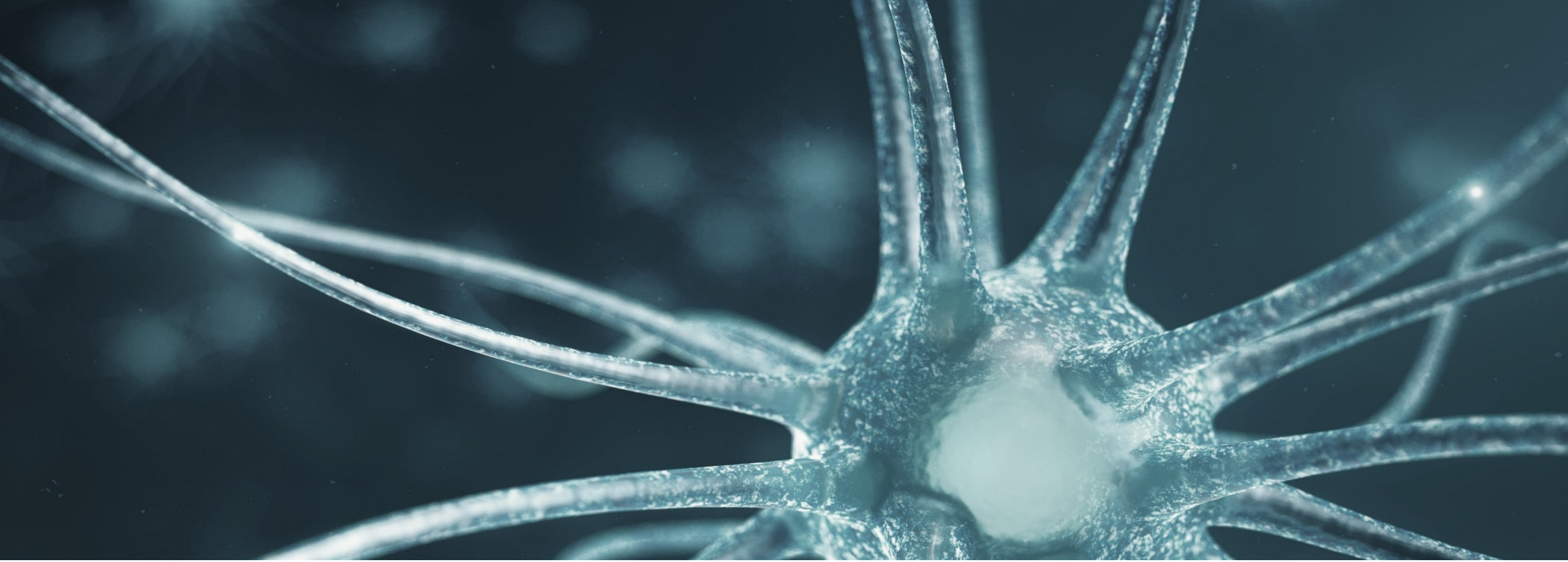

Discovery and initial clinical evaluation of [18F]ACI-12589, a novel and promising PET-tracer for a-synuclein …..and beyond

Francesca Capotosti, PhD | AAIC 2023 | July 18th

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Disclosures

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

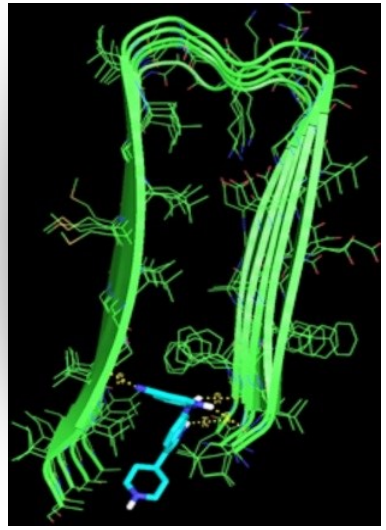
Funding

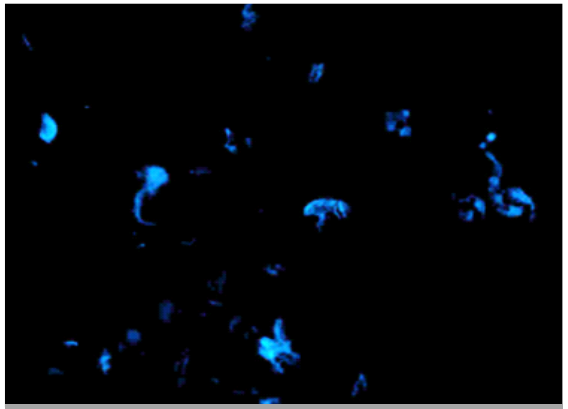
Grants from the Michael J Fox Foundation

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

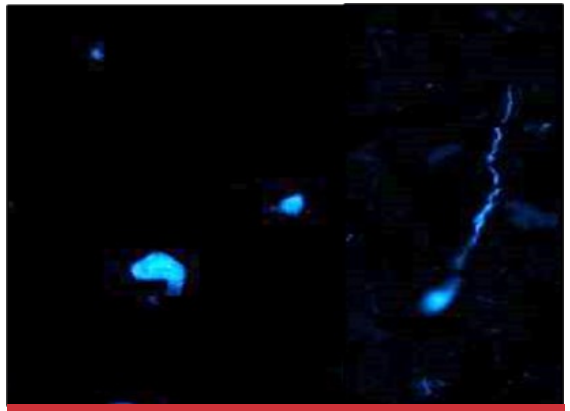
Precision medicine approach enabled by the Morphomer® platform

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

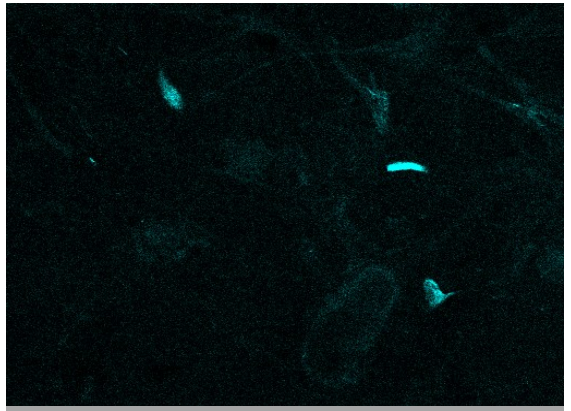




Tau NFTs[3]
PI-2620



a-syn[4] Lewy bodies
ACI-12589



TDP-43[5] inclusions

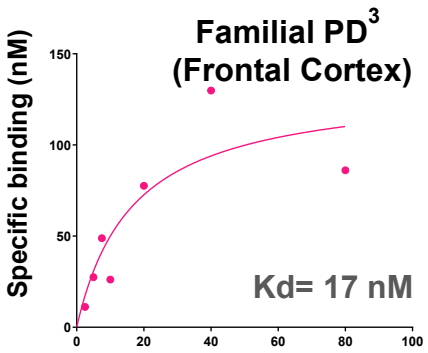
Leverage the Morphomer® small molecule platform:

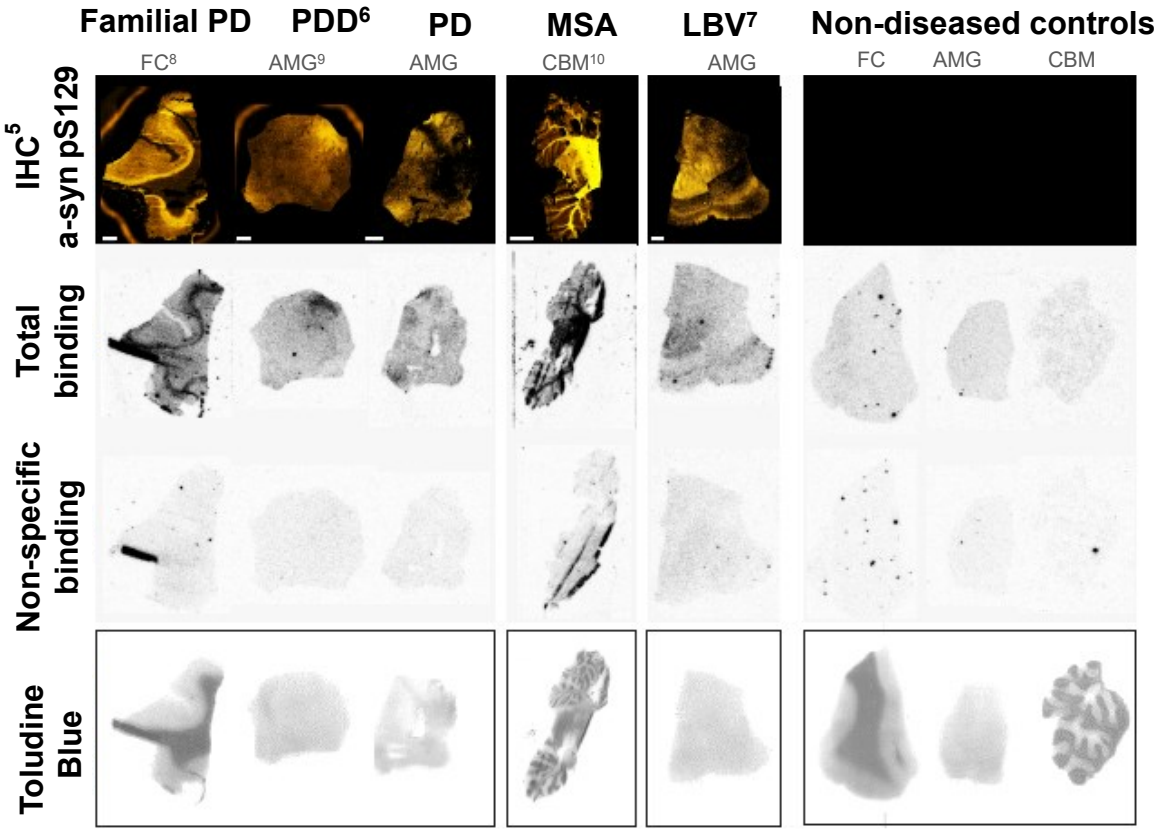
- Non-peptidic, small molecules with CNS-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, TDP-43)
- Pharmacokinetics suitable for brain PET imaging

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

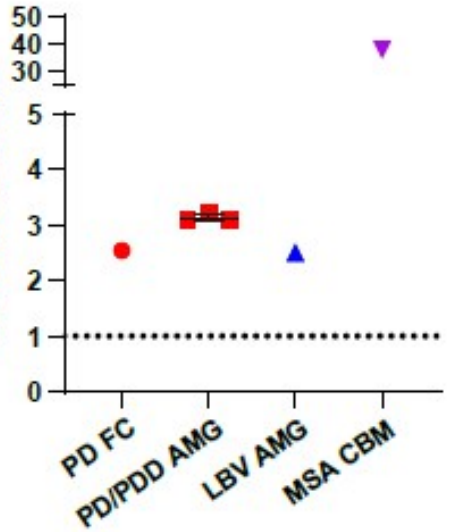
ACI-12589: a promising a-syn[1] PET[2] tracer

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





Ratio of specific signal in synucleinopathies over controls



In collaboration with Prof. A. Varrone
Ref.: Smith et. al, submitted

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

[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

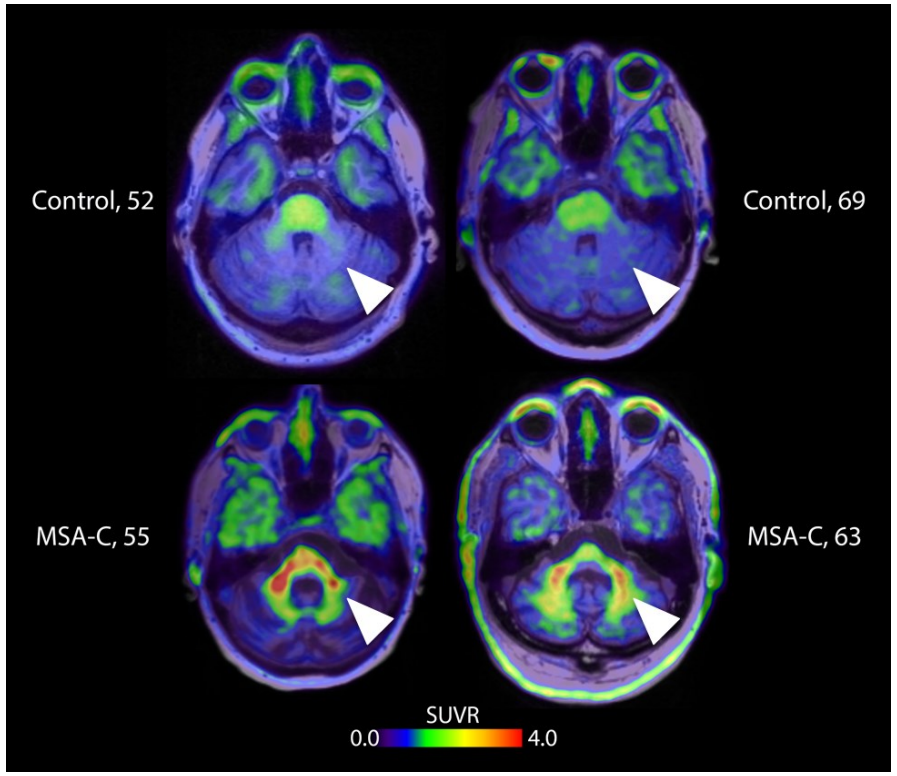
In collaboration with Prof. O. Hansson
Ref.: Smith et. al, submitted

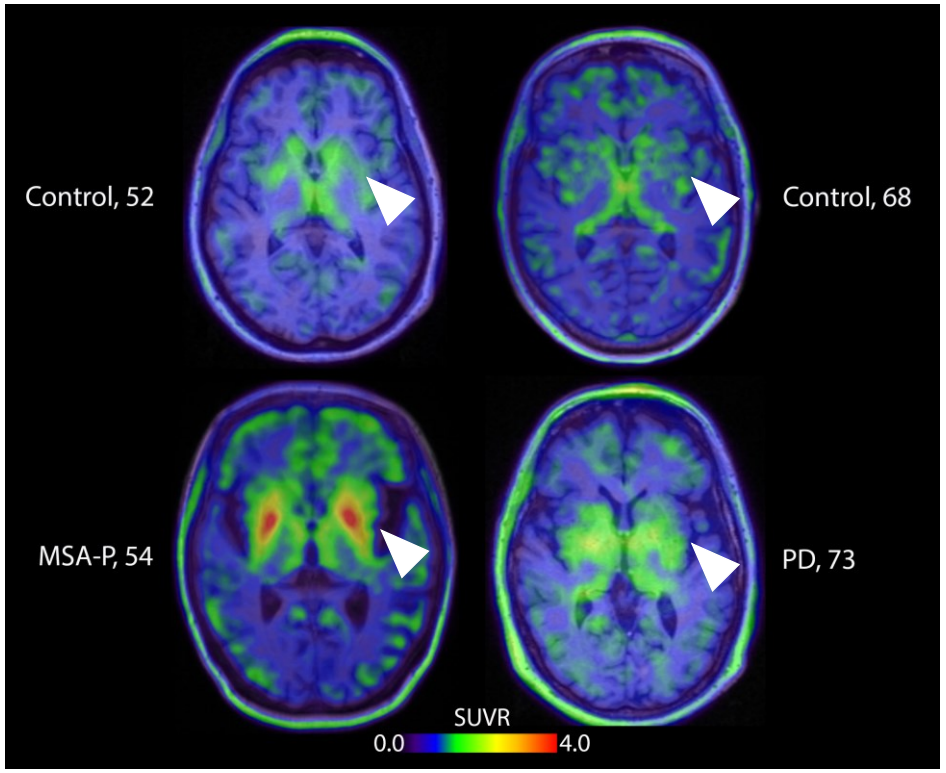
- [18F]ACI-12589 was evaluated in a total of 54 participants; 23 with a-syn-related disorders of which 13 MSA cases
- The initial 25 subjects underwent dynamic 0-90 min scans and the vast majority had arterial blood sampling while following scans were performed with shorted scan time

(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

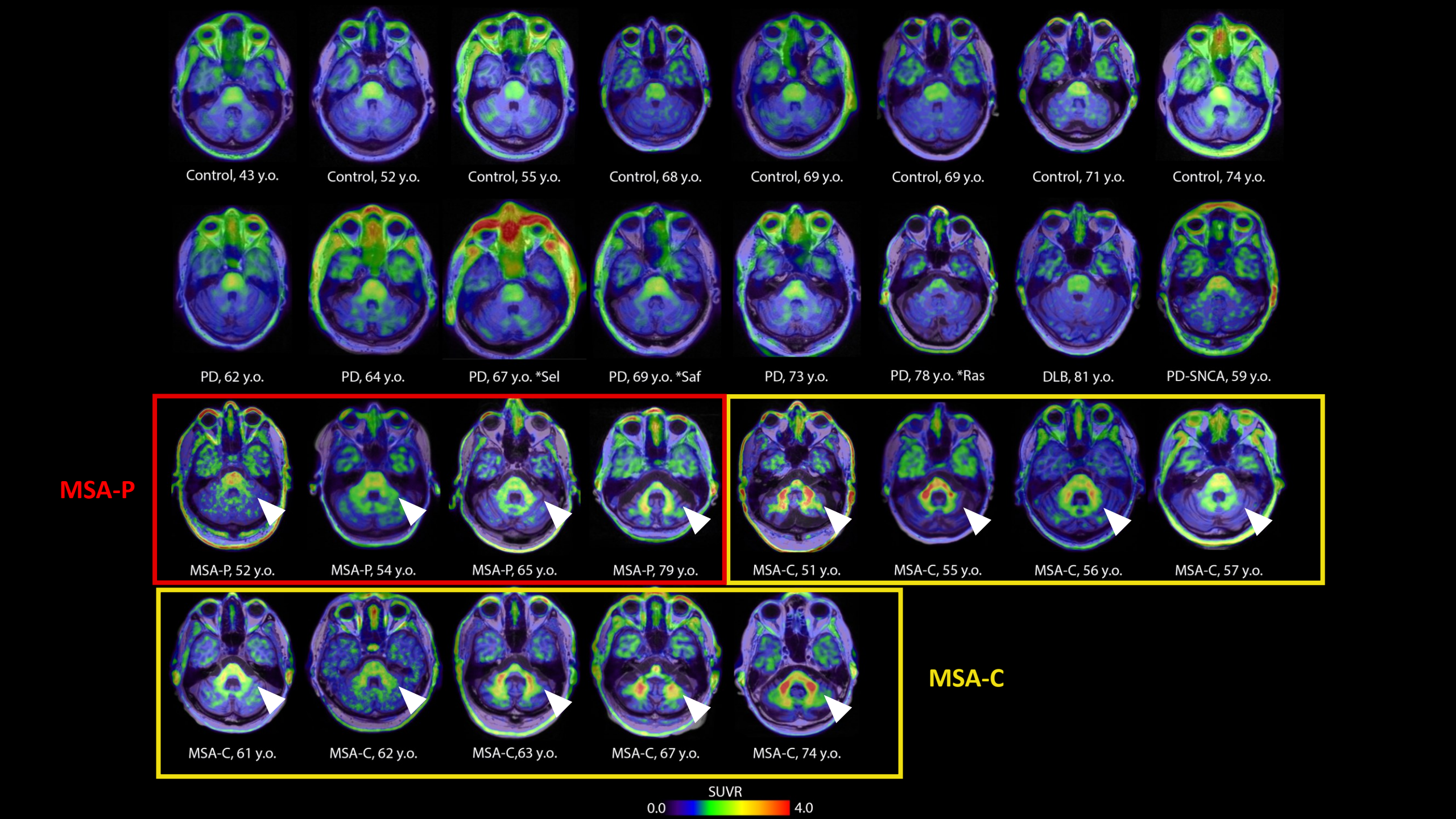
SUVR 60-90 min using occipital cortex as reference region

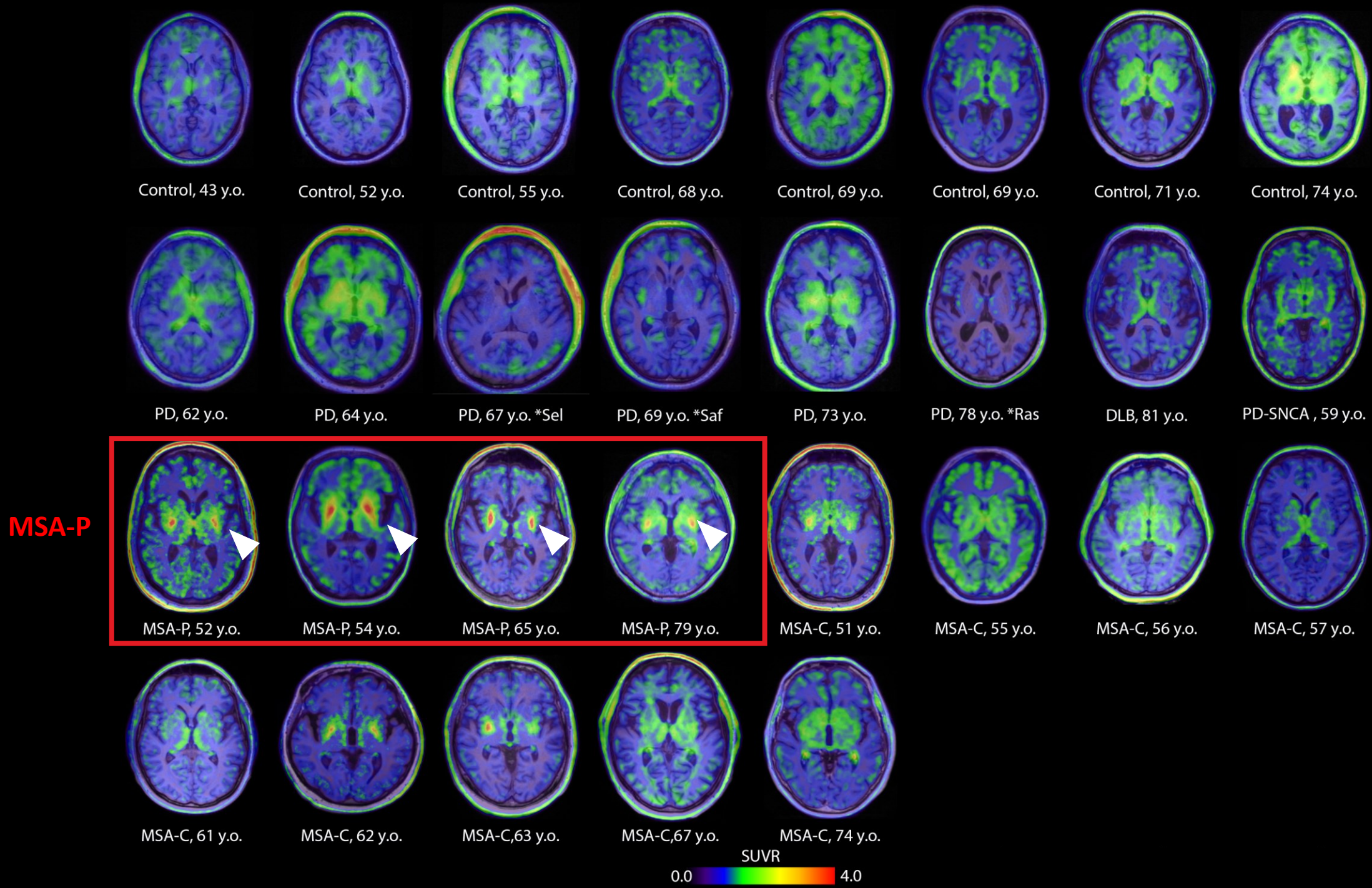




Ref.: Smith et. al, submitted

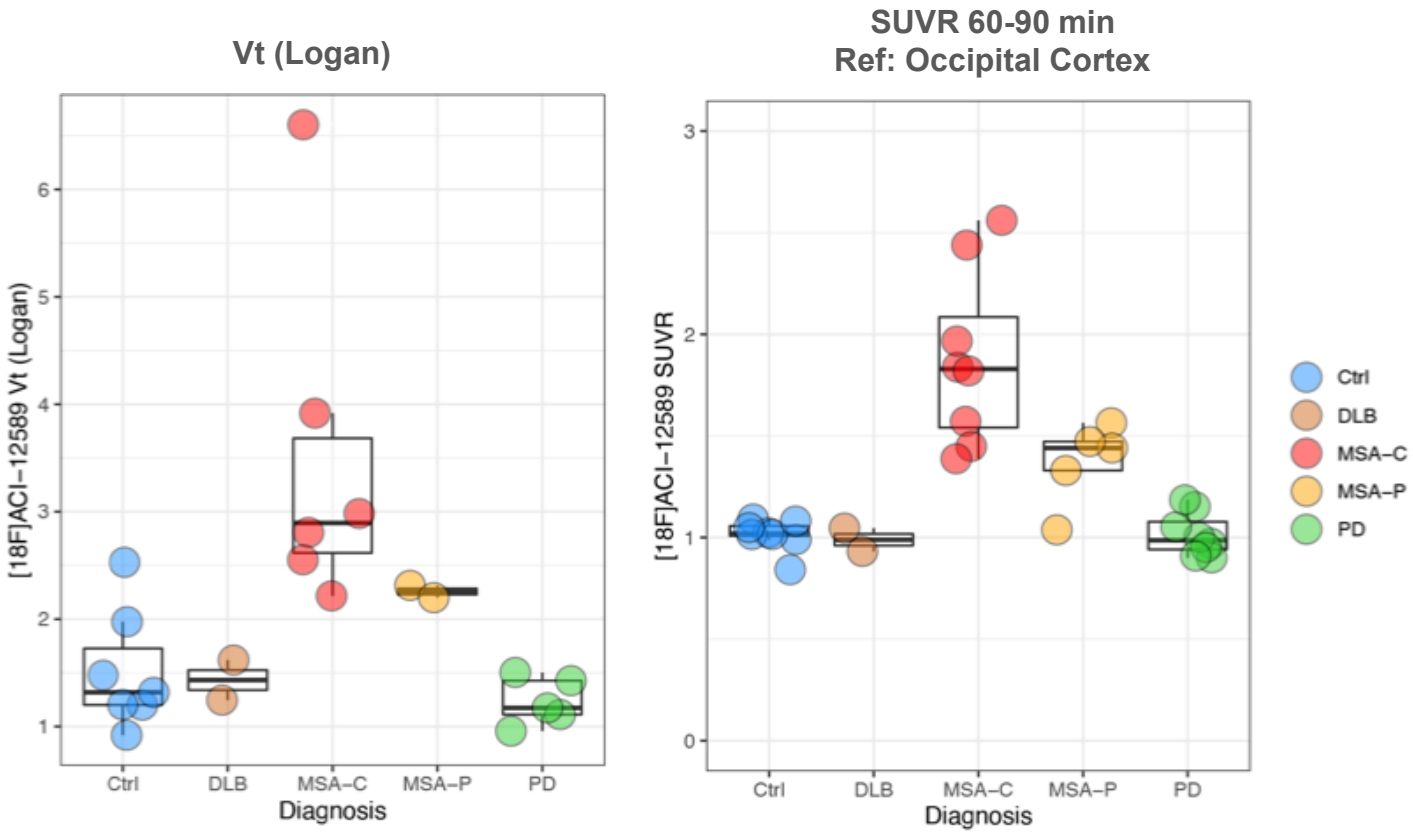
- Clear tracer retention in cerebellar white matter and cerebellar peduncles in MSA-C cases
- Increased basal ganglia uptake in MSA-P cases in comparison to controls and PD cases
- Overall, good correspondence between PET signal and the expected pathological a-syn distribution based on clinical presentation

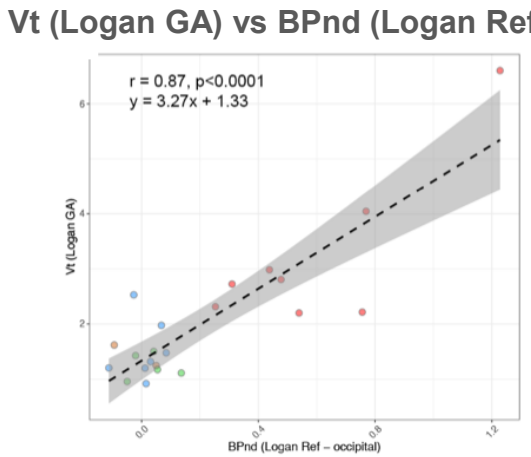

Control, 43 y.o.
Control, 52 y.o.
Control, 55 y.o.
Control, 68 y.o.
Control, 69 y.o.
Control, 69 y.o.
Control, 71 y.o.
Control, 74 y.o.
PD, 62 y.o.
PD, 64 y.o.
PD, 67 y.o. *Sel
PD, 69 y.o. *Saf
PD, 73 y.o.
PD, 78 y.o. *Ras
DLB, 81 y.o.
PD-SNCA, 59 y.o.
MSA-P
MSA-P, 52 y.o.
MSA-P, 54 y.o.
MSA-P, 65 y.o.
MSA-P, 79 y.o.
MSA-C, 51 y.o.
MSA-C, 55 y.o.
MSA-C, 56 y.o.
MSA-C, 57 y.o.
MSA-C, 61 y.o.
MSA-C, 62 y.o.
MSA-C,63 y.o.
MSA-C, 67 y.o.
MSA-C, 74 y.o.
MSA-C
SUVR
0.0
4.0

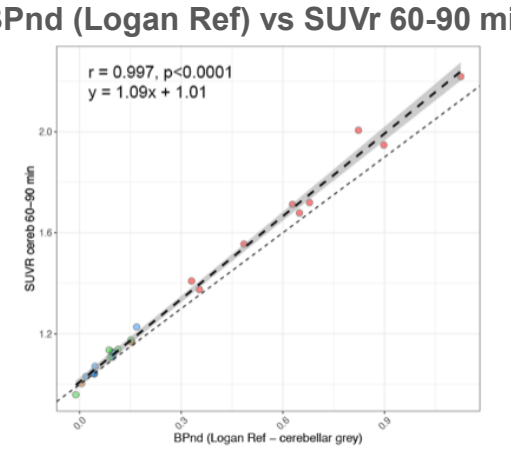

Control, 43 y.o.
Control, 52 y.o.
Control, 55 y.o.
Control, 68 y.o.
Control, 69 y.o.
Control, 69 y.o.
Control, 71 y.o.
Control, 74 y.o.
PD, 62 y.o.
PD, 64 y.o.
PD, 67 y.o. *Sel
PD, 69 y.o. *Saf
PD, 73 y.o.
PD, 78 y.o. *Ras
DLB, 81 y.o.
PD-SNCA , 59 y.o.
MSA-P
MSA-P, 52 y.o.
MSA-P, 54 y.o.
MSA-P, 65 y.o.
MSA-P, 79 y.o.
MSA-C, 51 y.o.
MSA-C, 55 y.o.
MSA-C, 56 y.o.
MSA-C, 57 y.o.
MSA-C, 61 y.o.
MSA-C, 62 y.o.
MSA-C,63 y.o.
MSA-C,67 y.o.
MSA-C, 74 y.o.
SUVR
0.0
4.0

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

Signal quantification in the cerebellar white matter







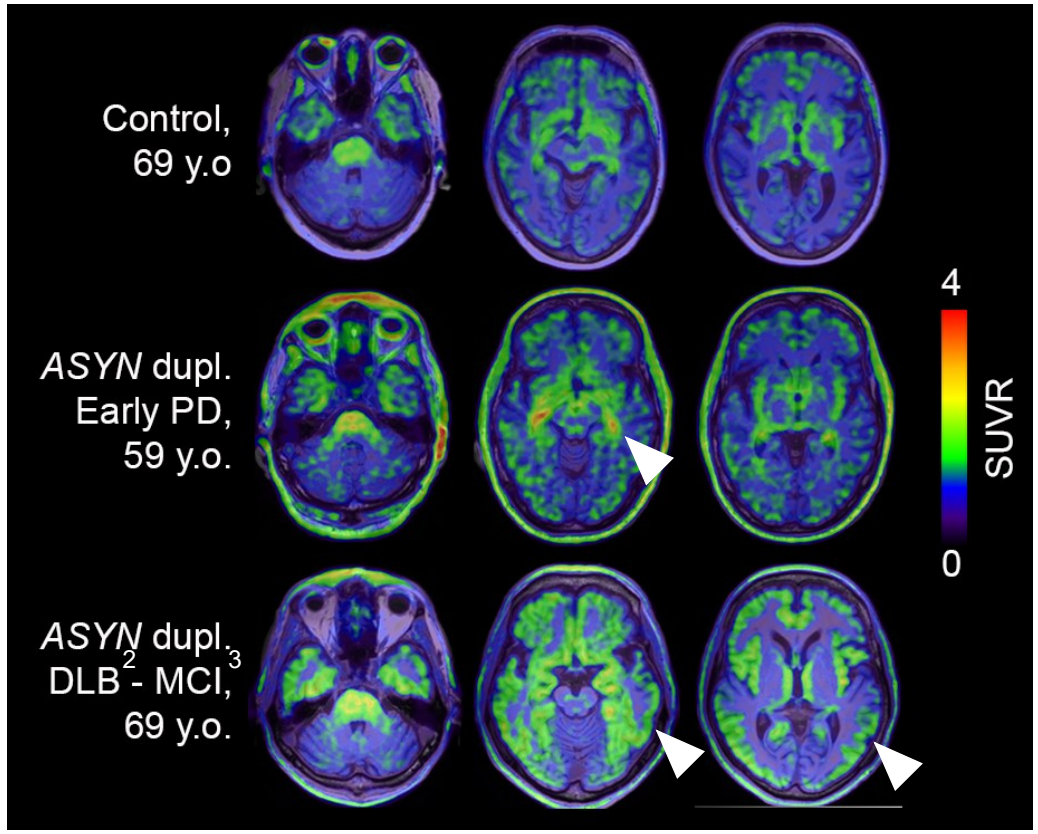
Diagnosis: Control DLB MSA-C MSA-P PD

Ref.: Smith et. al, submitted

- Cerebellar uptake clearly discriminate MSA cases from controls and other synucleinopathy cases with similar results obtained with different quantification methods

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

SUVr 60-90 minutes using cerebellar grey as reference region



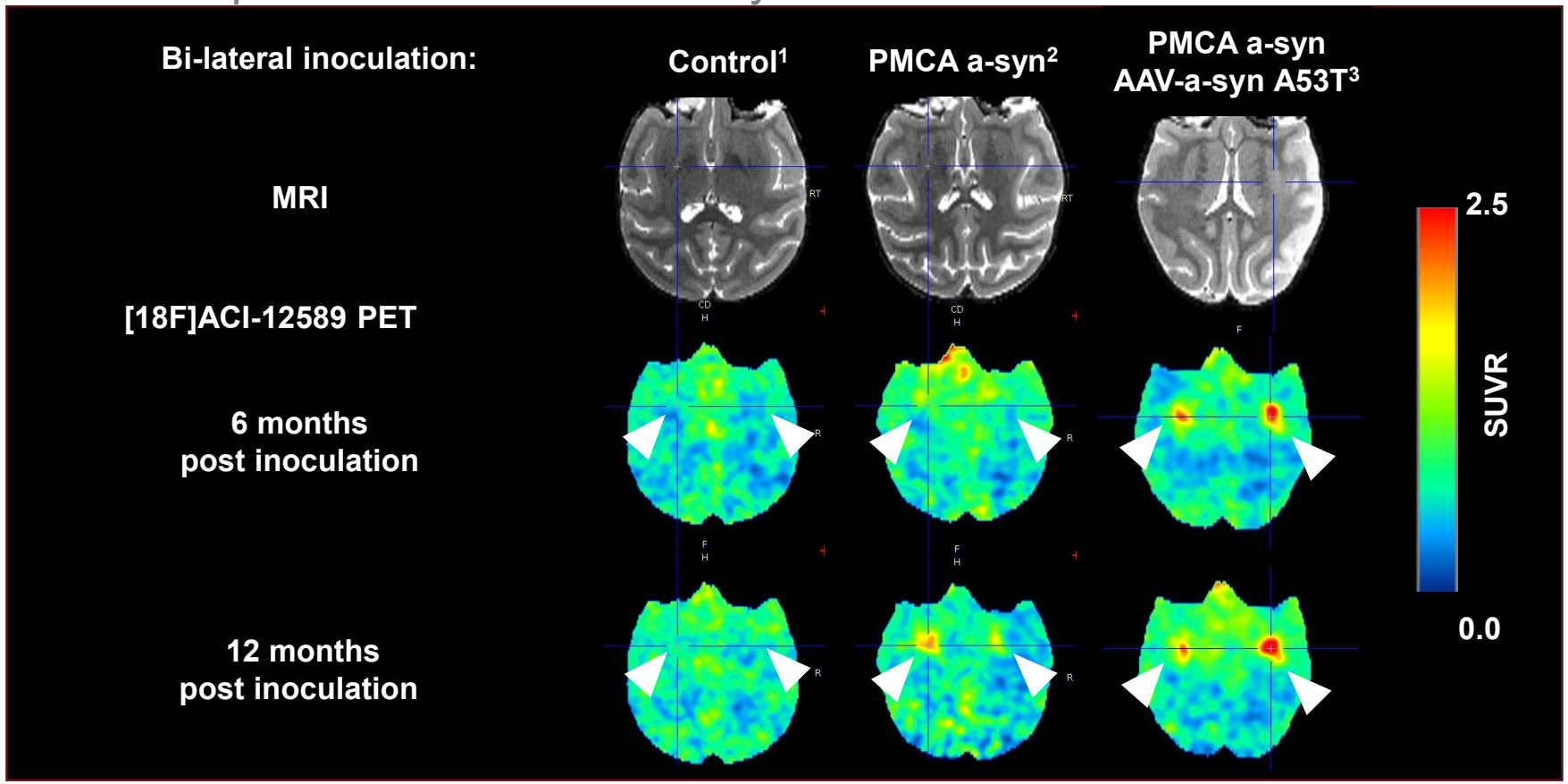
- Signal retention is observed in disease-relevant brain regions in genetic PD cases (SNCA duplication carriers)
- The retention is higher in the more advanced symptomatic case
- Signal distribution pattern is compatible with specificity of the signal for pathological a-syn

(1) Parkinson's disease; (2) Dementia with Lewy Body; (3) Mild cognitive impairment

Ref.: Smith et. al, submitted

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

Longitudinal brain uptake in two different a-syn inoculation models



- A longitudinal increase in [18F]ACI-12589 uptake is observed in both tested a-syn monkey models
- The higher retention observed in the PMCA-AAV model suggests that intensity of the PET signal depends on the pathological a-syn load

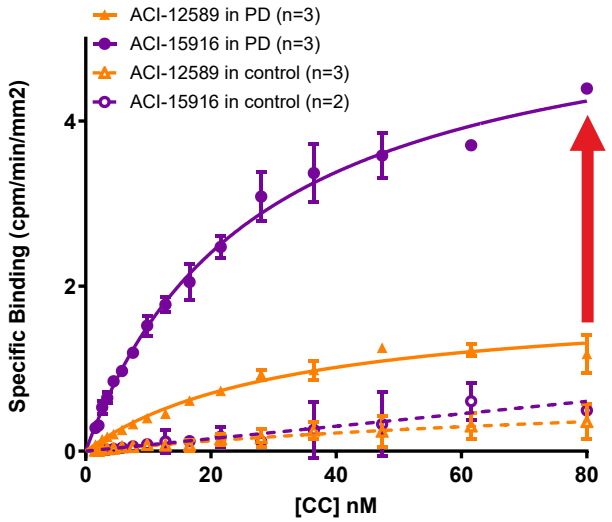
(1) PBS; (2) a-syn amplified by Protein misfolding Cyclic amplification from human PD seeds injected in the striatum at baseline and 6 months; (3) adeno-associated virus expressing human a-syn with the A53T mutation injected in the Subtantia Nigra at baseline; (4) Standardized uptake value ratio with whole cerebellum as reference

In collaboration with Olivier Barret, MIRCen CEA

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

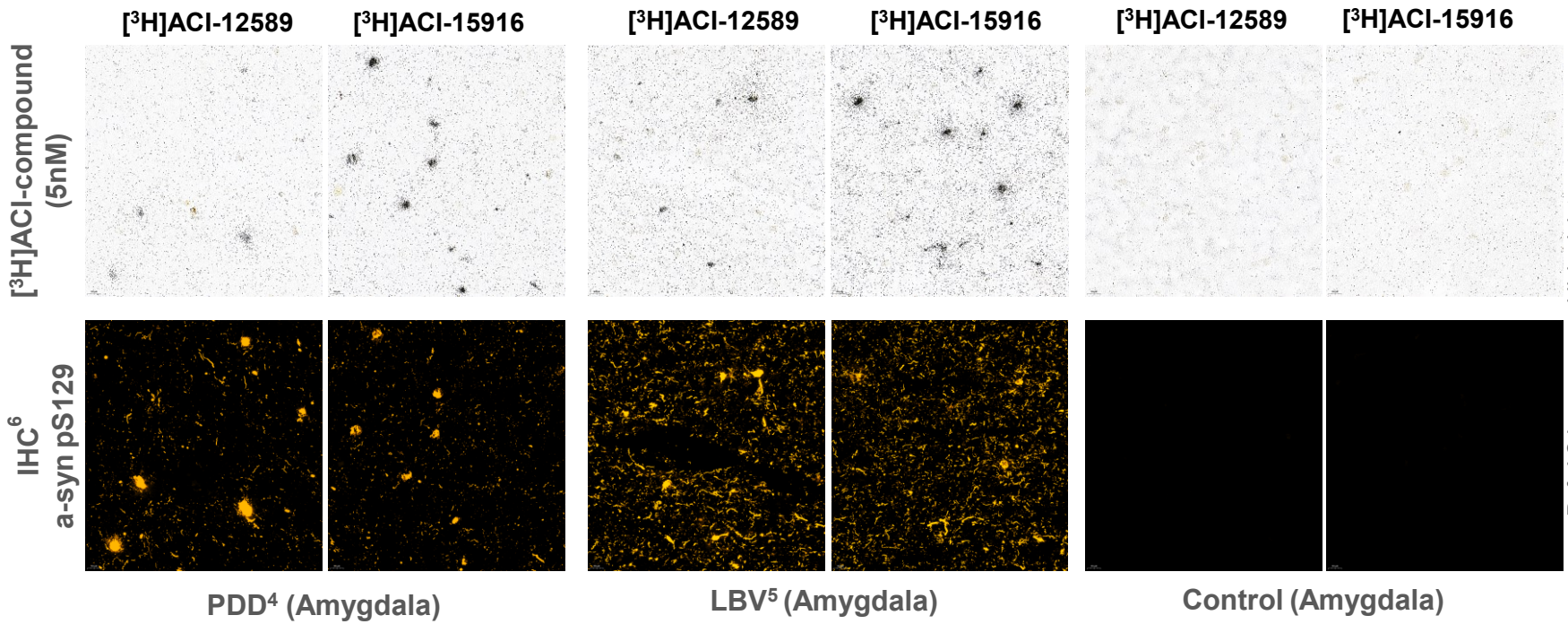
Improved target occupancy on brain tissue from different a-synucleinopathy cases

Saturation binding on total PD brain homogenates



4x improvement in Bmax/Kd

Target engagement by high resolution autoradiography



- Compared to ACI-12589, the newly identified ligand ACI-15916 shows significantly improved target occupancy on pathological a-syn aggregates in brain homogenates and sections from different a-synucleinopathy cases

(1) alpha-synuclein ; (2) Positron emission tomography; (3) Parkinson's disease; (4) Parkinson's disease with dementia; (5) Lewy body variant of Alzheimer's disease; (6) Immunohistochemistry

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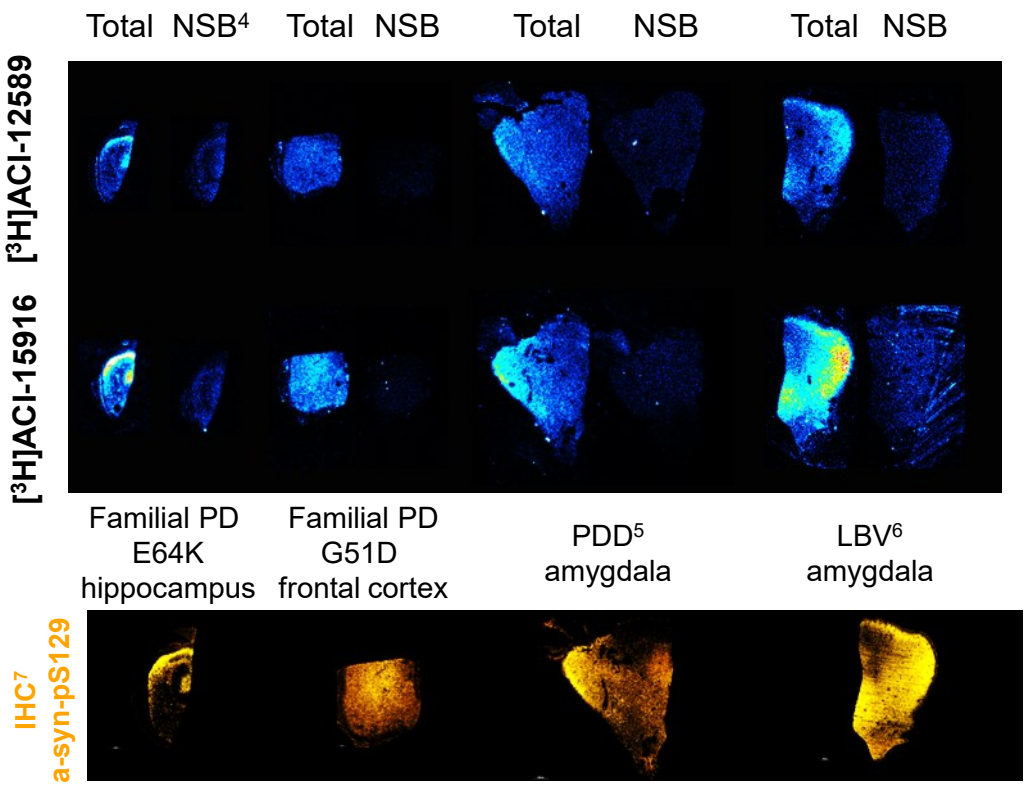
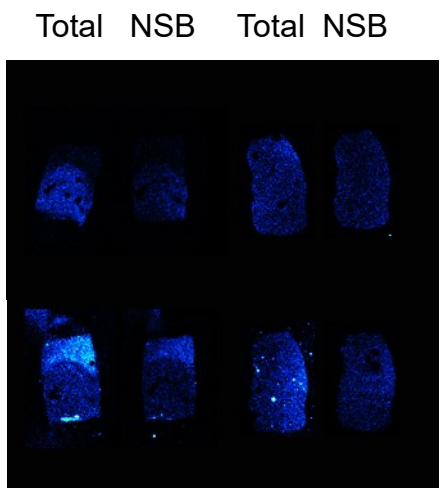
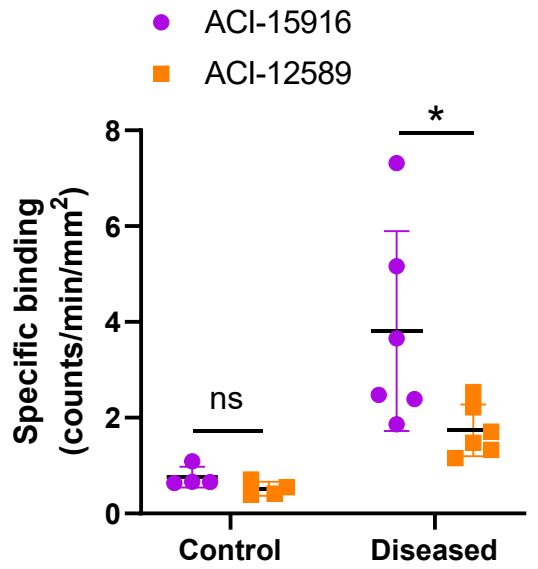
Next generation a-syn[1] PET[2] tracers for patients with PD[3]

Specific binding on brain tissue from different a-synucleinopathy cases

Autoradiography on a-synucleinopathy tissues







* p<0.05
2 way-ANOVA
Sidak's multiple comparison test

Ref: AC Immune unpublished data

- Compared to ACI-12589, ACI-15916 shows significantly improved specific binding to pathological a-syn aggregates in brain sections from different a-synucleinopathy cases

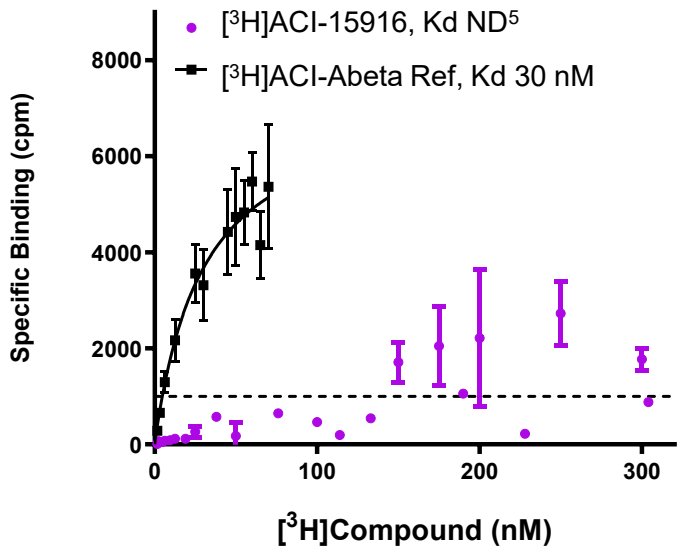
(1) alpha-synuclein ; (2) Positron emission tomography; (3) Parkinson's disease; (4) Nonspecific binding (5) Parkinson's disease with dementia; (6 Lewy body variant of Alzheimer's disease; (7) Immunohistochemistry

AC Immune

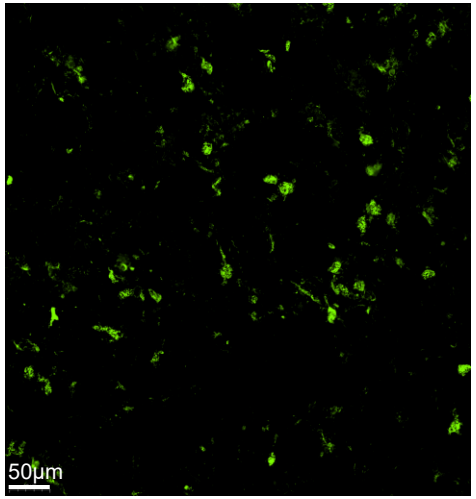
Next generation a-syn[1] PET[2] tracers for patients with PD[3]

Selectivity assessment using Alzheimer's disease tissue

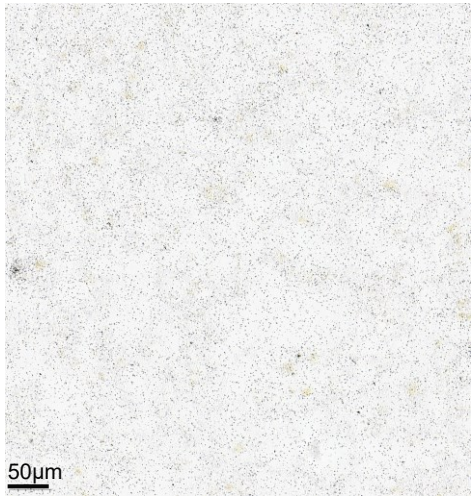
Radiobinding with AD[4] brain homogenates (Frontal Cortex)



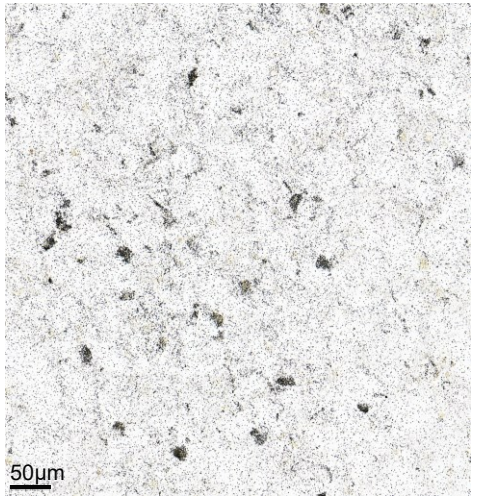
High-resolution ARG[6] on Tau rich AD sections (Entorhinal Cortex)



NFT[7] (Thioflavin S)
(adjacent section)



[3H]ACI-15916



[3H]PI-2620
Tau reference

Ref: AC Immune unpublished data

- ACI-15916 displays excellent selectivity versus co-pathologies such as Abeta and Tau and no off-target binding to MAO-B *in vitro*

(1) alpha-synuclein ; (2) Positron emission tomography; (3) Parkinson's disease; (4) Alzheimer's disease (5) Not determined; (6) Autoradiography; (7) Neurofibrillary tangles

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

- Preclinically, ACI-12589:
  - ✓ binds specifically and selectively to a-synuclein inclusions in different human synucleinopathy cases
  - ✓ shows longitudinally increasing uptake in different a-syn monkey models

- [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 [18F] candidates have the potential to detect synucleinopathies including PD[4], having:
  - ✓ significantly improved target occupancy on pathological a-syn and can detect very small aggregates
  - ✓ excellent selectivity versus potential co-pathologies
  - ✓ a pharmacokinetic profile in monkey suitable for their use as brain PET imaging agent

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

Acknowledgements

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

Oskar Hansson
Ruben Smith
Martin Schain
Tomas Ohlsson
Klas Brattby

Olivier Barret
Philippe Hantraye
Ronald Melki
Sonia Lavisse