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

Francesca Capotosti, PhD | AAIC 2022 | 31 July

AC Immune

Disclaimer

This presentation contains statements that constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Forward-looking statements are statements other than historical fact and may include statements that address future operating, financial or business performance or AC Immune's strategies or expectations. In some cases, you can identify these statements by forward-looking words such as "may," "might," "will," "should," "expects," "plans," "anticipates," "believes," "estimates," "predicts," "projects," "potential," "outlook" or "continue," and other comparable terminology. Forward-looking statements are based on management's current expectations and beliefs and involve significant risks and uncertainties that could cause actual results, developments and business decisions to differ materially from those contemplated by these statements. These risks and uncertainties include those described under the captions "Item 3. Key Information – Risk Factors" and "Item 5. Operating and Financial Review and Prospects" in AC Immune's Annual Report on Form 20-F and other filings with the Securities and Exchange Commission. These include: the impact of Covid-19 on our business, suppliers, patients and employees and any other impact of Covid-19. Forward-looking statements speak only as of the date they are made, and AC Immune does not undertake any obligation to update them in light of new information, future developments or otherwise, except as may be required under applicable law. All forward-looking statements are qualified in their entirety by this cautionary statement.

This presentation is strictly confidential, is being distributed to a limited range of invited persons solely for their own information, may not be distributed to the press or any other person, and may not be reproduced or published, in whole or in part, in any form.

Disclosures

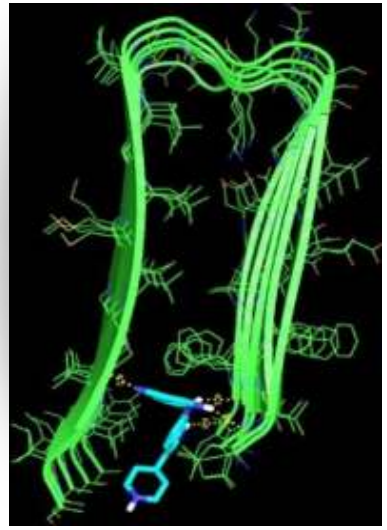
Francesca Capotosti is an employee of AC Immune entitled to stock options

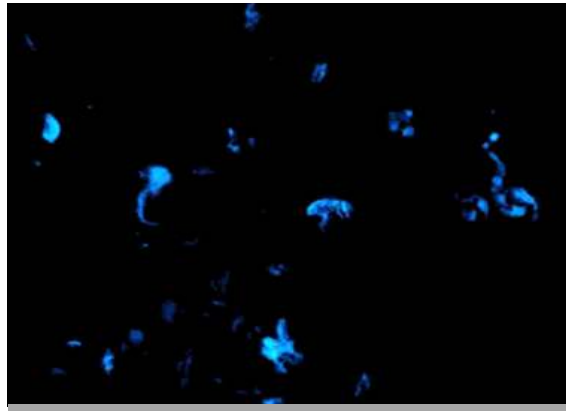
Funding

Grants from the Michael J Fox Foundation

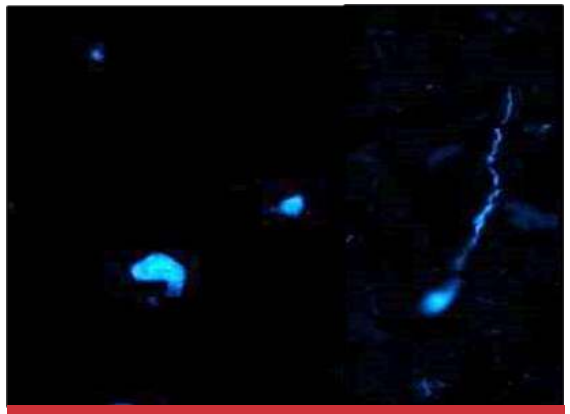
Precision medicine approach enabled by the Morphomer® platform

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

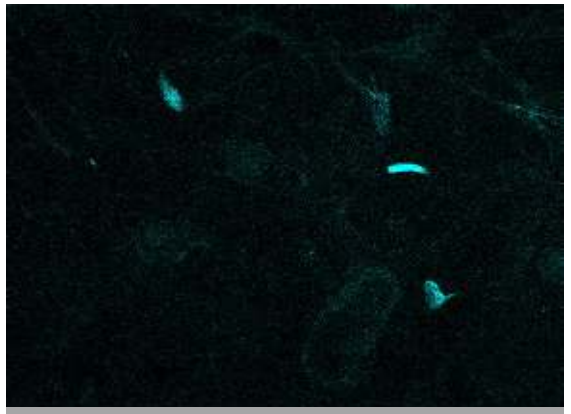




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

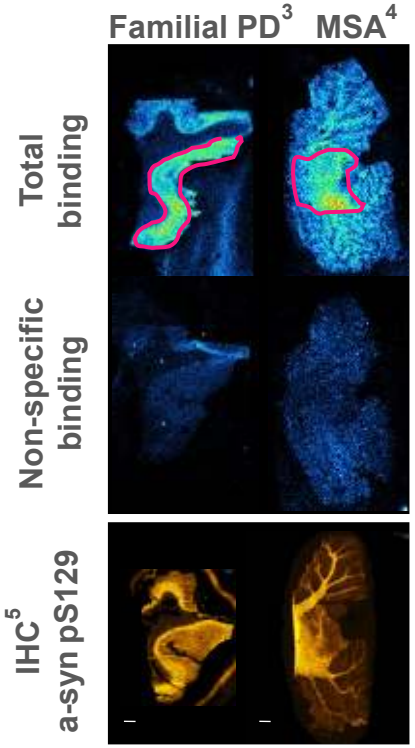
Leverage the Morphomer® small molecule platform:

- 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

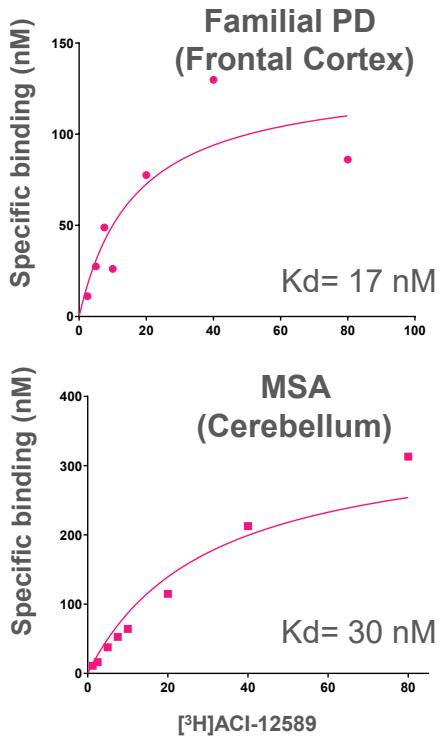
(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) Alpha synuclein; (5) TAR DNA binding protein-43

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

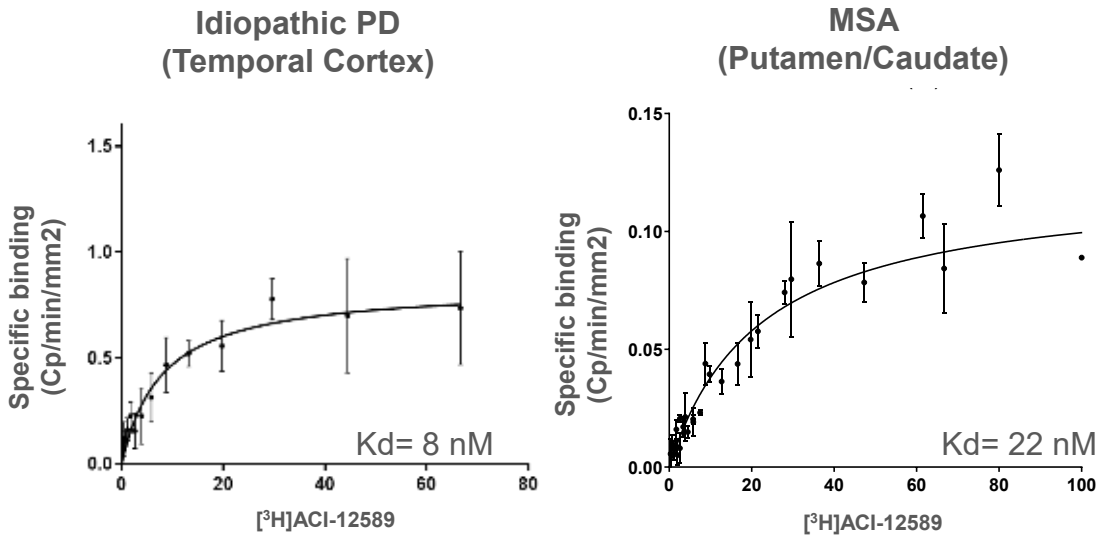
[3H]ACI-12589 specific binding on brain tissue from different a-synucleinopathy cases



Tissue slices



Tissue homogenates



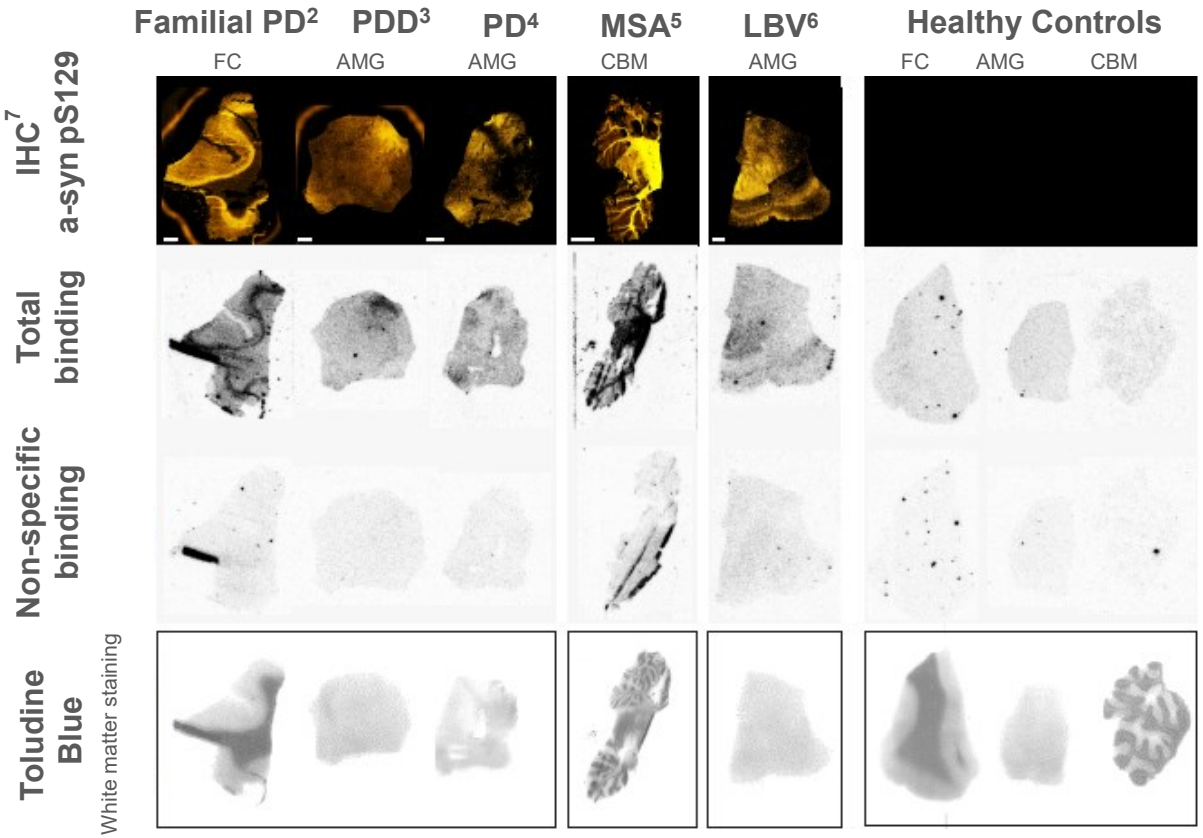
Ref.: Capotosti et al., ADPD 2022

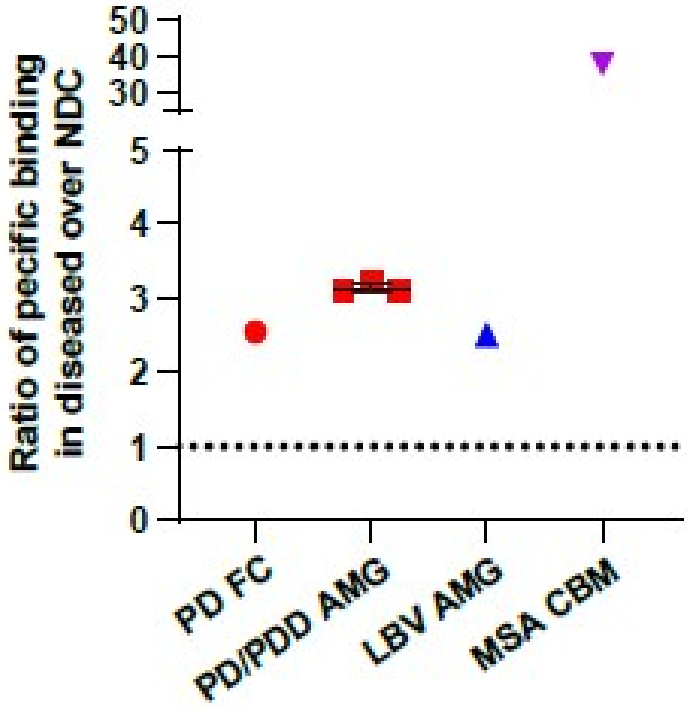
- ACI-12589 displays a clear autoradiography signal which correlates with the presence of pathological a-syn
- Binding affinities are measured in the range of 8-30 nM with Bmax/Kd ratios of ~ 5-10

(1) alpha-synuclein ; (2) Positron emission tomography; (3) Parkinson's disease with G51D SNCA mutation; (4) Multiple system atrophy; (5) Immunohistochemistry

ACI-12589: binding to a-syn[1] across different a-synucleinopathies

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





In collaboration with Prof. A. Varrone, Karolinska Institute

Karolinska Institutet

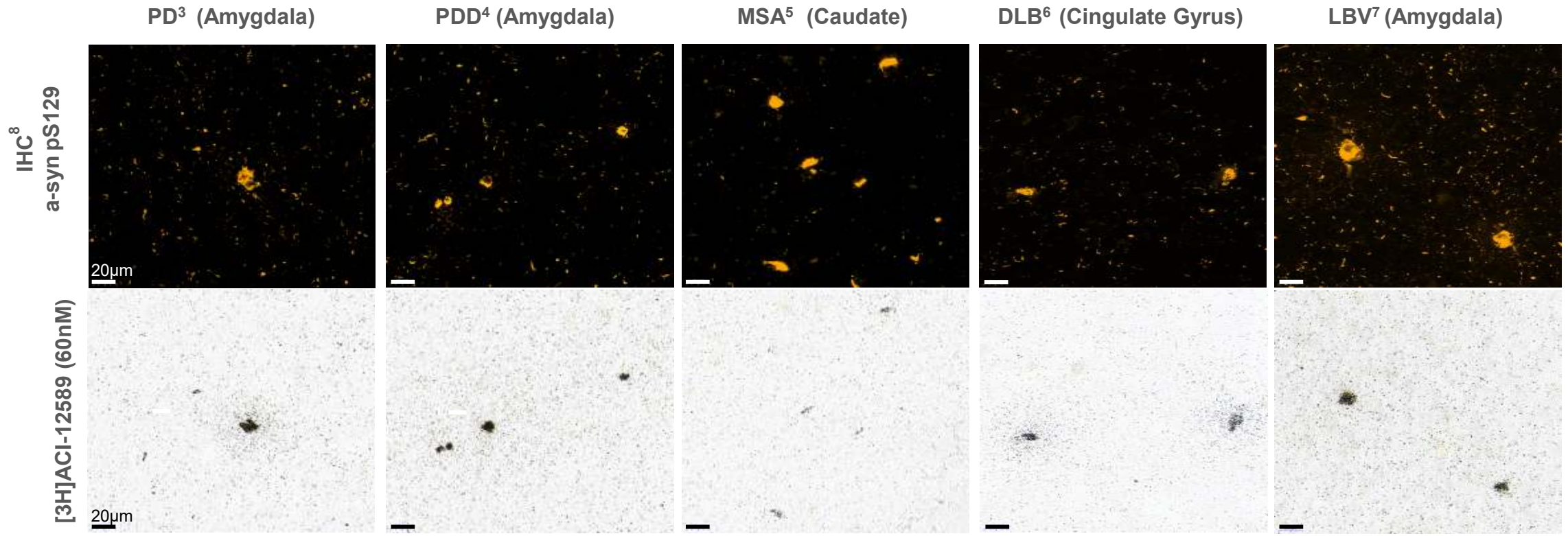
- Classical autoradiography experiments confirm specific binding across a wide range of a-synucleinopathies

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

AC Immune

ACI-12589: binding to a-syn[1] across different a-synucleinopathies

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



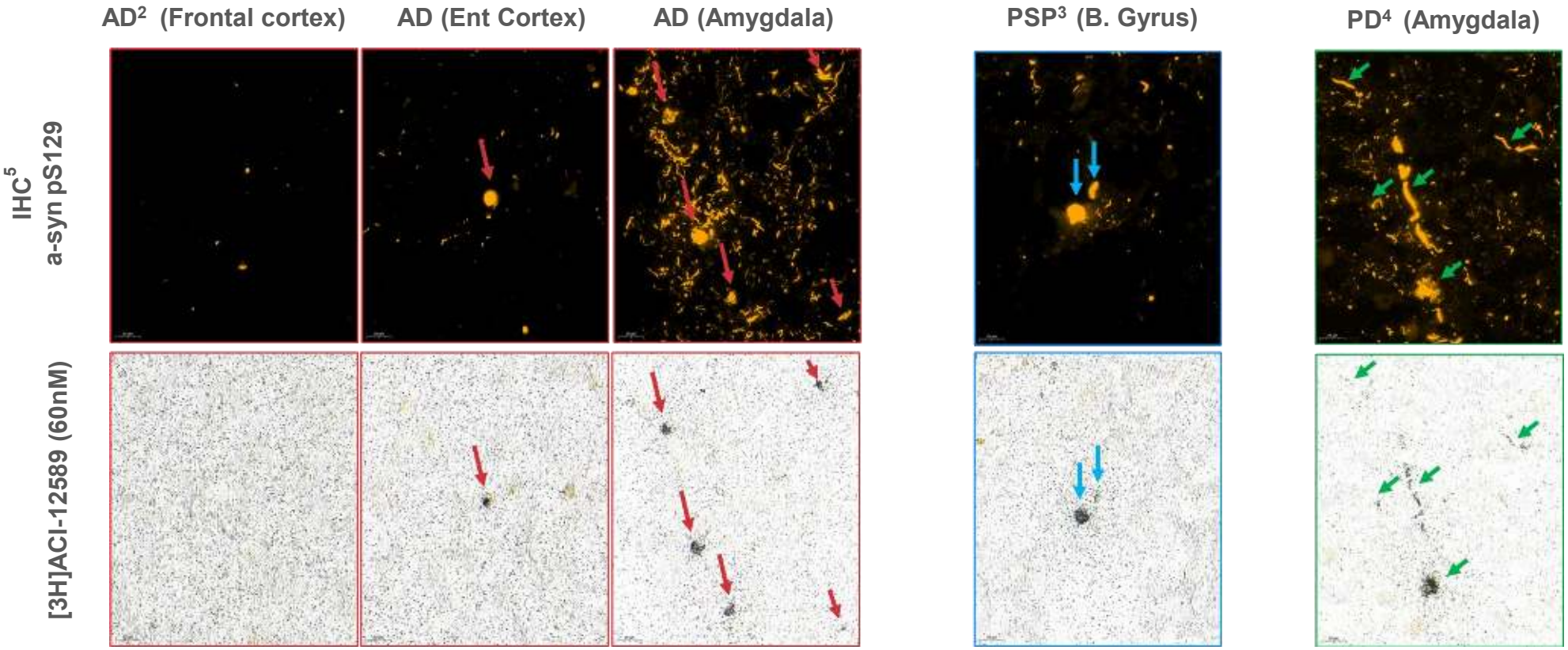
Ref.: Capotosti et., AAIC 2020

- 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: binding to a-syn[1] in different neurodegenerative diseases

[3H]ACI-12589 target engagement on a-syn co-pathology in AD and PSP



Ref: ACI unpublished data

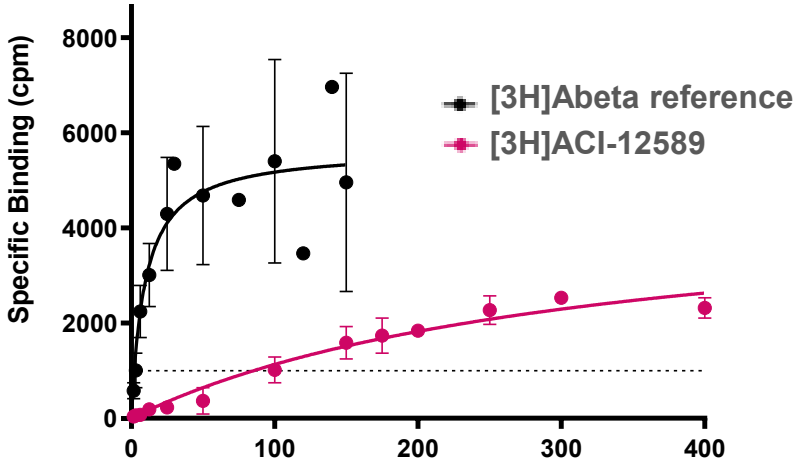
- In the presence of a-syn co-pathology, [3H]ACI-12589 binds to a-syn inclusions in AD and PSP tissues similarly to what observed in PD tissue

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

ACI-12589: selective *versus* Abeta and Tau

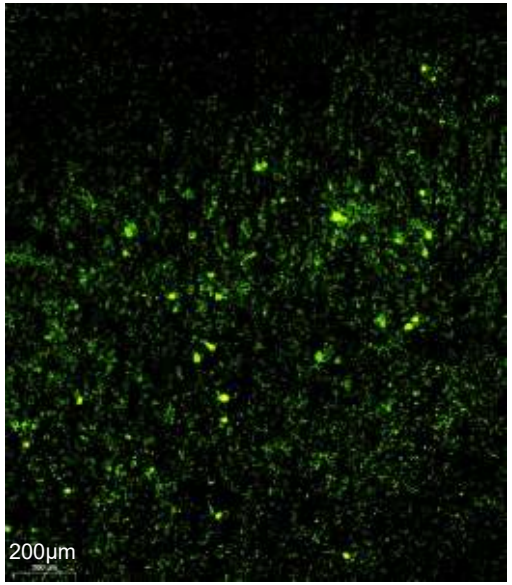
[3H]ACI-12589 assessed using Alzheimer's disease tissue

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

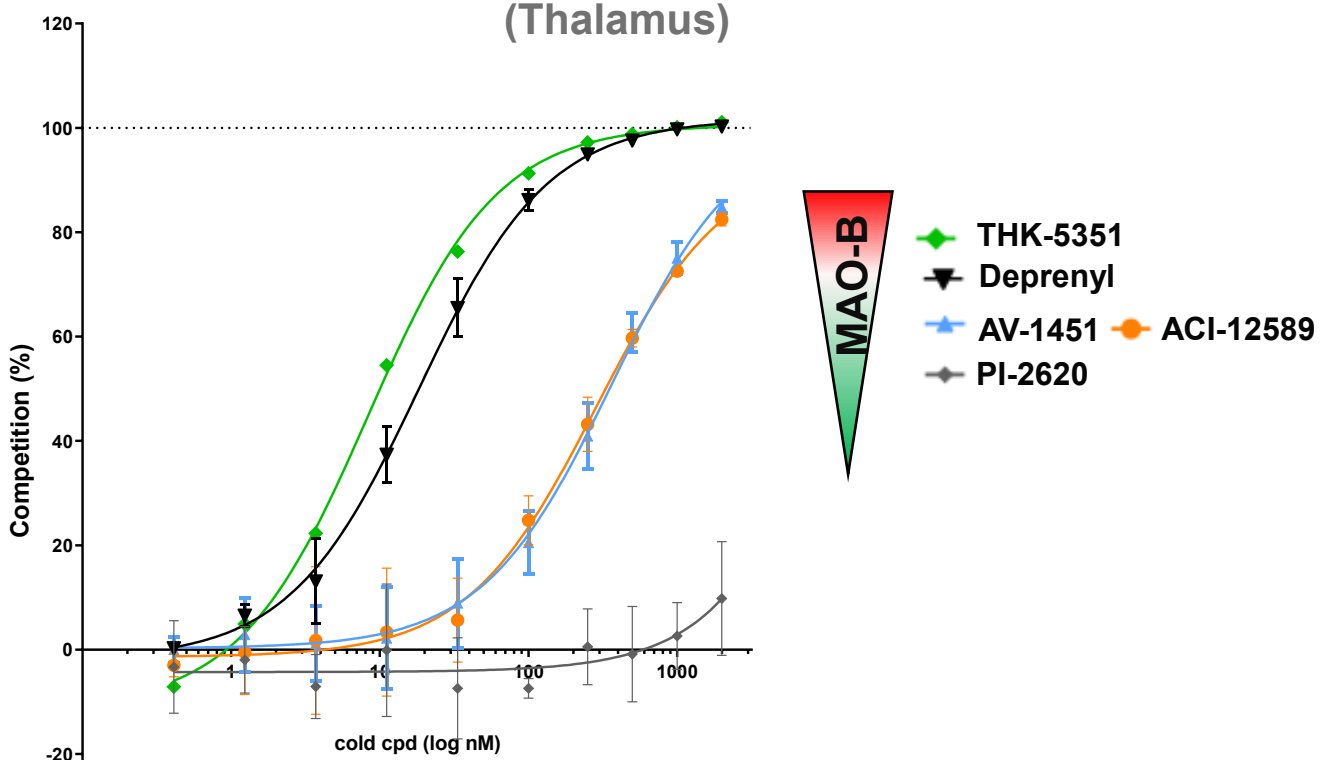
- ACI-12589 displays selectivity versus co-pathologies such as Abeta and Tau

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

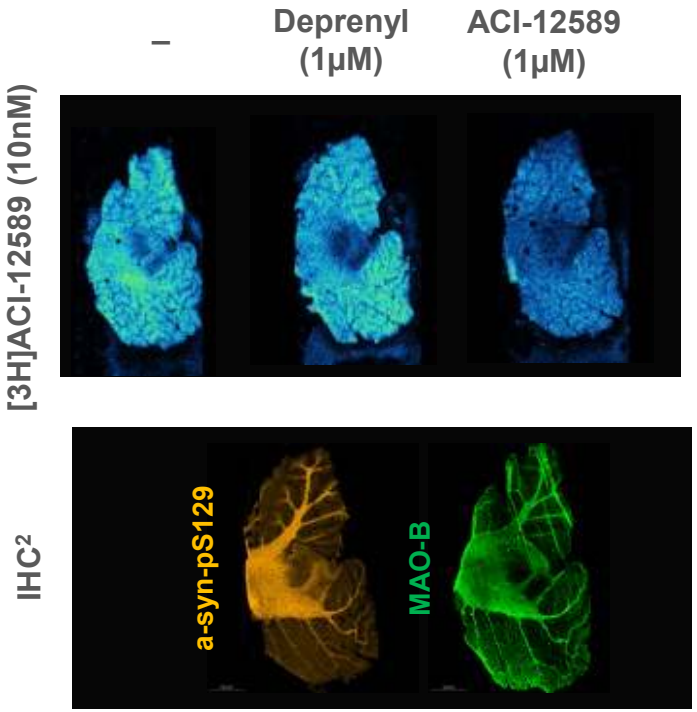
ACI-12589: minimal or no off-target binding

[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.: Capotosti et al., ADPD 2022

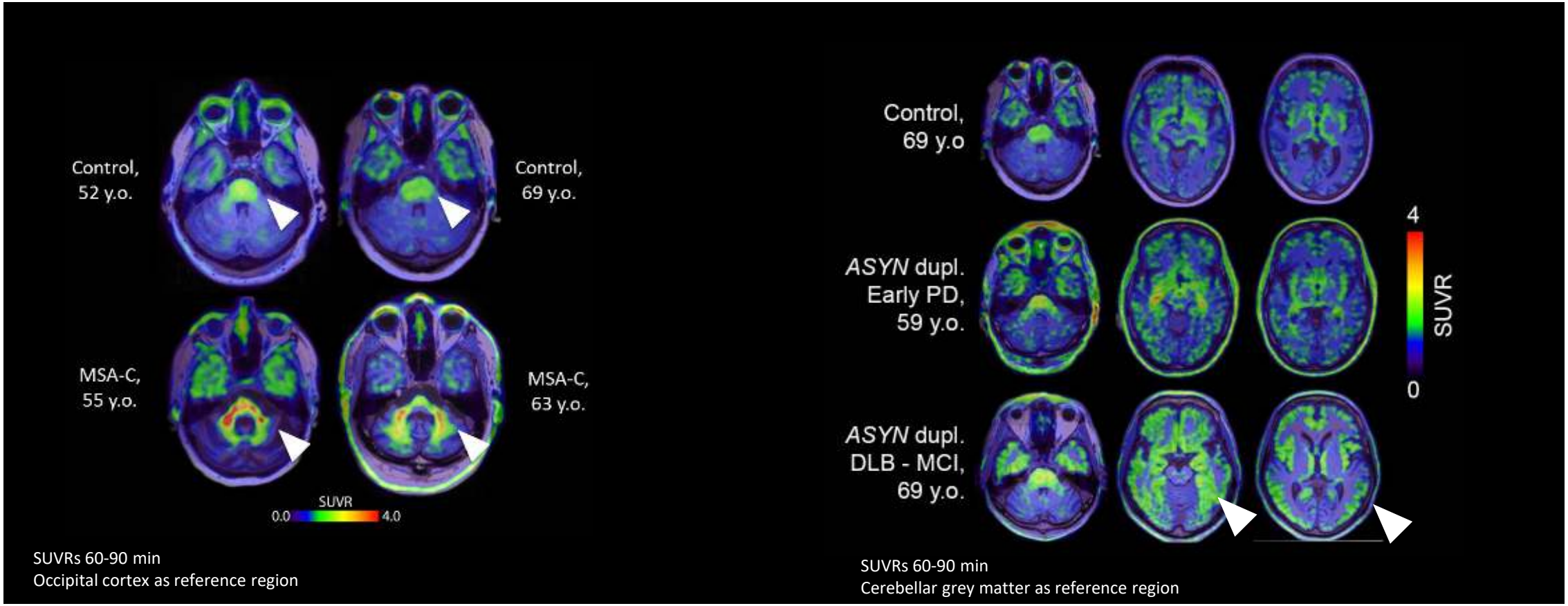
- When assessed against **133** receptors and enzymes, only a weak off-target binding was observed for MAO-B confirmed by limited displacement using the MAO-B inhibitor Deprenyl by autoradiography experiments

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

AC Immune

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

Representative PET scan images of controls, MSA and genetic PD cases



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

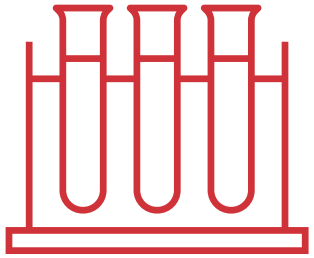
- Strong binding was observed in disease-affected brain areas in MSA cases
- Promising results were also obtained in genetic PD cases carrying an ASYN gene duplication

(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
- Potential to bind a-syn inclusions in different NDDs[4], such as AD[5] and PSP[6]
- Selectivity versus potential co-pathologies (Abeta, Tau and TDP-43)
- Pharmacokinetic profile suitable for use as a brain PET imaging agent

(1) Positron emission tomography; (2) Multiple system atrophy; (3) Alpha-synuclein; (4) Neurodegenerative diseases; (5) Alzheimer's disease; (6) Progressive Supranuclear Palsy

[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

Clinical data

- Rapid brain uptake and fast signal equilibration allowing a short scan time
- Substantial tracer retention seen in MSA in disease-affected brain regions
- Signal retention also observed in genetic PD cases
- Differentiation from other NDDs[3] and possibility to assess in vivo presence of a-syn co-pathology
- Overall, results demonstrate that [18F]ACI-12589 binds to a-syn and the retention can distinguish MSA cases from other neurodegenerative diseases

(1) Positron emission tomography; (2) Multiple system atrophy; (3) Neurodegenerative diseases

Acknowledgements

AC Immune

Efthymia Vokali
Jerome Molette
Myriam Ravache
Christophe Delgado
Jaqueline Kocher
Laure Pittet
Elpida Tsika
Kasia Piorkowska
Heiko Kroth
Tanja Jürgens
Ruth Luthi-Carter
Valerie Hliva
Olivier Sol
Andrea Pfeifer
Johannes Streffer
Marie Kosco-Vilbois

Lund University
Region Skane

Oskar Hansson
Ruben Smith
Martin Schain
Tomas Ohlsson
Klas Brattby

The Michael J. Fox Foundation for Parkinson's Research

Invicro

Karolinska Institutet

Netherlands Brain Bank
UCL