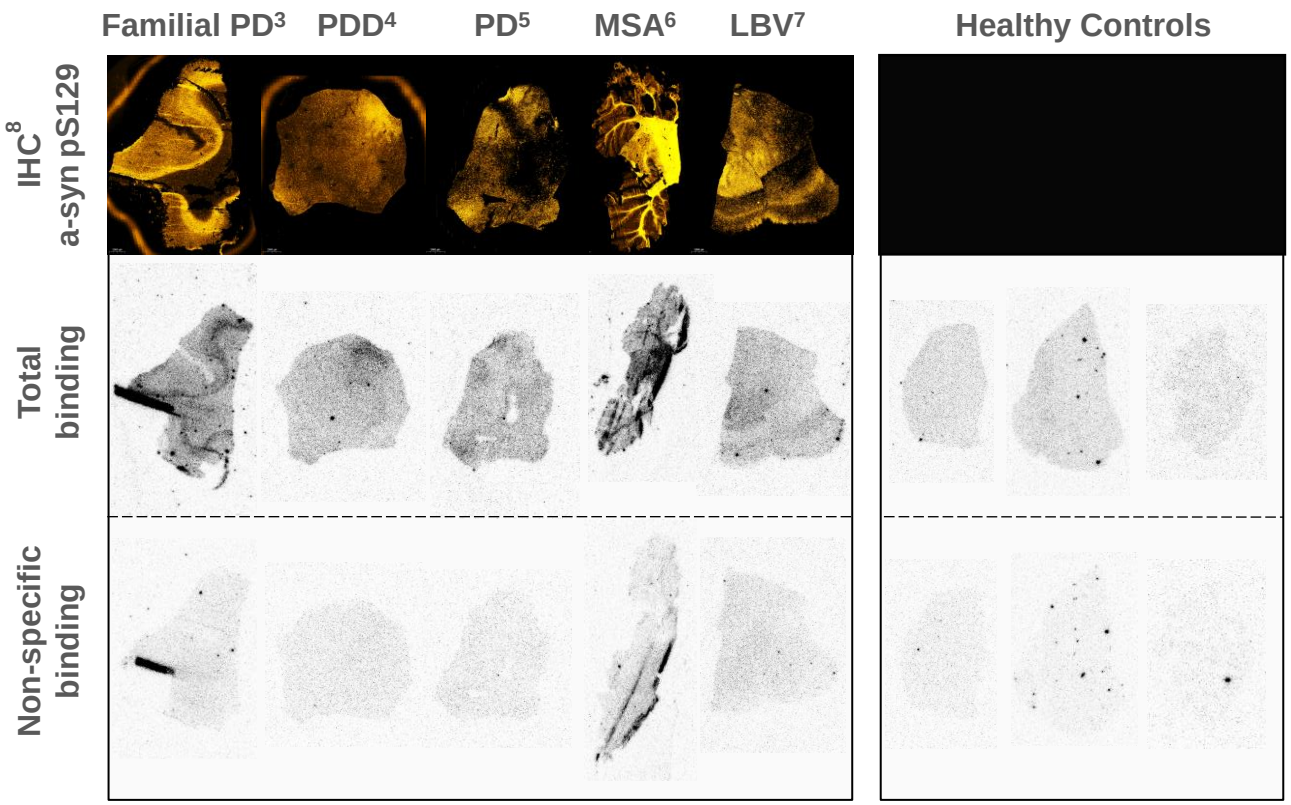
Ref.: Capotosti et., AAIC 2020

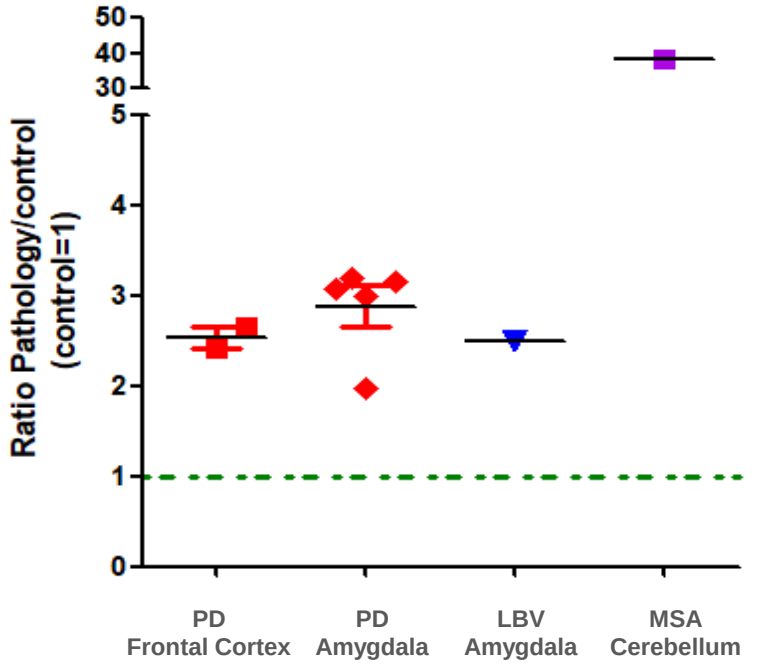
- ACI-12589 displays strong target engagement on Lewy bodies and Lewy neurites, as well as smaller a-syn inclusions, across a wide range of a-synucleinopathies

(1) alpha-synuclein ; (2) Positron emission tomography; (3) Parkinson's disease; (4) Parkinson's disease with dementia; (5) Multiple system atrophy; (6) Dementia with Lewy bodies; (7) Lewy body variant of Alzheimer's disease; (8) Immunohistochemistry

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

[18F]ACI-12589 specific binding on brain tissue from different a-synucleinopathy cases





In collaboration with Prof. A. Varrone, Karolinska Institute

Karolinska Institutet

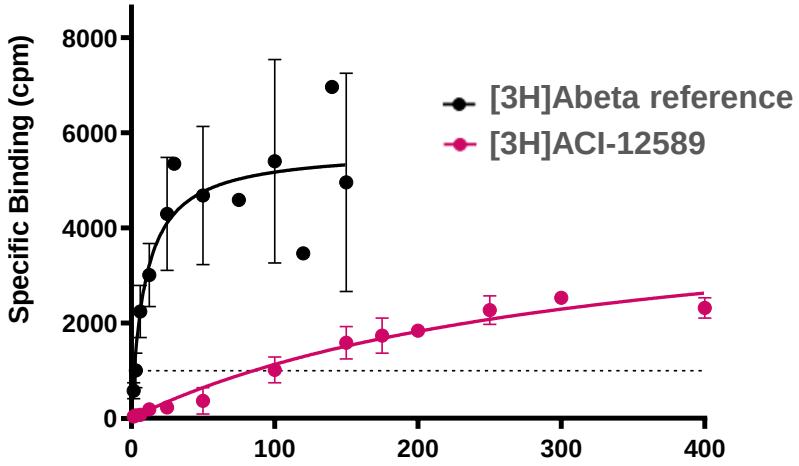
- Classical autoradiography experiments confirms specific binding across a wide range of a-synucleinopathies

(1) alpha-synuclein; (2) Positron emission tomography; (3) Parkinson's disease with G51D SNCA mutation; (4) Parkinson's disease with dementia; (5) Parkinson's disease ; (6) Multiple system atrophy; (7) Lewy body variant of Alzheimer's disease; (8) Immunohistochemistry

ACI-12589: selective *versus* Abeta and Tau

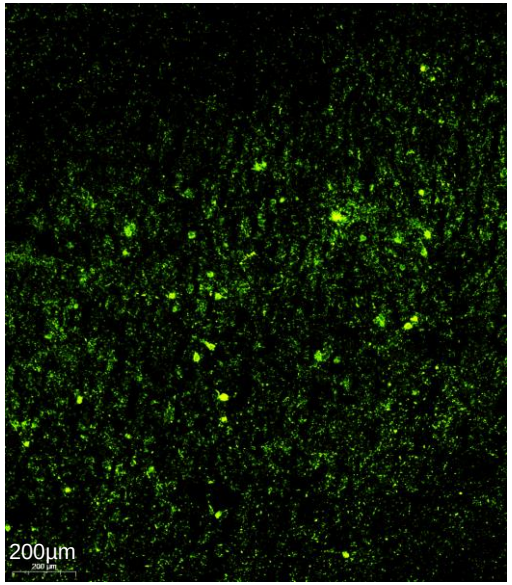
[3H]ACI-12589 assessed using Alzheimer's disease tissue

Radiobinding with AD[1] brain homogenates (Frontal Cortex)

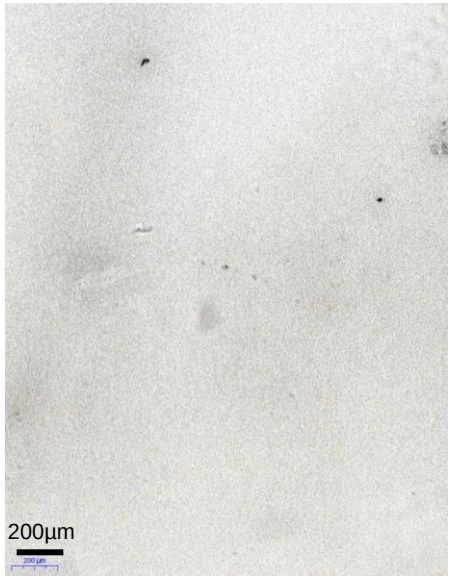


Compound	Kd
[3H]Abeta reference	10 nM
[3H]ACI-12589	317 nM

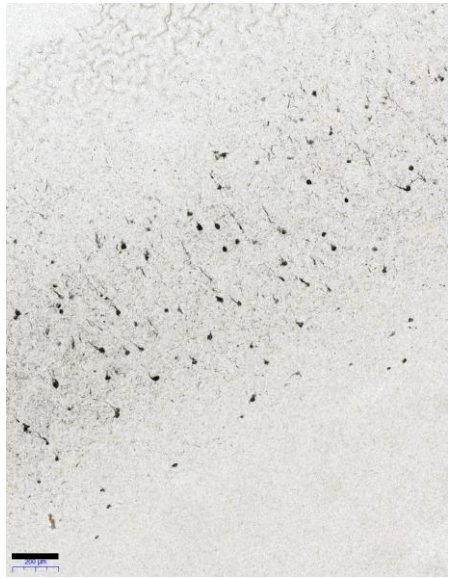
High-resolution ARG[2] on Tau rich AD sections (Entorhinal Cortex)



IHC[3] for Tau (MC1)



[3H]ACI-12589



[3H]PI-2620
Tau reference

Ref.: Capotosti et., AAIC 2020

- ACI-12589 displays selectivity versus co-pathologies such as Abeta and Tau

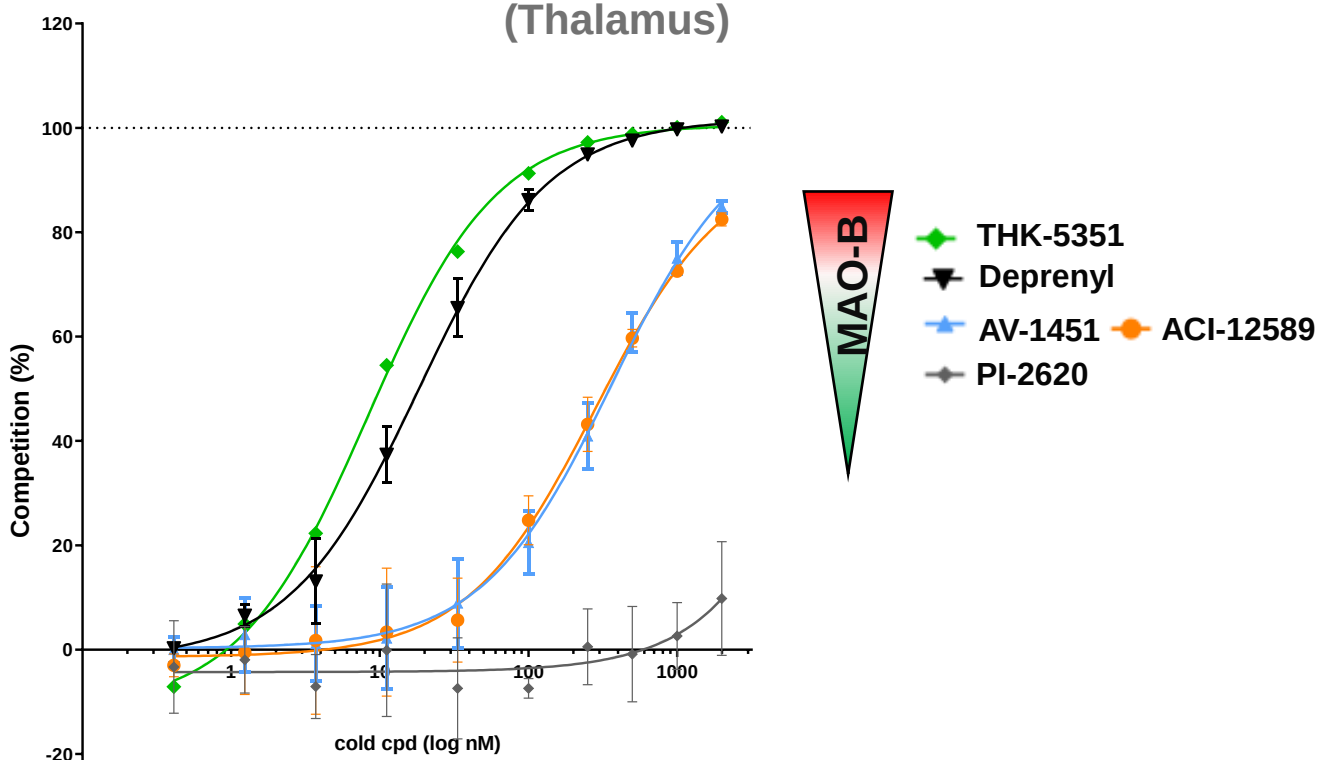
(1) Alzheimer's disease; (2) Autoradiography; (3) Immunohistochemistry

AC Immune

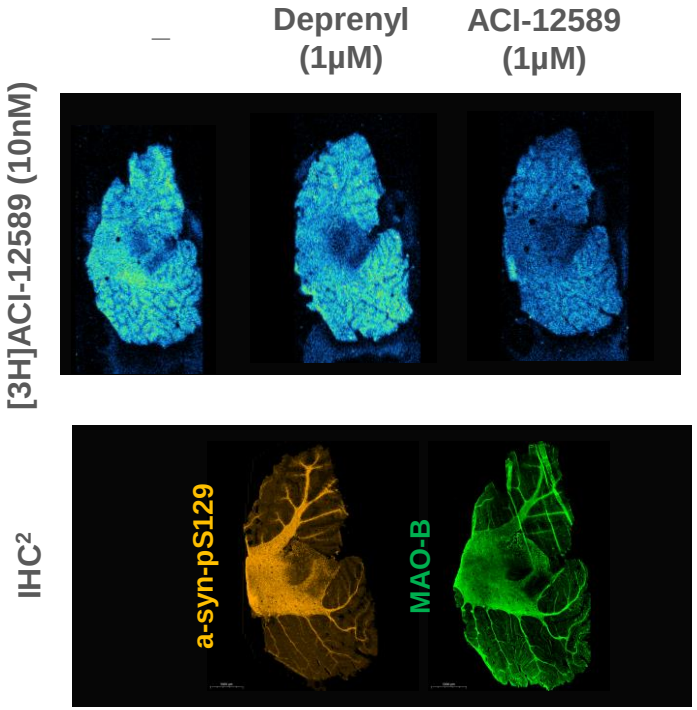
ACI-12589: minimal off-target binding

[3H]ACI-12589 assessed for off-target binding to MAO-B[1]

Radiobinding on brain homogenates from healthy donor (Thalamus)



Autoradiography on MSA (Cerebellum)



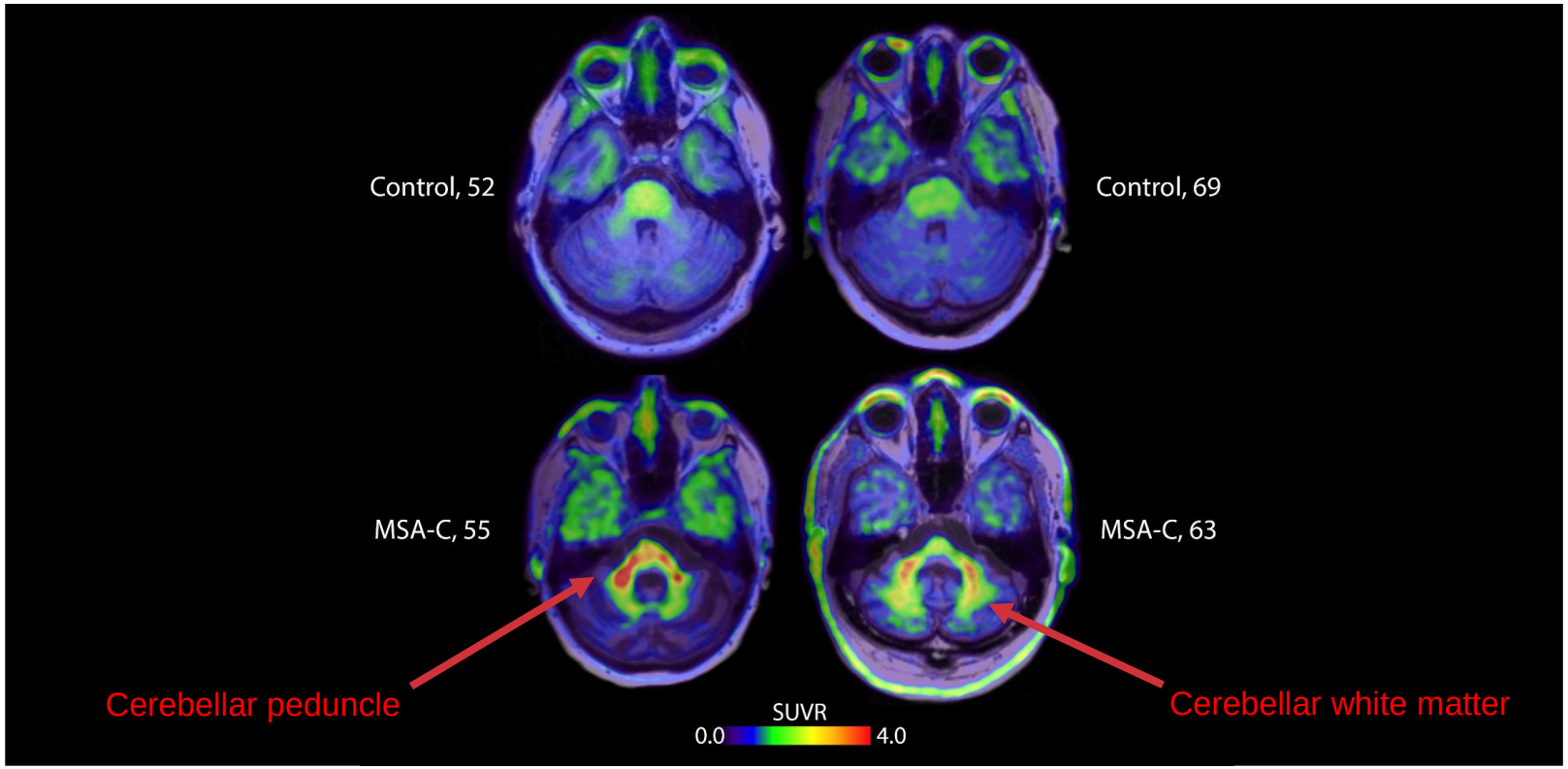
Ref.: AC Immune unpublished data

- When assessed against **133** receptors and enzymes, only a weak off-target binding was observed for MAO-B confirmed by limited displacement using the MAO-B inhibitor Deprenyl by autoradiography experiments

(1) Monoamine oxidase-B; (2) Immunohistochemistry

[18F]ACI-12589 as potential first-in-class PET[1] tracer for MSA[2]

Representative PET scan images of MSA and controls



In collaboration with Prof. O. Hanssosn, Skane University Hospital

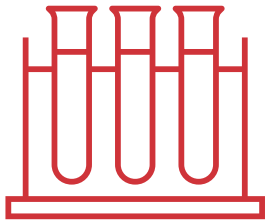
- PET scan images suggest tracer retention in areas affected by disease process in MSA such as the cerebellar white matter and the cerebellar peduncles
- Available clinical data will be presented by **Ruben Smith on March 18, 06:45 PM – 07:00 PM, Room Onsite: 114**

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

[18F]ACI-12589 as potential first-in-class PET[1] tracer for MSA[2]

Data support the further clinical development in MSA, and continuing evaluation in other synucleinopathies

Preclinical data



- Significantly improved target binding with clean off-target profile
- Recognition of a-syn[3] inclusions across different synucleinopathies
- Selectivity versus potential co-pathologies
- Pharmacokinetic profile suitable for use as a brain PET imaging agent

Clinical data

- Short scan time: good brain uptake and fast signal equilibration
- Substantial tracer retention seen in MSA in expected brain regions
- No clinically relevant *in vivo* block of cerebellar signal after MAO-B[4] blocking

(1) Positron emission tomography; (2) Multiple system atrophy; (3) Alpha-synuclein; (4) Monoamine oxidase-B

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