State-of-the-art of treatment and diagnosis of alpha-synuclein pathologies: Opening remarks

Andrea Pfeifer, PhD | ADPD 2024 | March 2024

AC Immune

Recent Developments in the Diagnosis of Synucleinopathies

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MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

OUTLINE

- The Concept of ‚Synucleinopathy‘
- Diagnostic Challenges
- Moving towards a ‘Biological‘ Definition

A Large Kindred with Autosomal Dominant Parkinson's Disease

Lawrence I. Golbe, MD,* Giuseppe Di Iorio, MD,† Vincenzo Bonavita, MD,† Douglas C. Miller, MD, PhD,‡ and Roger C. Duvoisin, MD*

Ann Neurol 1990;27:276–282

Mapping of a Gene for Parkinson's Disease to Chromosome 4q21–q23

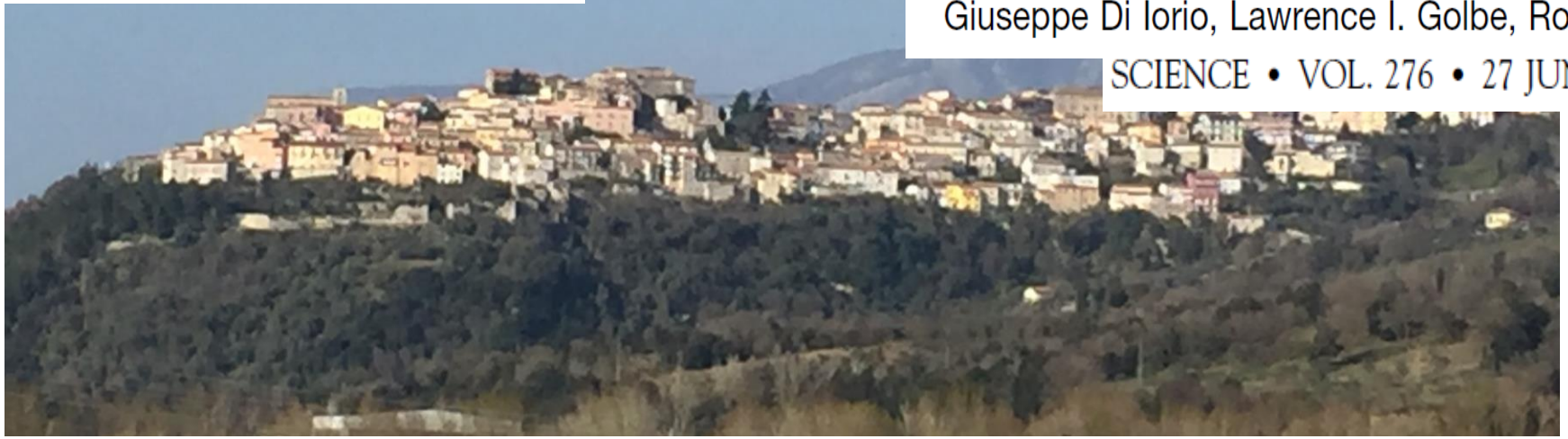
Mihael H. Polymeropoulos,* Joseph J. Higgins, Lawrence I. Golbe, William G. Johnson, Susan E. Ide, Giuseppe Di Iorio, Giuseppe Sanges, Edward S. Stenroos, Lana T. Pho, Alejandro A. Schaffer, Alice M. Lazzarini, Robert L. Nussbaum, Roger C. Duvoisin

SCIENCE • VOL. 274 • 15 NOVEMBER 1996

Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease

Mihael H. Polymeropoulos,* Christian Lavedan†, Elisabeth Leroy†, Susan E. Ide, Anindya Dehejia, Amalia Dutra, Brian Pike, Holly Root, Jeffrey Rubenstein, Rebecca Boyer, Edward S. Stenroos, Settara Chandrasekharappa, Aglaia Athanassiadou, Theodore Papapetropoulos, William G. Johnson, Alice M. Lazzarini, Roger C. Duvoisin, Giuseppe Di Iorio, Lawrence I. Golbe, Robert L. Nussbaum

SCIENCE • VOL. 276 • 27 JUNE 1997



Defining PD as a ‚Synucleinopathy‘

- Missense mutations in SNCA sufficient to cause dominantly inherited PD [1,3]
- Increase in SNCA wild-type gene dose (duplication; triplication) causes PD (or PDD) [4]
- Sequence variations in regulatory region of SNCA associated with PD risk [5]
- Lewy bodies and Lewy neurites in sporadic PD immunoreactive for α-synuclein [2]

1.Polymeropoulos &al.,Science. 1997 Jun 27;276(5321):2045-7; 2.Spillantini &al.,Nature. 1997 Aug 28;388(6645):839-40. 3.Krüger &al.,Nat Genet. 1998 Feb;18(2):106-8; 4.Singleton &al., Science. 2003 Oct 31;302(5646):841; 5.Blauwendraat &al., Lancet Neurol. 2020 Feb;19(2):170-178.

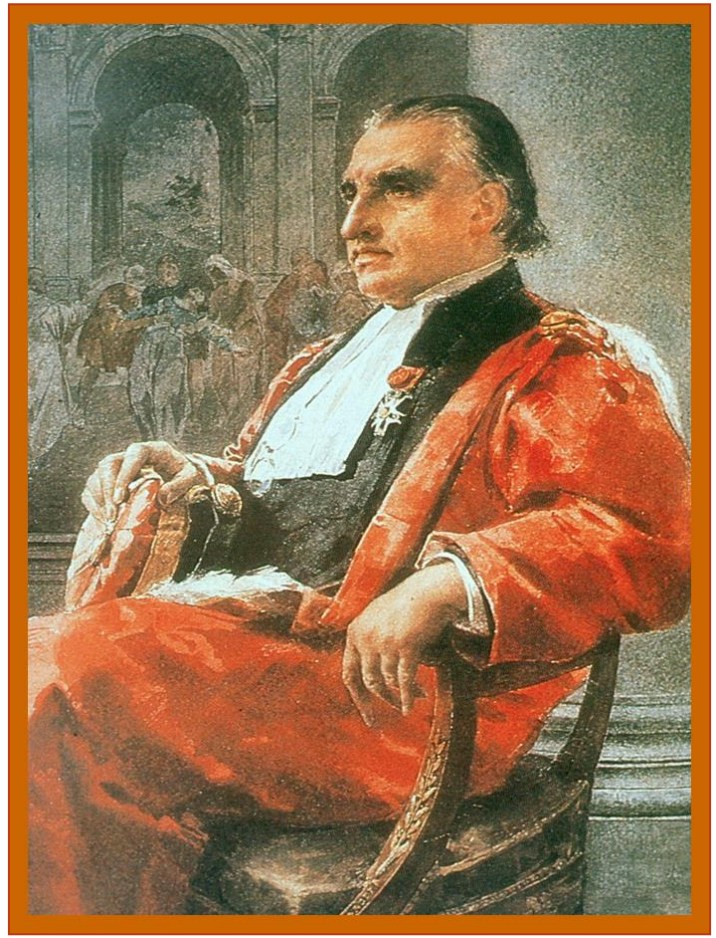
Clinical Entities defined by α-Synuclein Pathology

- Parkinson‘s Disease (PD)
- Dementia with Lewy Bodies (DLB)/ PDD
- Multiple System Atrophy
- Pure Autonomic Failure (PAF)

- Idiopathic REM Sleep Behaviour Disorder

Diagnosing PD on the Street

‚….I have seen such patients everywhere on the streets of Rome, of Amsterdam, in Spain – it is always the same picture. They can be identified from afar, you do not need a medical history….‘



Charcot, Lecons du Mardi 1888 (quoted in: Lees A; Brain 2017:40:843-848)

MDS Clinical Diagnostic Criteria for Parkinson‘s Disease

1: Presence of a parkinsonian syndrome:

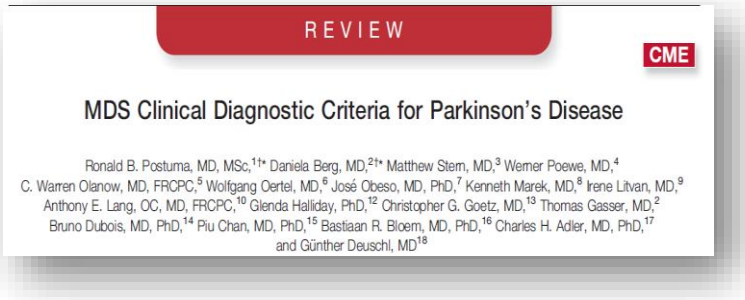
Bradykinesia,

plus at least one of :

- Limb rigidity
- 4 - 6 Hz Rest Tremor

2: Presence of supportive criteria for PD

3: Absence of Exclusion Criteria


REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2]
Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17]
and Günther Deuschl, MD[18]

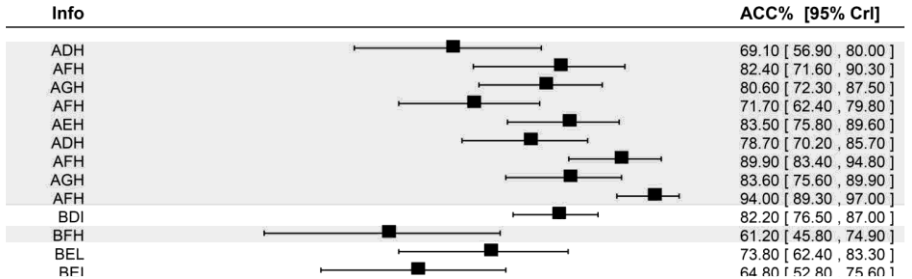
Postuma et al, Mov Disord. 2015 ;30(12):1591-601.

Accuracy of a Clinical Diagnosis of PD

- Meta-Analysis of 11 clinico-pathological studies

➢ Non MD experts	73.8 % {67.8-79.6}
➢ MD experts - 1st visit	79.6 % {46.0-95.1}
➢ MD experts - after FU	83.9 % {69.7-92.6}
➢ Use of formal UKBB criteria	82.7 % {62.6-93.0}

- **Pooled diagnostic accuracy of 80.6 %**



Rizzo & al, Neurology 2016

RESEARCH ARTICLE

Pathological Validation of the MDS Criteria for the Diagnosis of Multiple System Atrophy

Sasivimol Virameteekul, MD, MSc,[1,2] Tamas Revesz, PhD, FRCPath,[1] Zane Jaunmuktane, MD, FRCPath,[1]
Thomas T. Warner, FRCP, PhD,[1,2] and Eduardo De Pablo-Fernández, MD, PhD[1,2*]

318 consecutive cases of sporadic, adult-onset parkinsonism or cerebellar ataxia

QSBB (2009-2019)

103 MSA vs 215 non-MSA

248 with parkinsonism

70 with cerebellar ataxia

Dx Criteria	Sensitivity	Specificity	Accuracy
Late Disease (final visit)			
MDS probable	**95.1**	**94.0**	**94.3**
MDS established	**51.5**	**100.0**	**84.3**
2nd Consensus possible	96.1	81.9	86.5
2nd consensus probable	75.7	96.7	89.9
Clinical	90.3	91.2	90.9

Movement Disorders, 2023 . DOI: 10.1002/mds.29304

RESEARCH ARTICLE

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Sasivimol Virameteekul, MD, MSc,[1,2] Tamas Revesz, PhD, FRCPath,[1] Zane Jaunmuktane, MD, FRCPath,[1]
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318 consecutive cases of sporadic, adult-onset parkinsonism or cerebellar ataxia

QSBB (2009-19)

103 MSA vs 215 non-MSA

248 with parkinsonism

70 with cerebellar ataxia

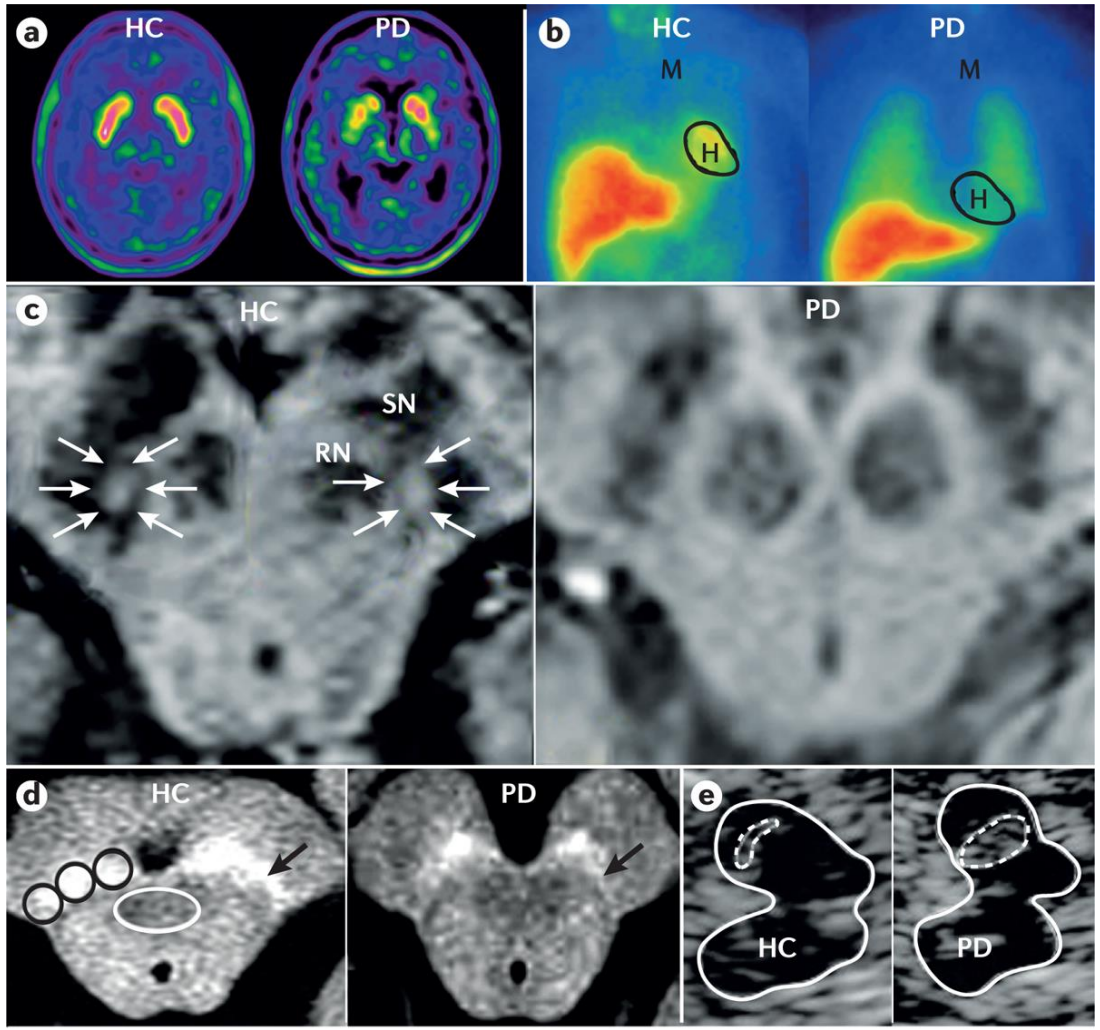
Dx Criteria	Sensitivity	Specificity	Accuracy
Early disease (<3yrs)			
MDS probable	**62.1**	**95.3**	**84.6**
MDS established	**20.4**	**100.0**	**74.2**
2nd Consensus possible	60.2	88.4	79.2
2nd consensus probable	39.8	97.7	78.9
Clinical	40.8	93.5	76.4

Movement Disorders, 2023 . DOI: 10.1002/mds.29304

Imaging Methods to Diagnose Synucleinopathies

Radiotracer Imaging

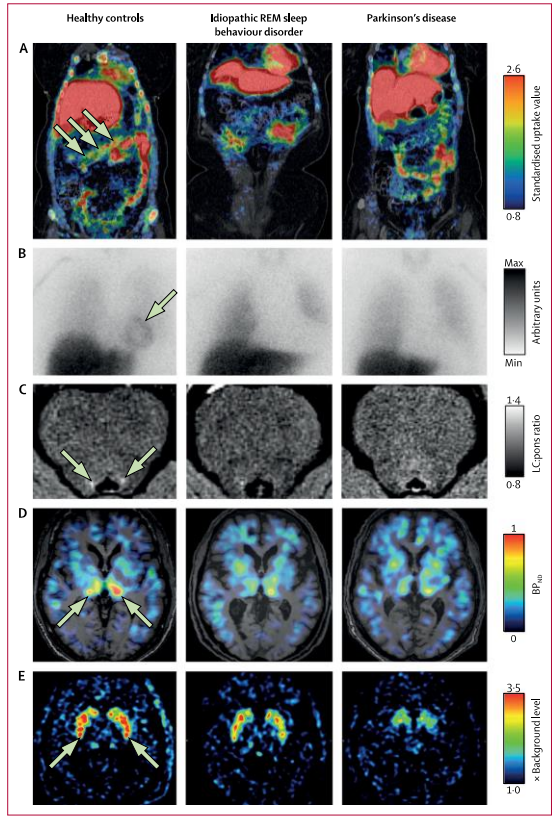
MR Imaging



Nature Reviews | Disease Primers

Poewe, W. *et al.* (2017) Parkinson disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2017.13

TCS



Multimodal Imaging

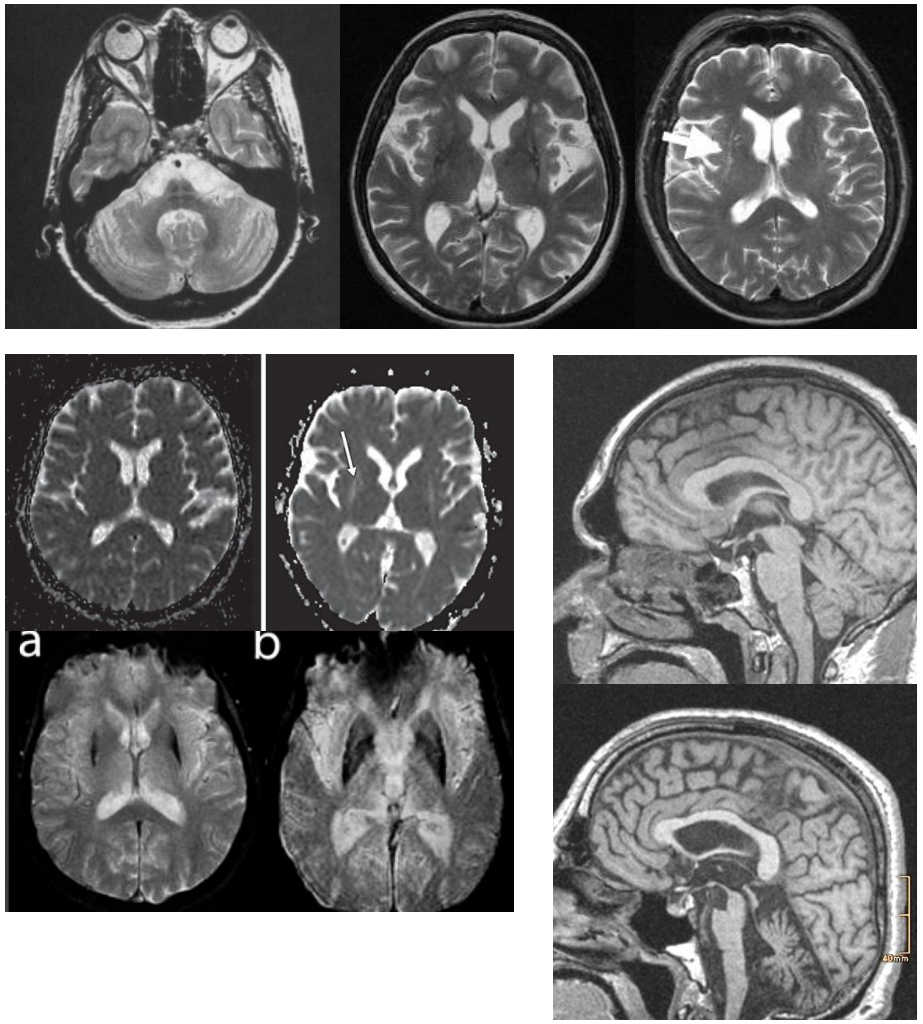
Knudsen&al. Lancet Neurology 2018;17:618-28

Structural MRI at 1.5T in MSA (vs PD)

”RED FLAGS”: MSA signs (Sensitivity >50%; Specificity >90%)

- putaminal atrophy
- putaminal hypointensity
- putaminal rim sign,
- pontocerebellar atrophy,
- MCP atrophy a./o. hyperintensity
- hot cross bun sign,
- ↑putaminal diffusivity

- hypointensity on GRE T2* or SWI at higher field strengths



Seppi K, Poewe W. Neuroimaging Clin N Am. 2010.; Mitchell T, et al. JAMA Neurol. 2021.

Diagnostic potential of automated subcortical volume segmentation in atypical parkinsonism

Figure 3 A 3-node C4.5 decision tree calculated from the training set

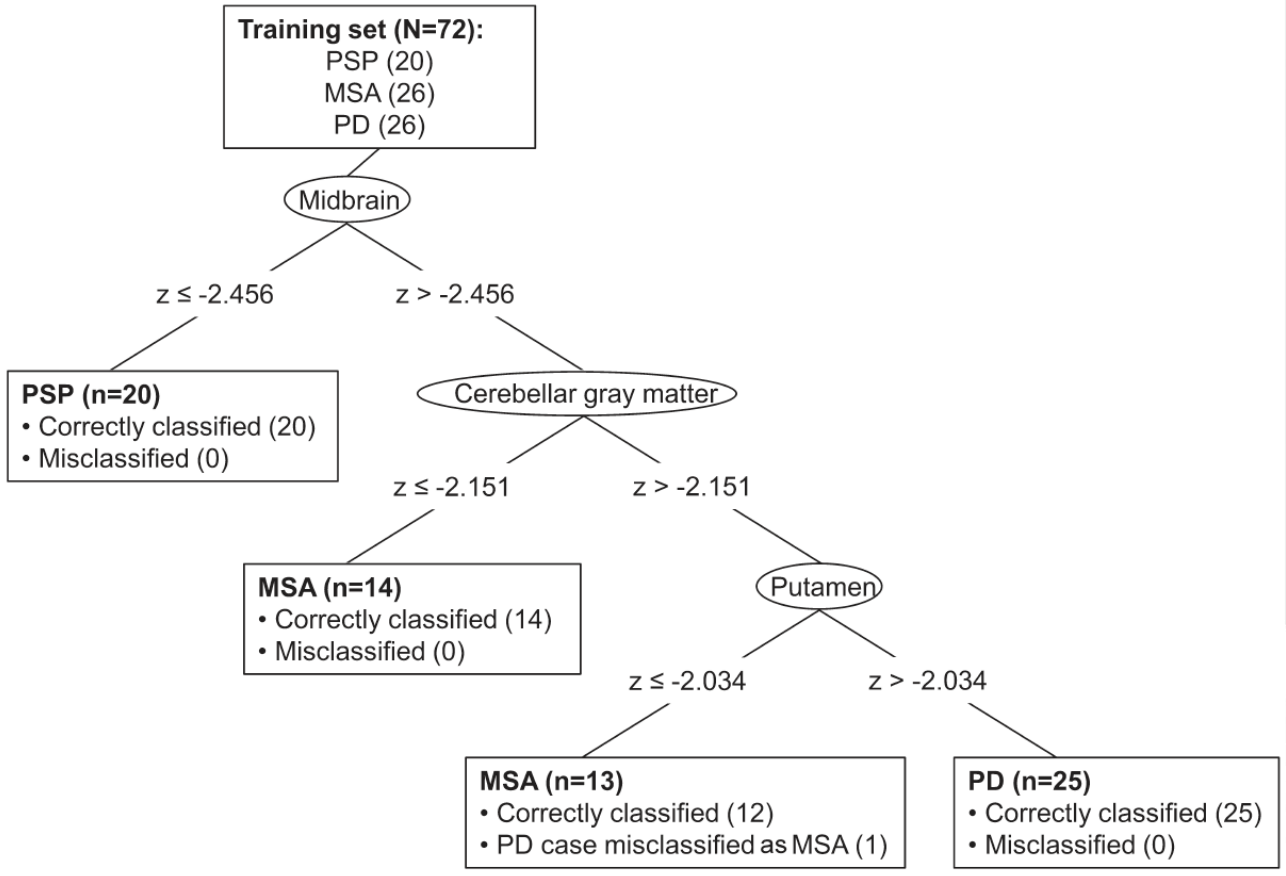
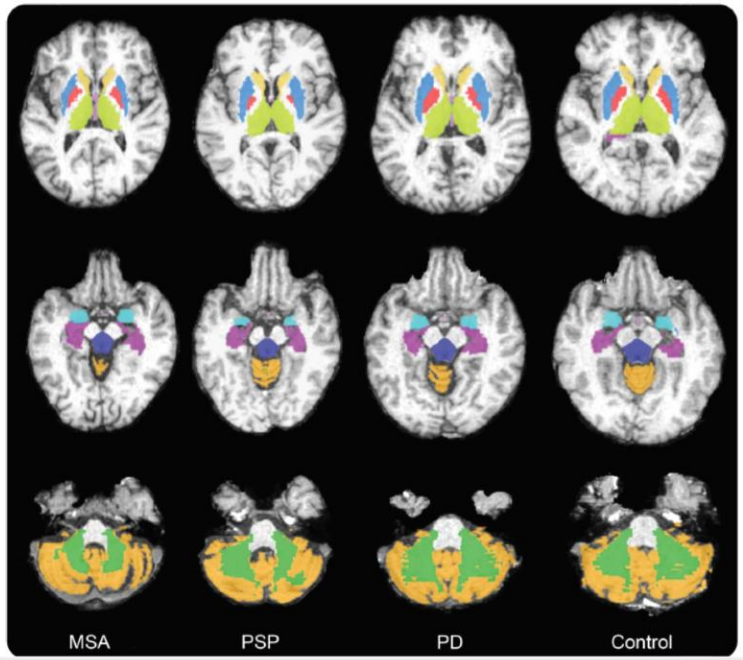


Figure 2 Subcortical volume reduction in a patient with multiple system atrophy (MSA) and progressive supranuclear palsy (PSP)

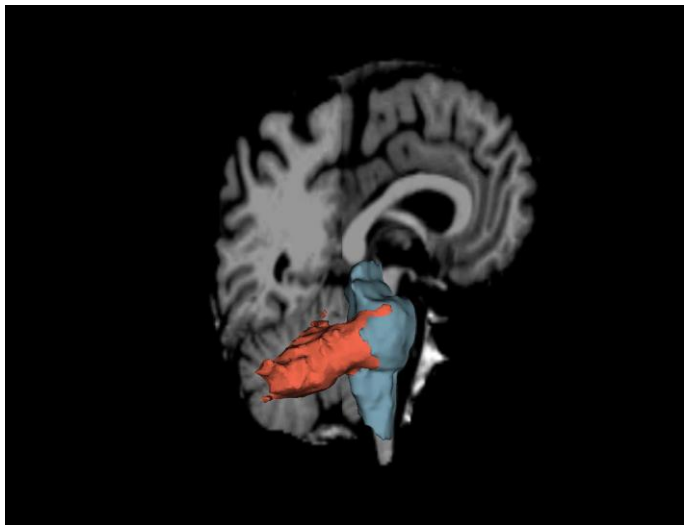


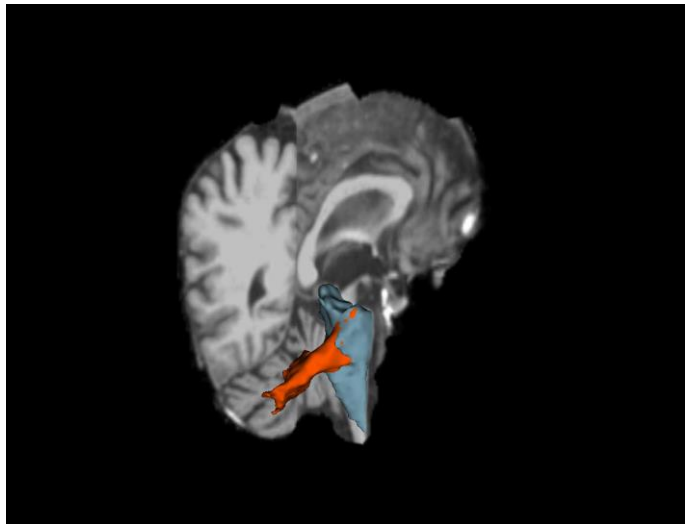
overall accuracy: 97%

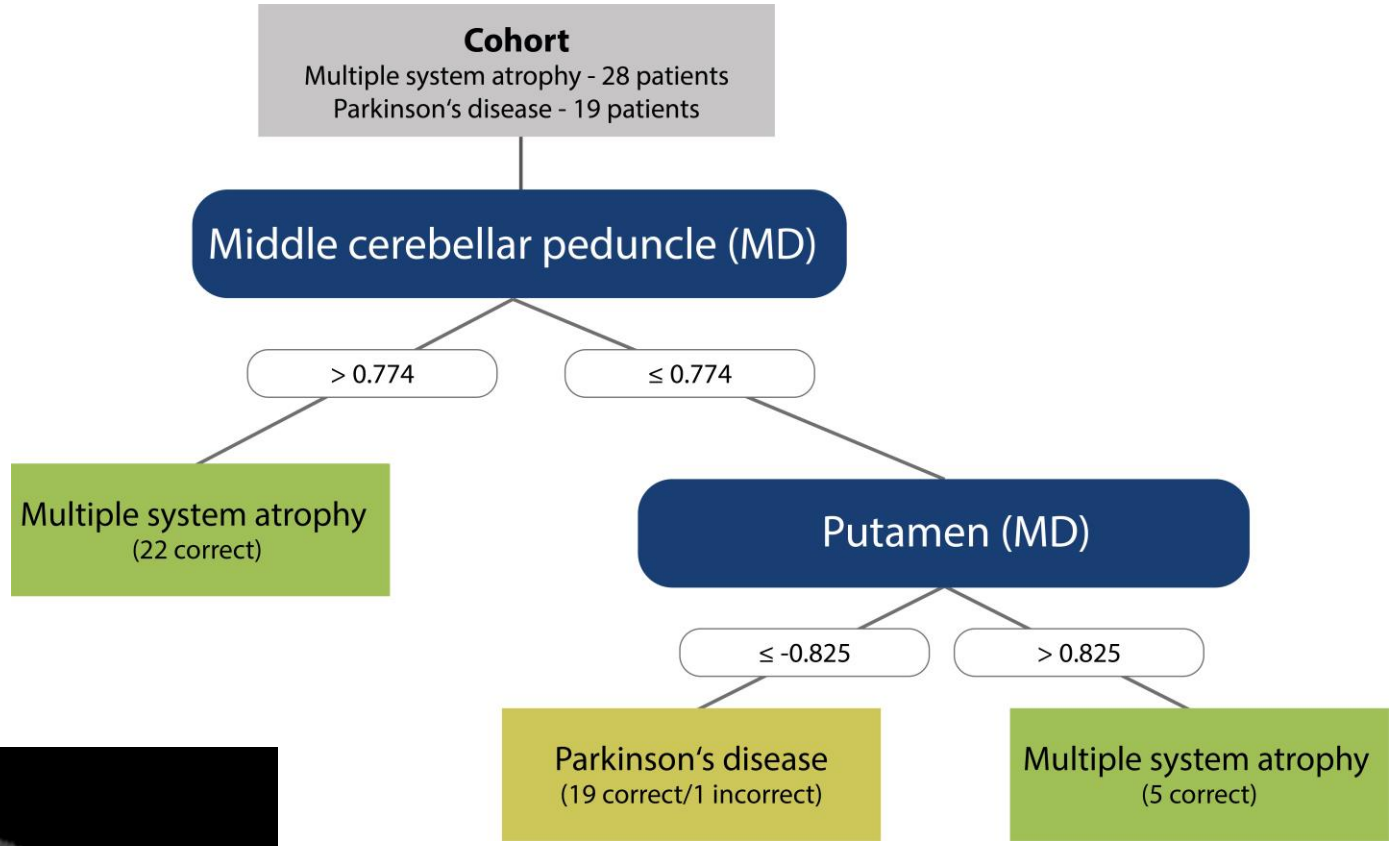
Scherfler et al. 2016

Automated Analysis of Diffusion-Weighted Magnetic Resonance Imaging for the Differential Diagnosis of Multiple System Atrophy from Parkinson's Disease

Florian Krismer, PhD,[1,2] Vincent Beliveau, PhD,[1,2] Klaus Seppi, MD,[1,2] Christoph Mueller, MD,[1,2] Georg Goebel, PhD,[3] Elke R. Gizewski, MD,[2,4] Gregor K. Wenning, PhD,[1] Werner Poewe, MD,[1,2] and Christoph Scherfler, MD[1,2*]







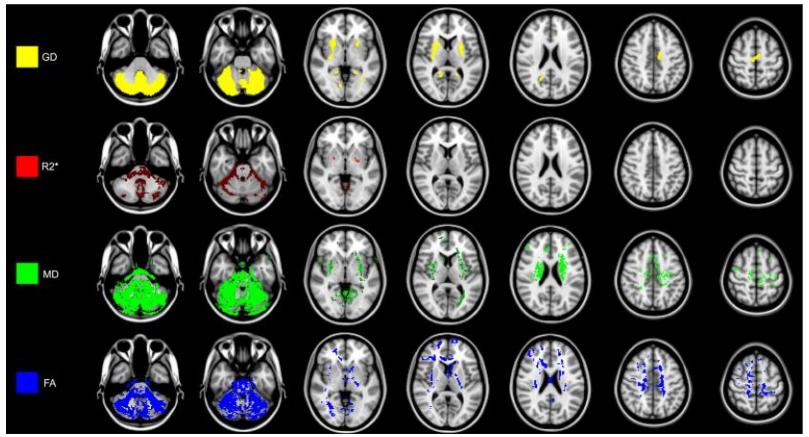
Overall diagnostic accuracy: 91.4 %

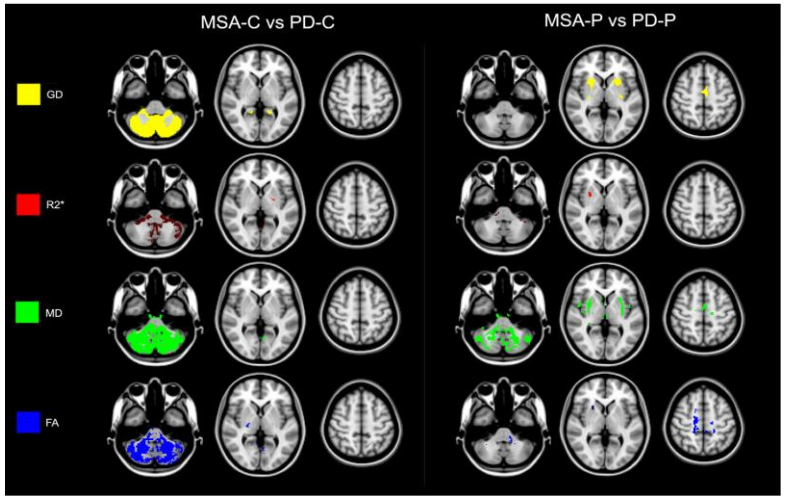
MD = mean diffusivity

Movement Disorders, Vol. 36, No. 1, 2021

Multimodal MRI to distinguish PD from MSA

- 26 PD vs 29 MSA vs 26 HC
- Multimodal 3-T MRI incl. T1, R2*, DWI
- Whole brain voxel-based analysis
- Significant differences between MSA and PD in **cerebellum, putamen**, MCP, corona radiata

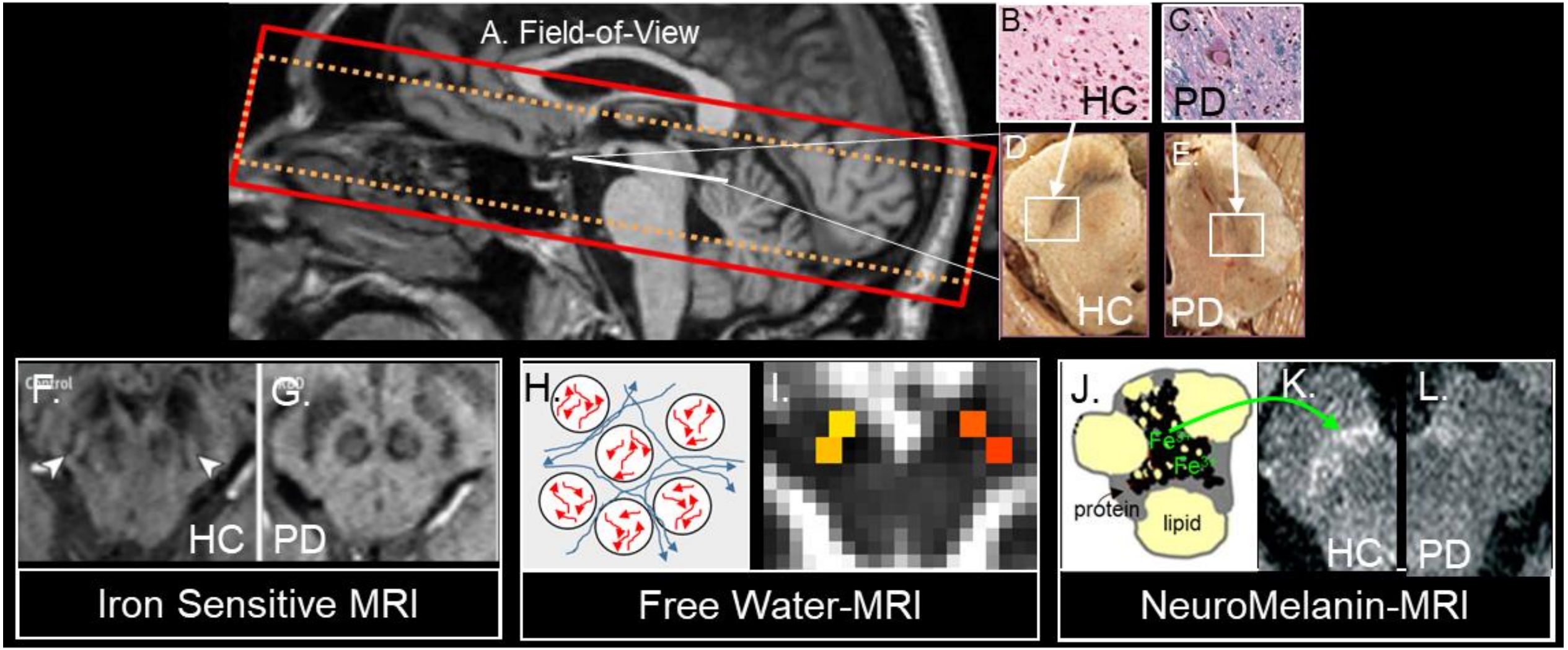




Combination of 2 markers in logistic regression yielded > 95% discrimination

Peran & al., Movement Disorders 2018; 33: 600-8

MR Imaging of S. Nigra Pathology



Vaillancourt etal, Neurology, 2009; de Marzi et al, Ann Neurol 2016; Erminger et al BRAIN 2016; Poston et al JPD (2020); Ryman et al (2020) PRD, Mitchell et al JAMA Neurology 2021; Zhang et al; JPD 2022

‚Nigrosome-1‘ Imaging (loss of DNH) in Prodromal PD

Loss of Dorsolateral Nigral Hyperintensity on 3.0 Tesla Susceptibility-Weighted Imaging in Idiopathic Rapid Eye Movement Sleep Behavior Disorder

Roberto De Marzi, MD,[1]
Klaus Seppi, MD,[1,2] Birgit Högl, MD,[1]
Christoph Müller, MD,[1]
Christoph Scherfler, MD,[1,2]
Ambra Stefani, MD,[1] Alex Iranzo, MD,[3]
Eduardo Tolosa, MD,[3]
Joan Santamaria, MD,[3]
Elke Gizewski, MD,[2,4]
Michael Schocke, MD,[2,4]
Elisabeth Skalla, MD,[2,4]
Christian Kremser, PhD,[2,4] and
Werner Poewe, MD[1,2]

We assessed loss of dorsolateral nigral hyperintensity (DNH) on high-field susceptibility-weighted imaging (SWI), a novel magnetic resonance imaging marker for Parkinson's disease (PD), in 15 subjects with idiopathic rapid eye movement sleep behavior disorder (iRBD) and compared findings to 42 healthy controls (HCs) and 104 PD patients. We found loss of DNH in at least two thirds of iRBD subjects, which approaches the rate observed in PD and is in contrast to findings in HCs. We propose that absence of DNH on high-field SWI could identify prodromal degenerative parkinsonism in iRBD.

ANN NEUROL 2016;79:1026–1030

ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE

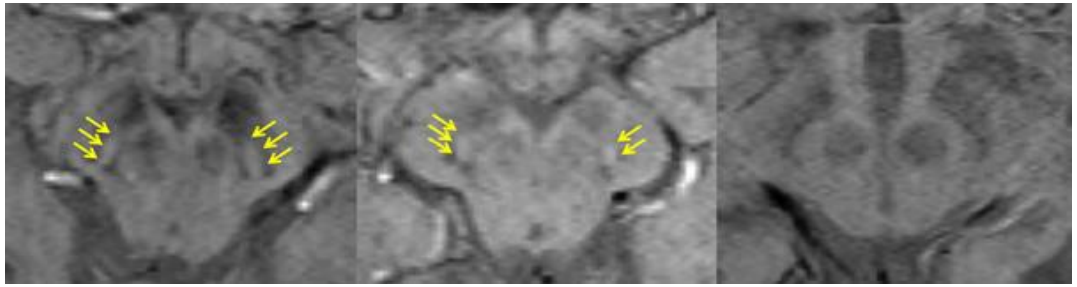
Annals of Clinical and Translational Neurology 2020; 7(1): 26–35

Nigrosome 1 imaging in REM sleep behavior disorder and its association with dopaminergic decline

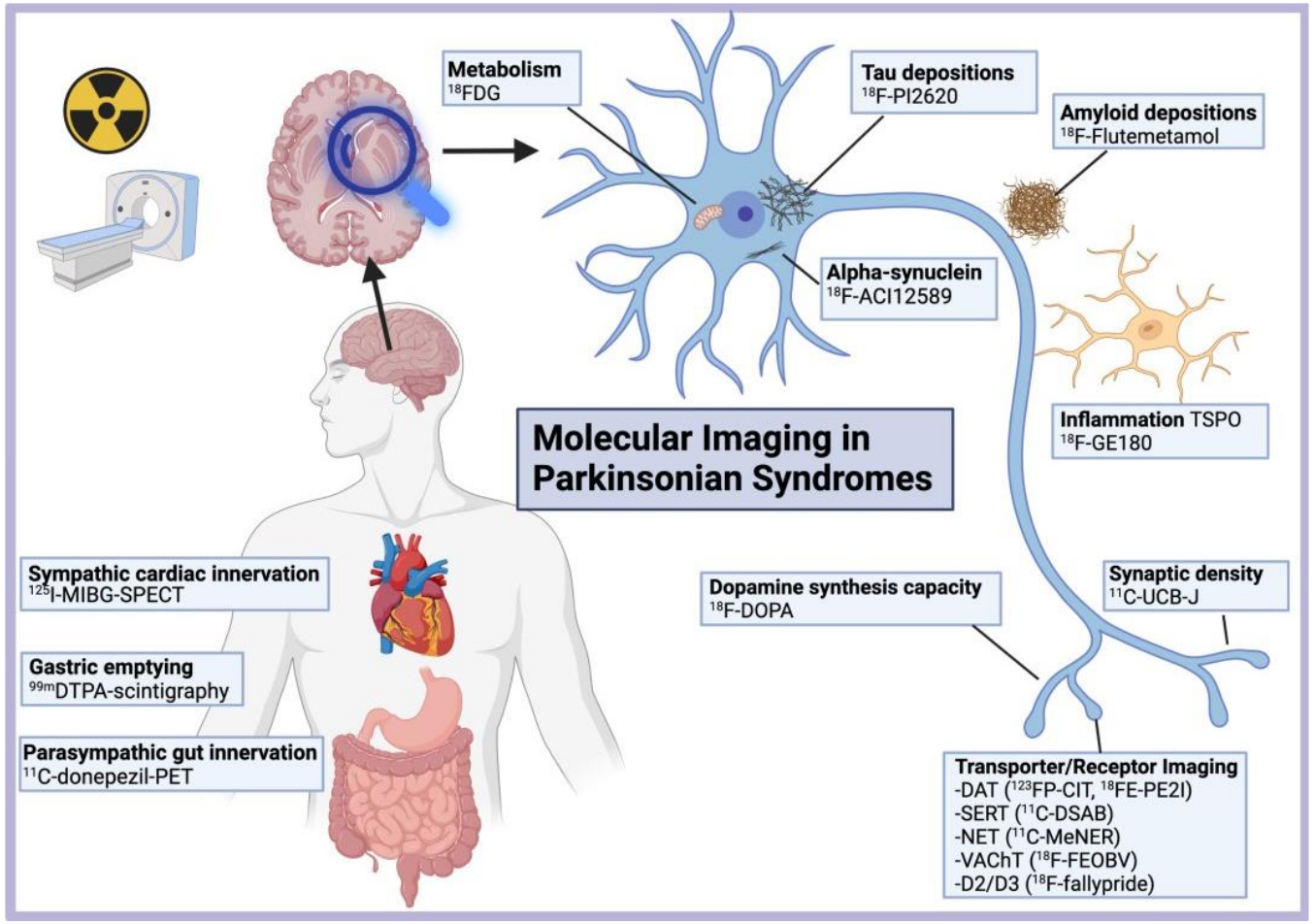
Thomas R. Barber[1,2,3], Ludovica Griffanti[1,2,4], Kevin M. Bradley[5], Daniel R. McGowan[6], Christine Lo[1,2], Clare E. Mackay[1,3], Michele T. Hu[1,2] & Johannes C. Klein[1,2,3,4]

Loss of DNH signal:

PD 92%/96% , RBD 27%/77% , HC 3%/8%

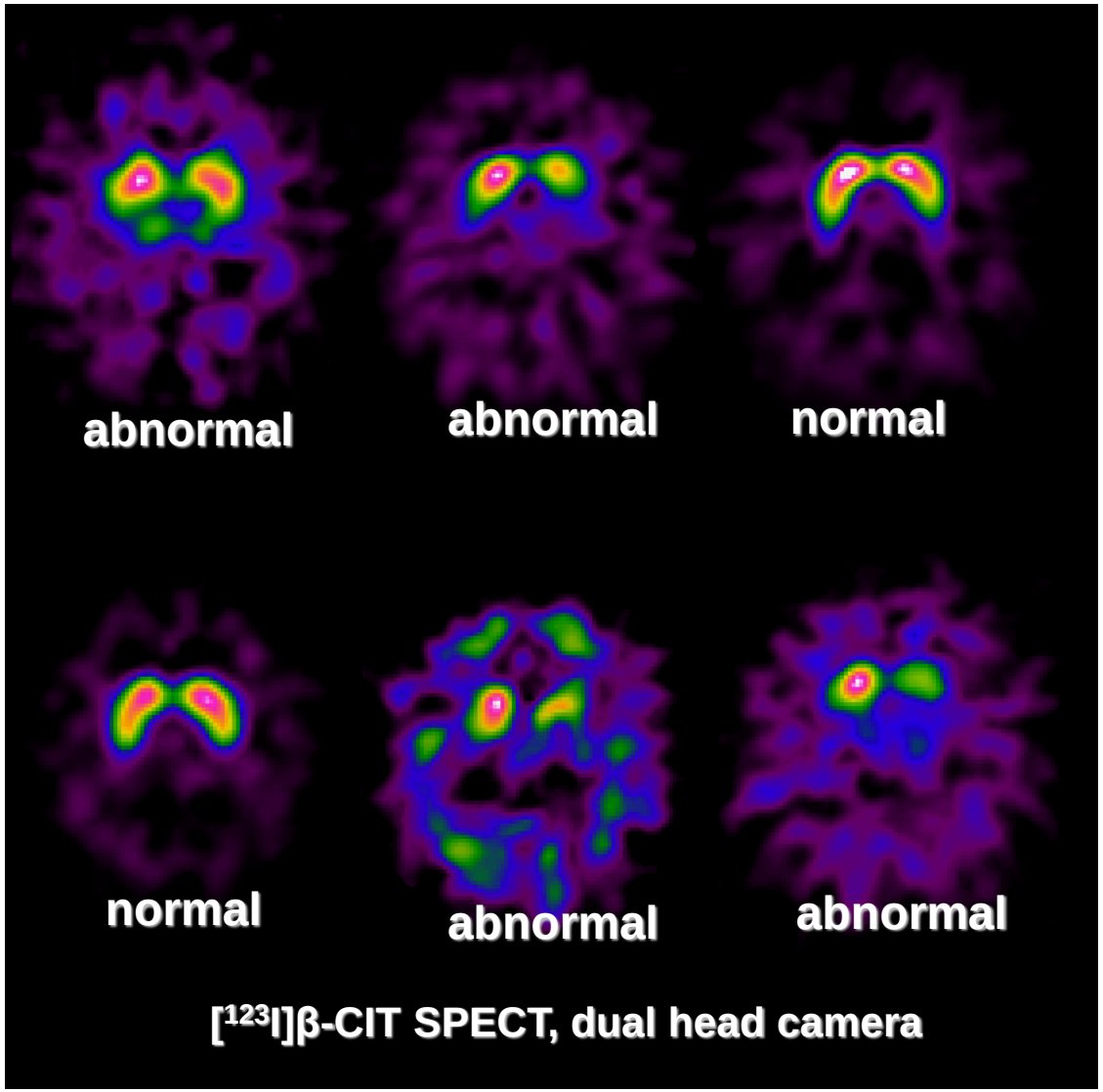


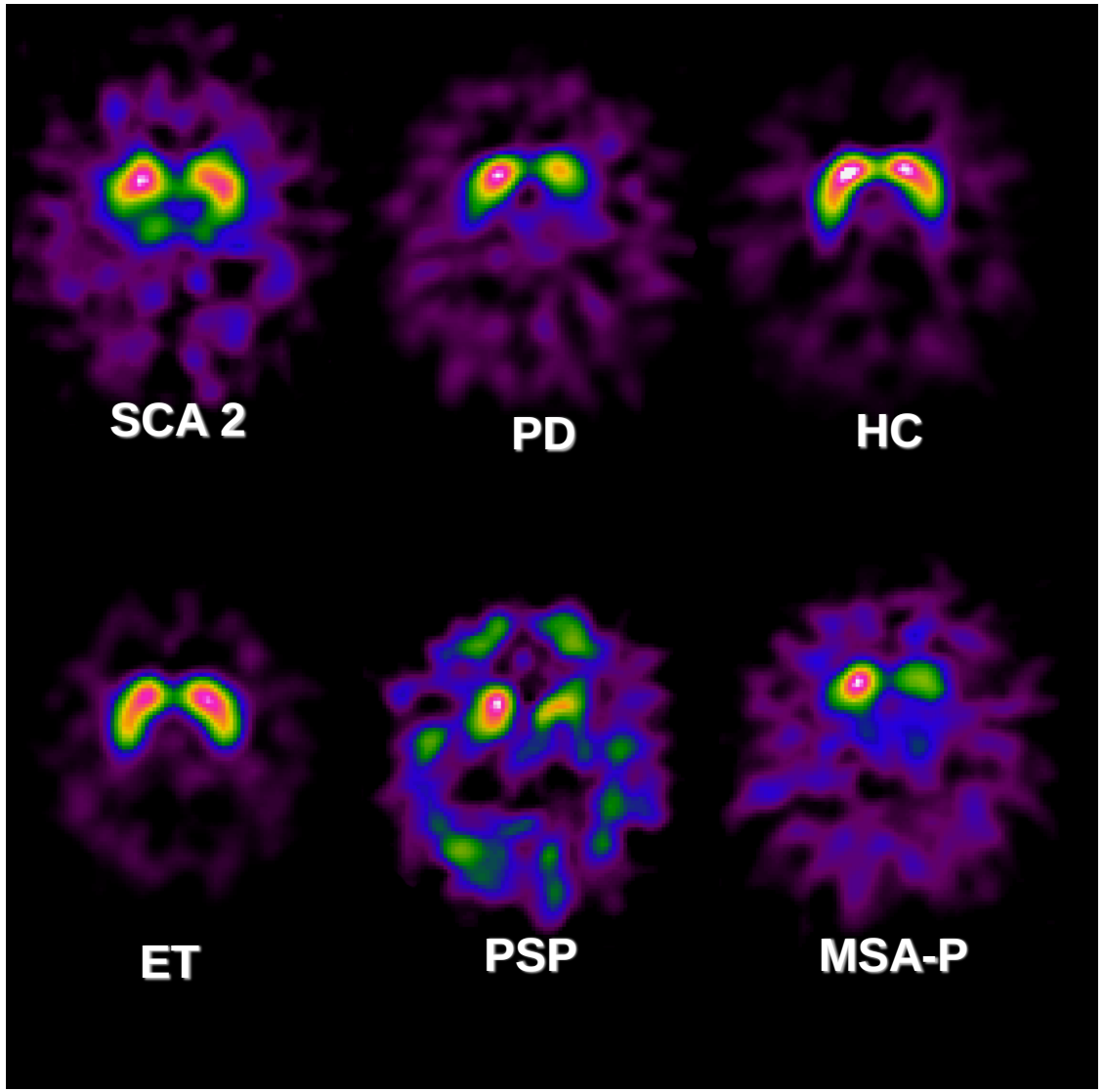
Diagnostic Potential of Radiotracer Imaging in Degenerative Parkinsonism



Prange & al. Brain Sci 2022;12: 1146

DAT-SPECT as a Biomarker for Synucleinopathies?

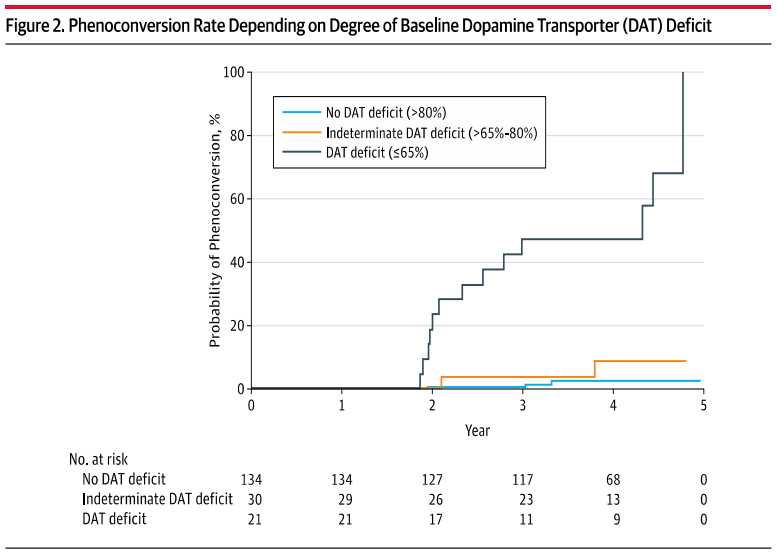




Scherfler& al. Mov Disord. 2007; 22:1239-48

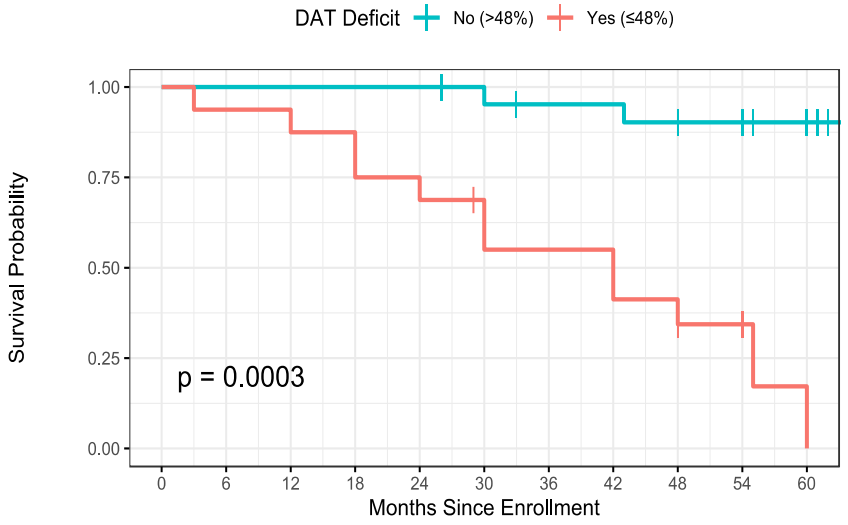
Predicting Conversion in PD Risk Subjects by DAT-Binding Deficit

Hyposmia



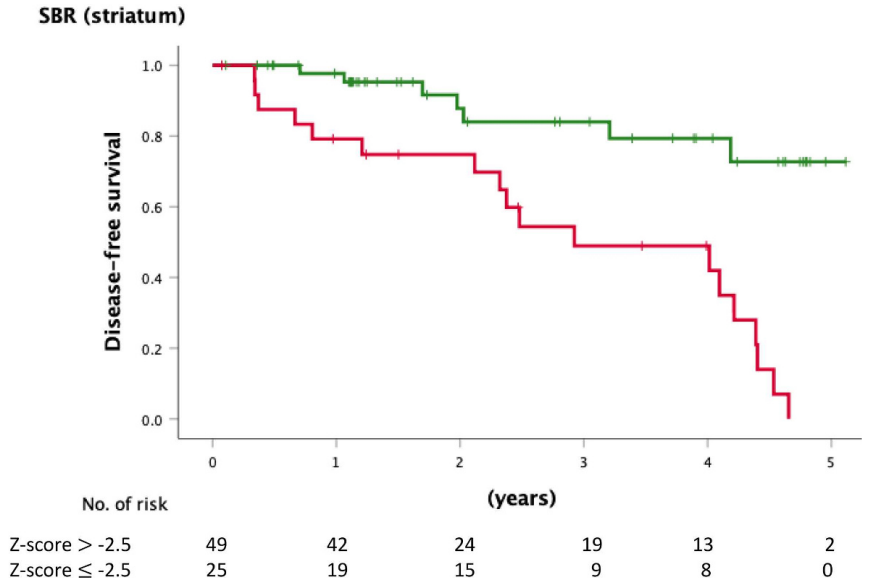
Jennings et al. JAMA Neurology 2017;

iRBD



Chahine et al. Ann Clin Trans Neurology 2021; 8: 201-12

iRBD



Miyamoto et al.J Neurol Sci 414 (2020) 116821

nature communications

Article

https://doi.org/10.1038/s41467-023-42305-3

The α-synuclein PET tracer [18F] ACI-12589 distinguishes multiple system atrophy from other neurodegenerative diseases

Received: 17 May 2023

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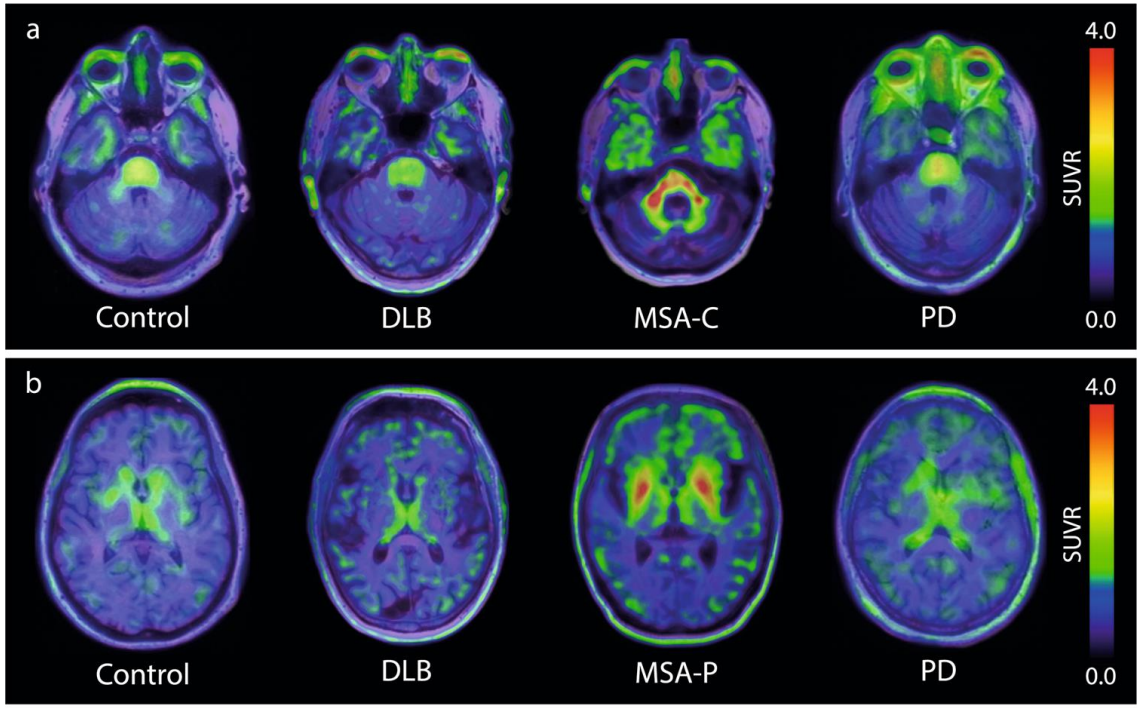
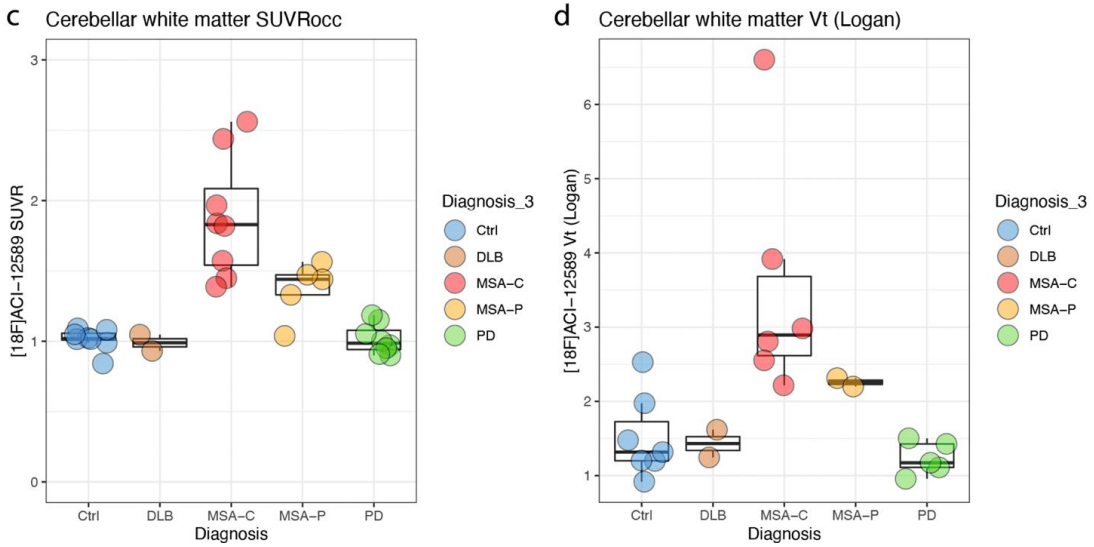
Published online: 27 October 2023

Check for updates

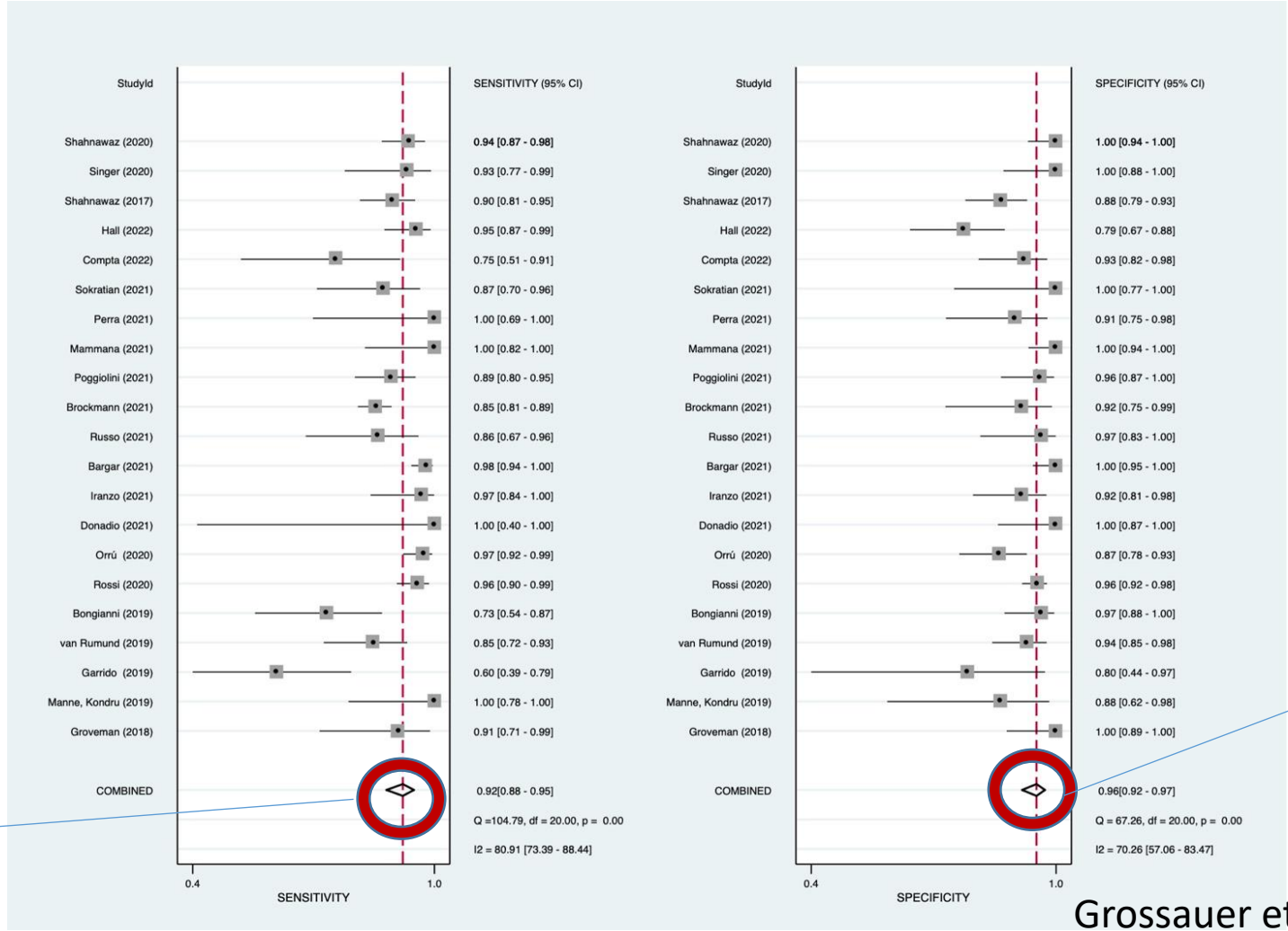
Ruben Smith[1,2,15], Francesca Capotosti[3,15], Martin Schain[1,4,5], Tomas Ohlsson[6], Efthymia Vokali[3], Jerome Molette[3], Tanja Touilloux[3], Valerie Hliva[3], Ioannis K. Dimitrakopoulos[3], Andreas Puschmann[2,7,8], Jonas Jögi[9], Per Svenningsson[10], Mattias Andréasson[10], Christine Sandiego[11], David S. Russell[11], Patricia Miranda-Azpiazu[12], Christer Halldin[12], Erik Stomrud[1,13], Sara Hall[1,13], Klas Bratteby[6], Elina Tampio L'Estrade[6], Ruth Luthi-Carter[3], Andrea Pfeifer[3], Marie Kosco-Vilbois[3], Johannes Streffer[3,14] ✉ & Oskar Hansson[1,13] ✉

n= 13 MSA (mean age 61+ 8yrs)
n= 8 Ctrls. (mean age 63+ 11yrs)
n= 8 PD (mean age 68+ 6yrs)
n= 2 DLB (mean age 81+ 1yrs)





Diagnostic Performance of CSF α-Synuclein SAA (PD/DLB vs. Ctrls.)



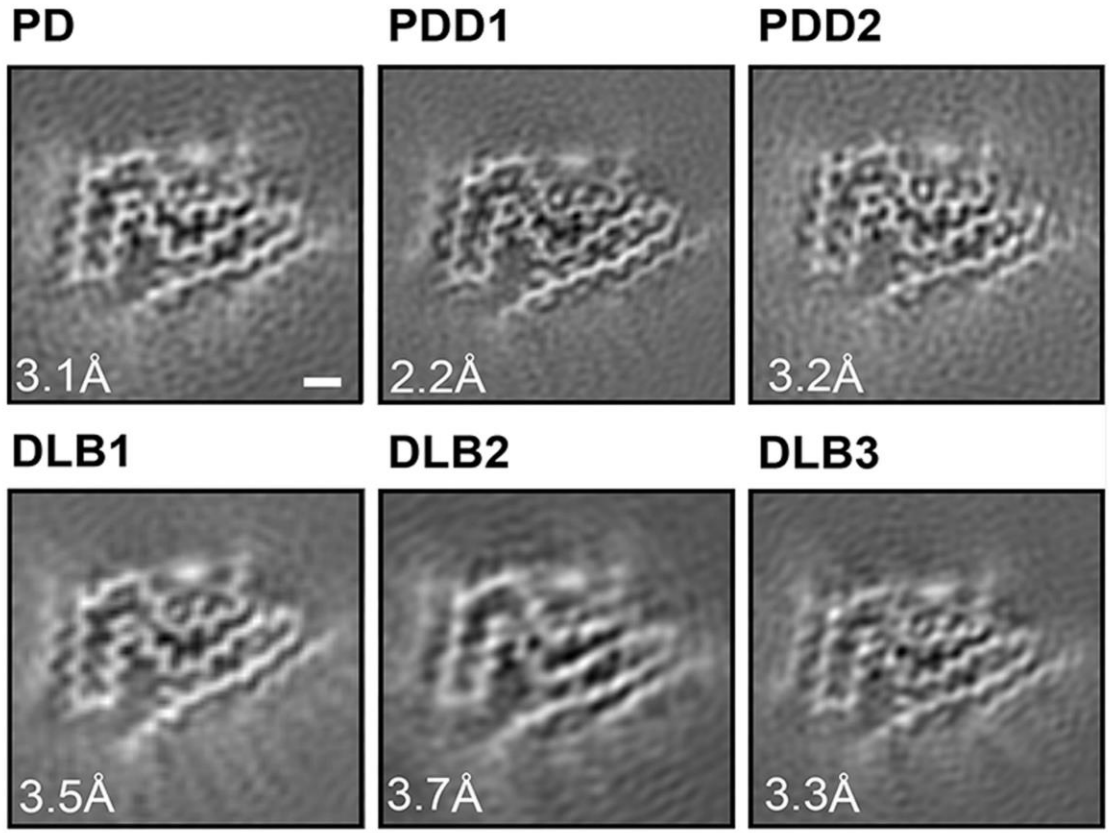
sensitivity : 92%

specificity : 96%

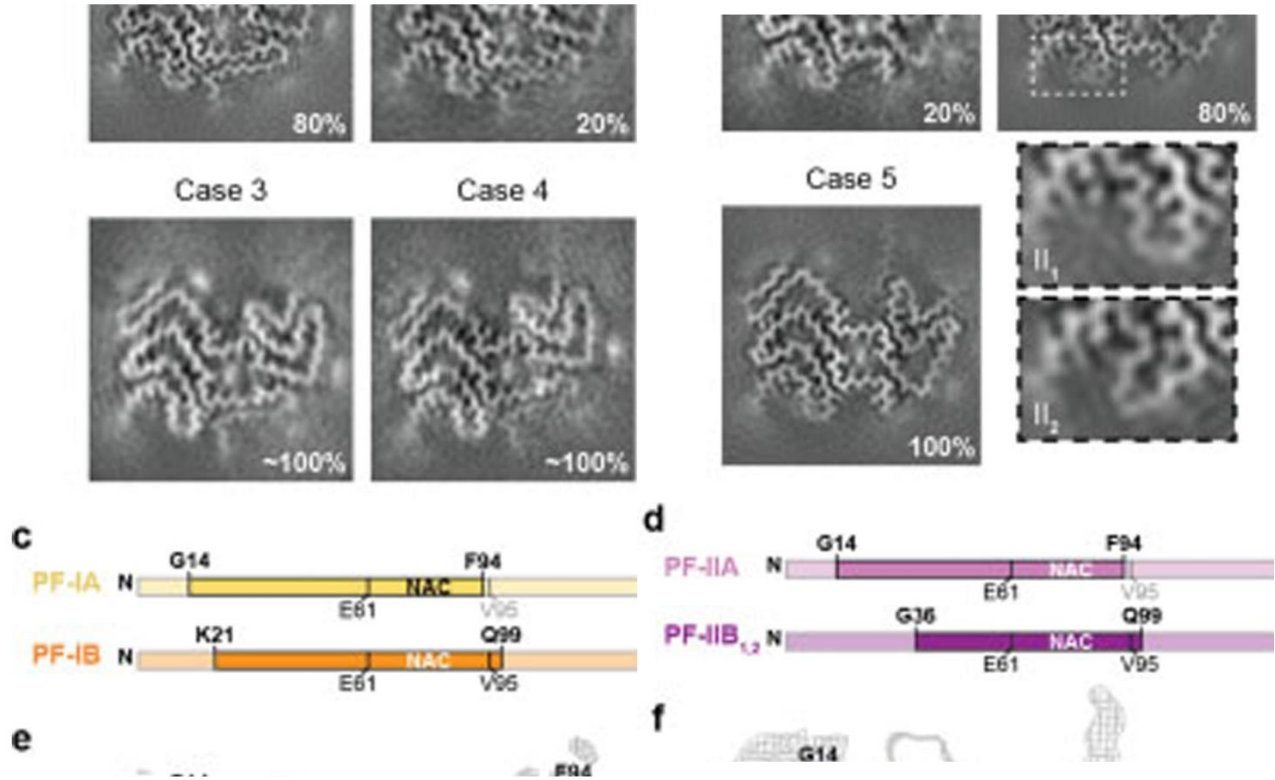
Grossauer et al; Mov Dis Clin Pract , 2023

Distinct Molecular Structures of α-Synuclein Assemblies in MSA vs LB-Diseases

PD/DLB α-syn filaments = single protofilaments vs. MSA α-syn filaments = 2 protofilaments



Yang et al. Nature 2022



Schweighauser et al. Nature 2020

α-Synuclein SAA's: Can they distinguish between Synucleinopathies?

Table 3 Diagnostic Performances of α-Syn SAAs in Differentiating Among Synucleinopathies

		Matrix	Sens	Spec	Reference
MSA (65)	PD (88)	CSF	94%[a]	97%[a]	Shahnawaz et al. (2020)[23]
MSA[b] (31)	PD (71)	CSF	94%	94%	Rossi et al. (2020)[22]
MSA (11)	PD (18)	OM	65%	84%	De Luca et al. (2020)[30]
MSA[b] (65)	PD (116)	CSF	91%	96%	Quadalti et al. (2021)[44]
MSA-C (10)	MSA-P (20)	OM	90%	100%	Bargar et al. (2021)[35]
MSA-P (20)	PD (13)	OM	82%	100%	Bargar et al. (2021)[35]
MSA (18)	PD (75)	Saliva	61%	94%	Luan et al. (2022)[38]

Abbreviations: MSA = multiple system atrophy; MSA-C = multiple system atrophy cerebellar variant; MSA-P = multiple system atrophy parkinsonian variant; OM = olfactory mucosa; PD = Parkinson disease.
[a] Calculated on positive SAA samples.
[b] MSA provided an overall negative response.

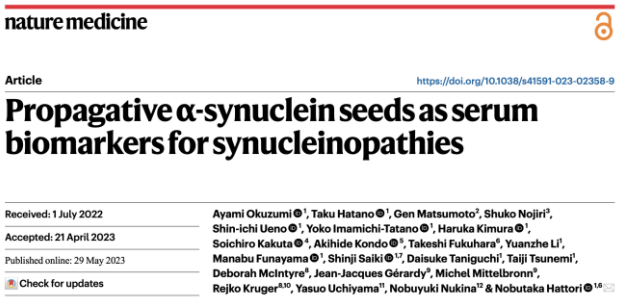
Bellomo et al, Neurology 2022;99:195-205

Sensitivity of serum α-synuclein IP/RT-QuIC

Table 2 | Serum α-synuclein IP/RT-QuIC results and α-synuclein IP/RT-QuIC assay characteristics per diagnosis

Diagnosis	*n*	IP/RT-QuIC results +/−	Positive results
Synucleinopathies			
PD	221	210/11	95%
MSA	39	25/14	64%
DLB	10	9/1	90%
RBD	9	4/5	44%
Non-synucleinopathies			
PSP	30	1/29	3%
AD	25	4/21	16%
PRKN	17	0/17	0%
Controls	128	11/117	8.5%

Data are presented as numbers. *n*, number of participants who received IP/RT-QuIC.


nature medicine

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Propagative α-synuclein seeds as serum biomarkers for synucleinopathies

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Check for updates

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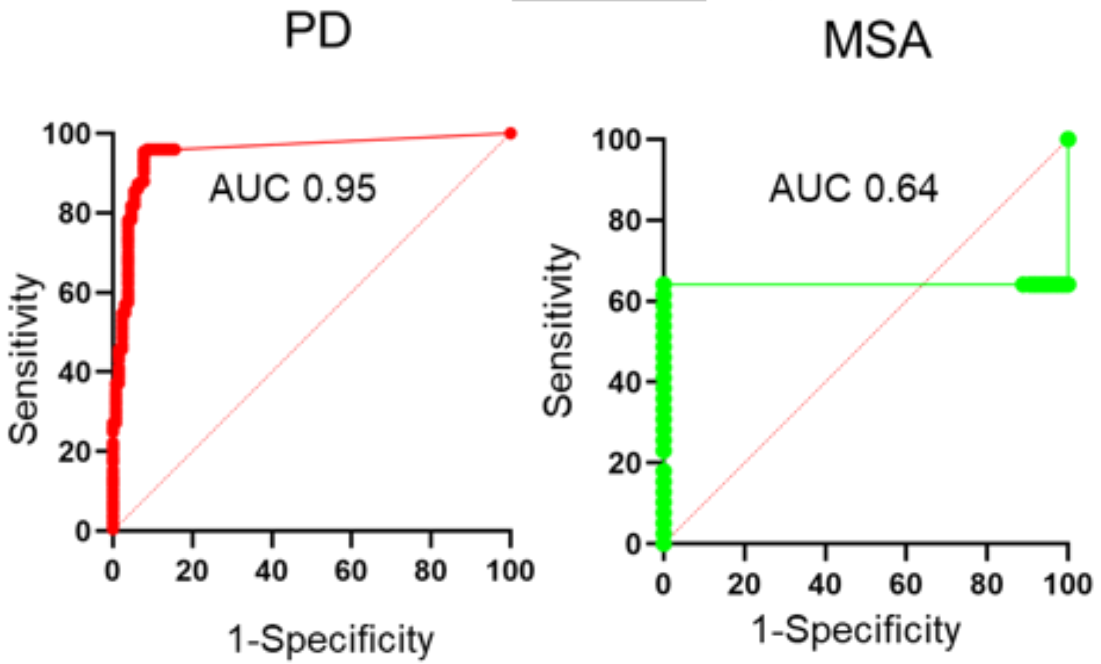


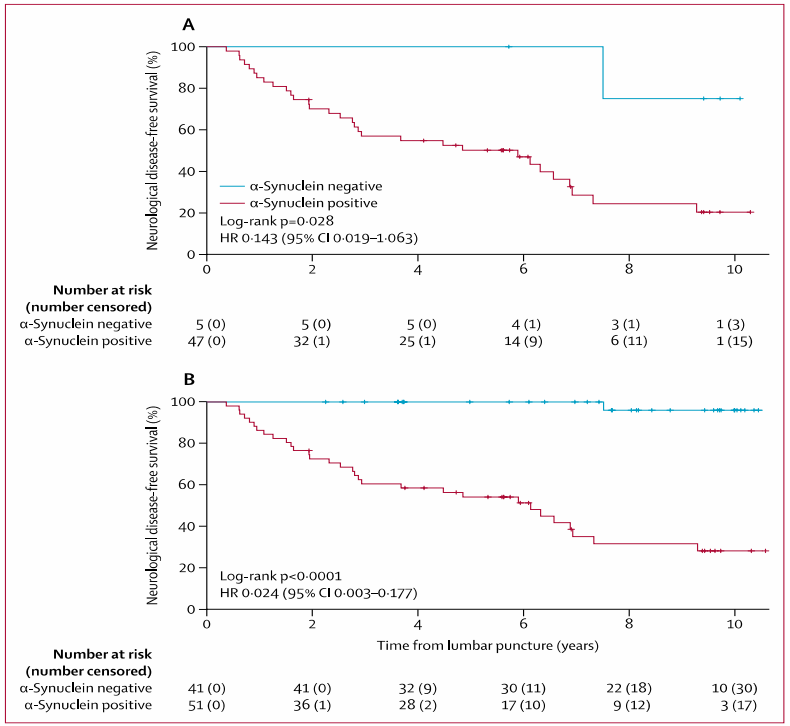
PD: Parkinson's disease
MSA: Multiple system atrophy
DLB:Dementia with Lewy bodies

Okuzumi A, Hatano T, et al. Nature Medicine 2023

α-Synuclein Seeding Amplification Assays (SAA): Performance in Prodromal PD

Detection of α-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study

Alex Iranzo, Graham Fairfoul, Anutra Chumbala Na Ayudhaya, Monica Serradell, Ellen Gelpi, Isabel Vilaseca, Raquel Sanchez-Valle, Carles Gaig, Joan Santamaria, Eduard Tolosa, Renata L Riha, Alison J E Green



Lancet Neurol 2021; 20: 203–12

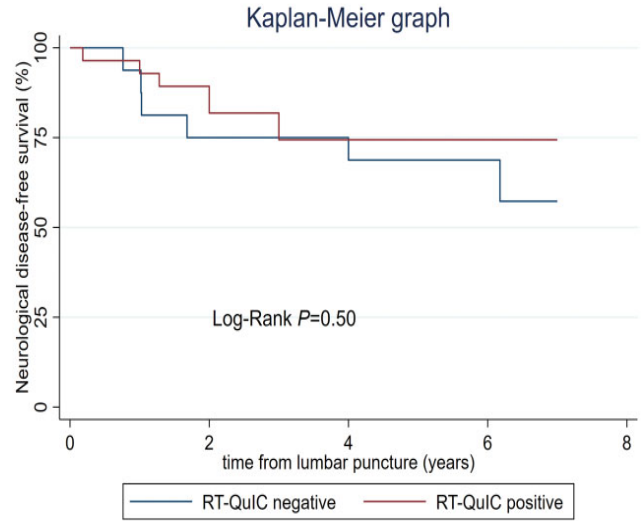
- 52 & 45 iRBD vs 40 & 55 matched HC's
- Baseline CSF a-syn RT-QuIC
- Long term follow-up
- 64%-90% of iRBD vs 4%-10% of HC's RT-QuIC pos
- 31%-62% vs 0 HC's of iRBD converted to PD/DLB
- 64% -97% of converters RT-QuIC positive at baseline

https://doi.org/10.1093/brain/awab431 BRAIN 2022: 145; 584–595 | 362

BRAIN
ORIGINAL ARTICLE

Diagnostic value of cerebrospinal fluid alpha-synuclein seed quantification in synucleinopathies

Ilaria Poggiolini,[1,†] Vandana Gupta,[1,†] Michael Lawton,[2] Seoyun Lee,[1] Aadil El-Turabi,[3] Agustin Querejeta-Coma,[1] Claudia Trenkwalder,[4,5] Friederike Sixel-Döring,[5,6] Alexandra Foubert-Samier,[7,8] Anne Pavy-Le Traon,[9] Giuseppe Plazzi,[10,11] Francesco Biscarini,[12] Jacques Montplaisir,[13,14] Jean-François Gagnon,[13,15] Ronald B. Postuma,[13,16] Elena Antelmi,[17] Wassilios G. Meissner,[8,18] Brit Mollenhauer,[4,5] Yoav Ben-Shlomo,[2] Michele T. Hu[1] and Laura Parkkinen[1]



Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study

Andrew Siderowf, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kieburtz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†*

Lancet Neurol 2023; 22: 407–17

- 1123 PPMI Study Participants 2010-2019
- 545 early PD
- 163 healthy controls

- **51 ‚prodromal PD' subjects (Hyposmia, RBD)**
- **310 asymptomatic LRRK2 or GBA carriers**
- **86% of ‚prodromal' subjects SAA positiv**

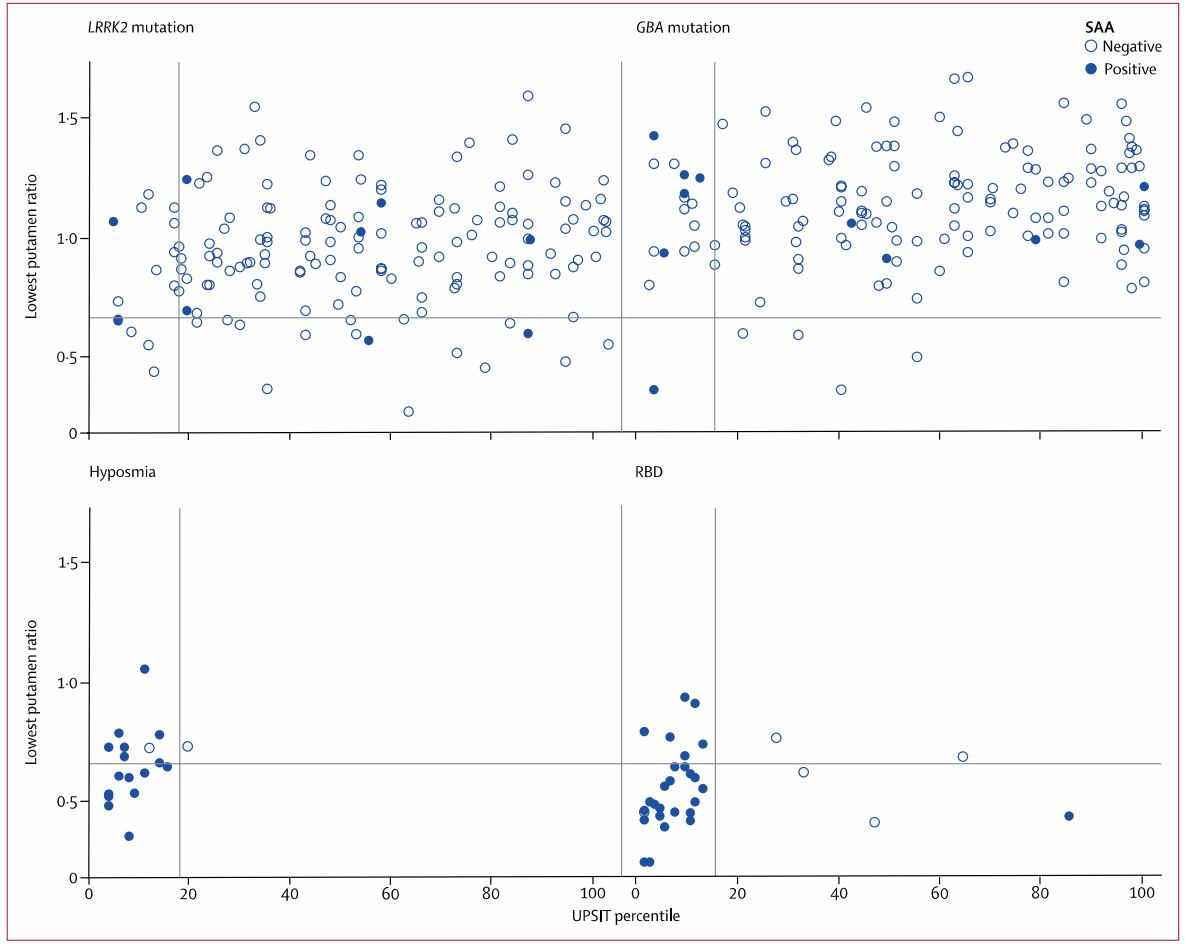


Figure 2: Association between dopamine transporter binding, olfaction, and α-synuclein SAA results among prodromal and non-manifesting carriers of either *LRRK2* or *GBA* variants

Among prodromal and at-risk groups, 44 (86%) of 51 of participants with RBD or hyposmia had positive α-synuclein SAA (16 of 18 with hyposmia, and 28 of 33 with RBD). 25 (8%) of 310 non-manifesting carriers (14 of 159 [9%] LRRK2 and 11 of 151 [7%] GBA) were positive.

Are we Ready for a Biological Definition of Parkinson‘s Disease ?

- **S = α- Synuclein pathology**
  - Positive seeding assay (CSF, skin, olfactory mucosa, blood)
  - (Positive α- Synuclein-PET)
- **G = genetic marker**
  - Monogenic mutation (SNCA, LRRK2,VPS35,CHCHD2; Parkin, PINK1,DJ-1)
  - Risk-Genes (GBA, polygenic risk scores)
- **N = Neurodegeneration**
  - dopaminergic deficit in molecular imaging (FP-CIT Spect, Fluorodopa-PET, 11C-PE2I-PET)
  - MR Indices of nigral pathology (DHN, NM –Imaging)
  - cardiosympathetic denervation (MIBG-Spect)

A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria

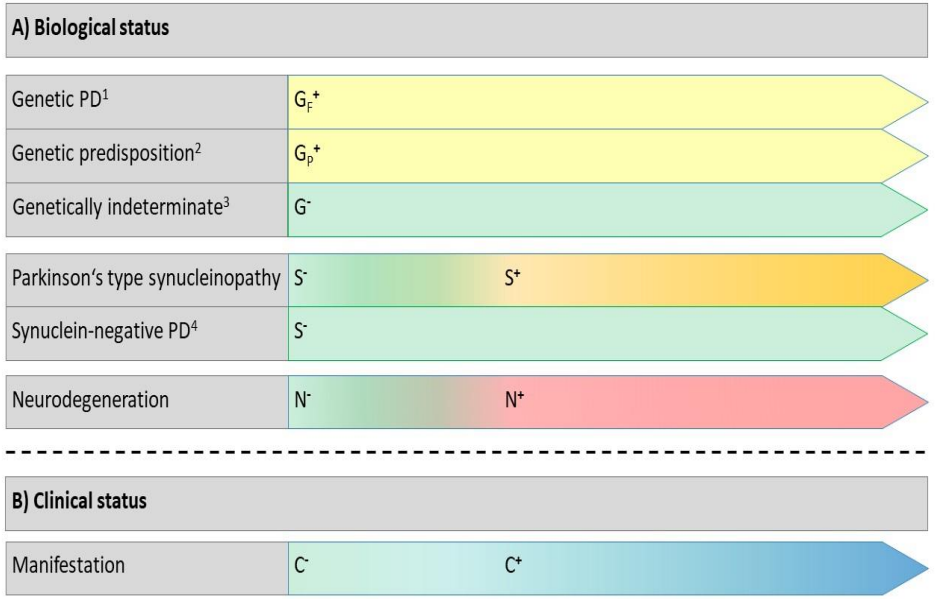
Günter U Höglinger, Charles H Adler, Daniela Berg, Christine Klein, Tiago F Outeiro, Werner Poewe, Ronald Postuma, A Jon Stoessl, Anthony E Lang

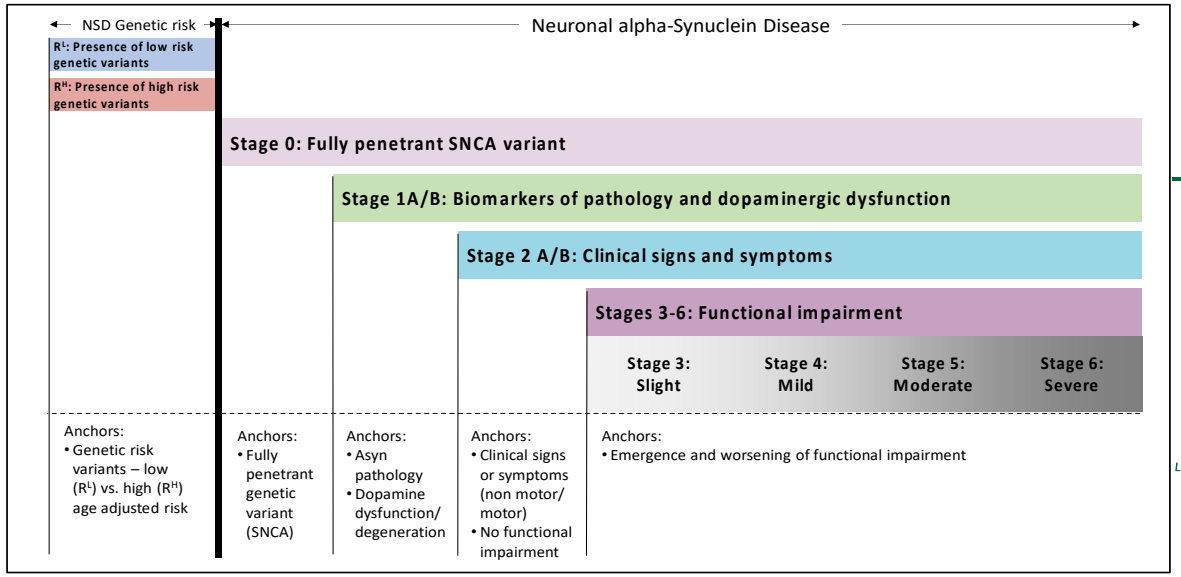
With the hope that disease-modifying treatments could target the molecular basis of Parkinson's disease, even before the onset of symptoms, we propose a biologically based classification. Our classification acknowledges the complexity and heterogeneity of the disease by use of a three-component system (SynNeurGe): presence or absence of pathological α-synuclein (S) in tissues or CSF; evidence of underlying neurodegeneration (N) defined by neuroimaging procedures; and documentation of pathogenic gene variants (G) that cause or strongly predispose to Parkinson's disease. These three components are linked to a clinical component (C), defined either by a single high-specificity clinical feature or by multiple lower-specificity clinical features. The use of a biological classification will enable advances in both basic and clinical research, and move the field closer to the precision medicine required to develop disease-modifying therapies. We emphasise the initial application of these criteria exclusively for research. We acknowledge its ethical implications, its limitations, and the need for prospective validation in future studies.

Lancet Neurol 2024; 23: 191–204

See Comment pages 130 and 133

Department of Neurology, University Hospital, Ludwig-Maximilians-University (LMU) and German Center for Neurodegenerative Diseases, Munich, Germany (Prof G U Höglinger MD); **Munich Cluster for Systems Neurology (SyNergy), Munich, Germany** (Prof G U Höglinger);





A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research

Tanya Simuni, Lana M Chahine*, Kathleen Poston, Michael Brumm, Teresa Buracchio, Michelle Campbell, Sohini Chowdhury, Christopher Coffey, Luis Concha-Marambio, Tien Dam, Peter DiBiaso, Tatiana Foroud, Mark Frasier, Caroline Gochanour, Danna Jennings, Karl Kieburtz, Catherine M Kopil, Kalpana Merchant, Brit Mollenhauer, Thomas Montine, Kelly Nudelman, Gennaro Pagano, John Seibyl, Todd Sherer, Andrew Singleton, Diane Stephenson, Matthew Stern, Claudio Soto, Caroline M Tanner, Eduardo Tolosa, Daniel Weintraub, Yuge Xiao, Andrew Siderowf, Billy Dunn, Kenneth Marek*

Lancet Neurol 2024; 23: 178–90

Parkinson's disease and dementia with Lewy bodies are currently defined by their clinical features, with α-synuclein

Summary

- **Synucleinopathies are currently defined as clinical entities**
- **Clinical diagnostic criteria have major shortcomings**
  - Suboptimal accuracy
  - Insensitive for early disease
  - Do not capture prodromal or pre-clinical disease
  - Agnostic ref pathogenetic subtypes
- **Biomarkers offer major advances for research & clinical practice**
  - Enhance diagnostic accuracy
  - Enable pathogenetic subtyping
  - Allow for a ‚biological‘ definition of disease
  - Facilitate disease-modification trials
  - May ultimately enable disease-prevention programs for PD

From the clinical utility of a-synuclein PET imaging in Multiple System Atrophy to the possible diagnosis of Parkinson's disease

Francesca Capotosti, PhD | ADPD 2024 | March 2024

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.

Disclosures

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

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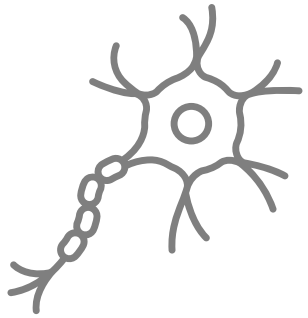
THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

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

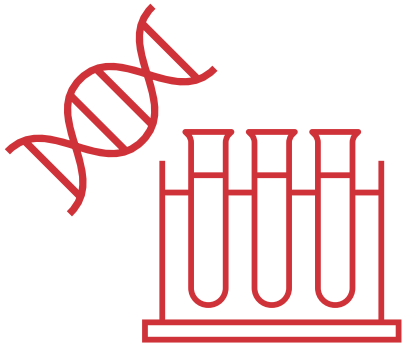
Needed to best enable precision medicine for a-synucleinopathies

Early diagnosis and treatment is key in NDD



- 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

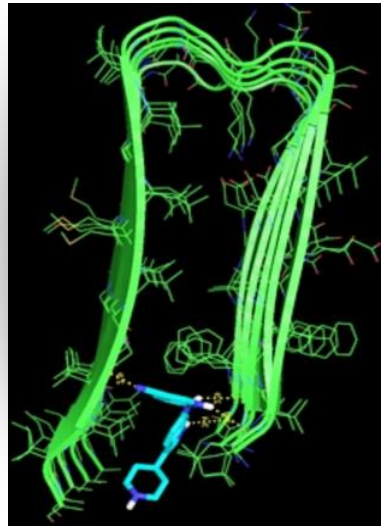
Benefits of PET tracers for imaging have been validated

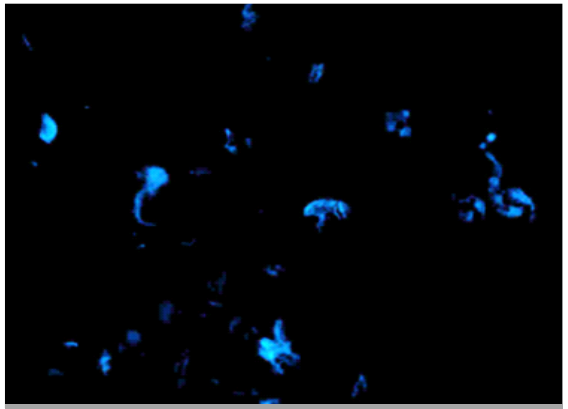
- Better designed clinical trials using PET tracer for recruitment and monitoring
- May enable combination treatment of co-pathologies

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

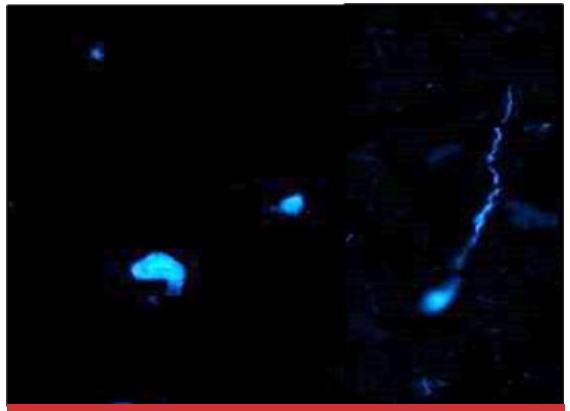
Precision medicine approach enabled by the Morphomer® platform

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

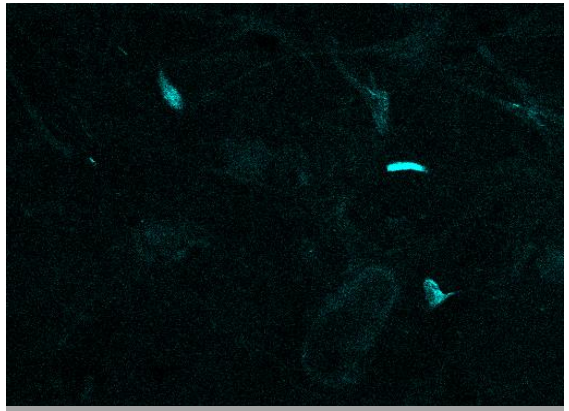




Tau NFTs[3]
PI-2620



a-syn[4] Lewy bodies
ACI-12589



TDP-43[5] inclusions

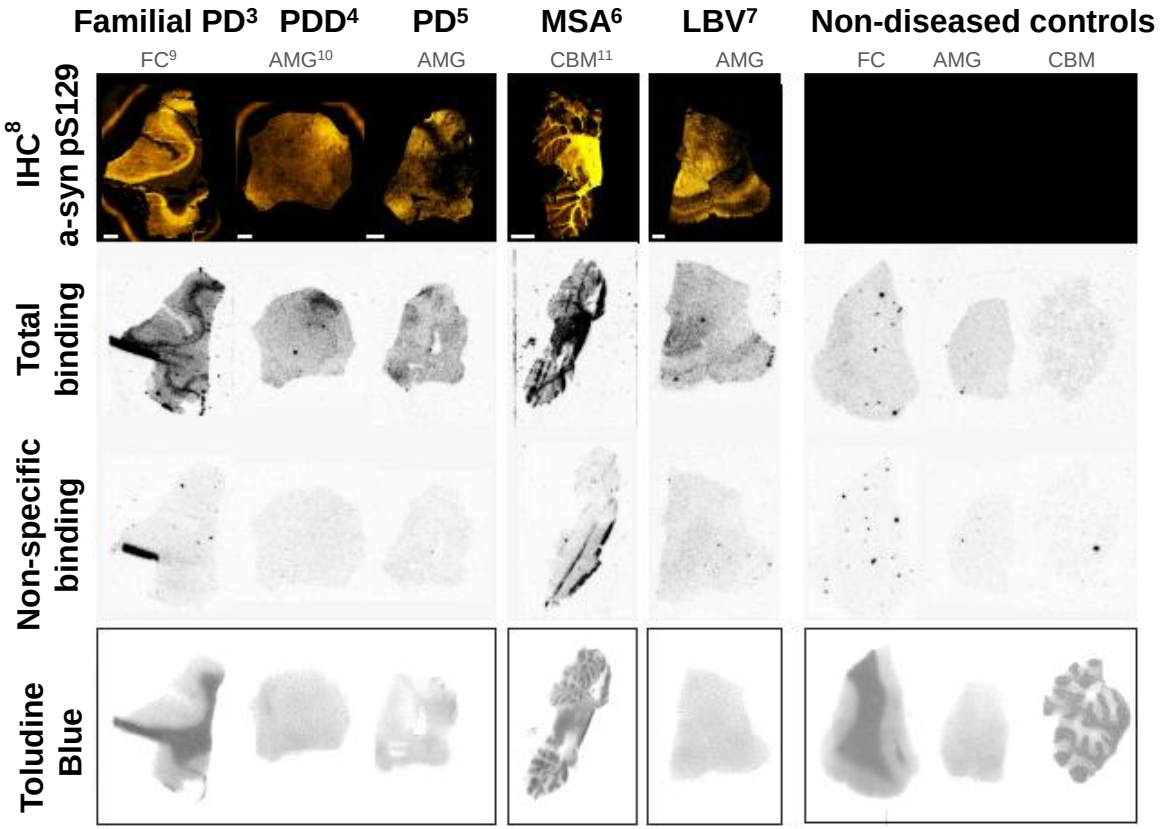
Leverage the Morphomer® small molecule platform:

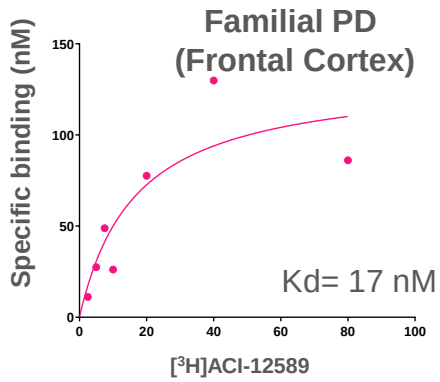
- Non-peptidic, small molecules with CNS-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, TDP-43)
- Pharmacokinetics suitable for brain PET imaging

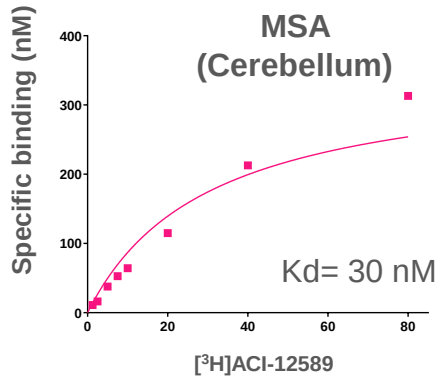
(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) Alpha synuclein; (5) TAR DNA binding protein-43

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

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







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

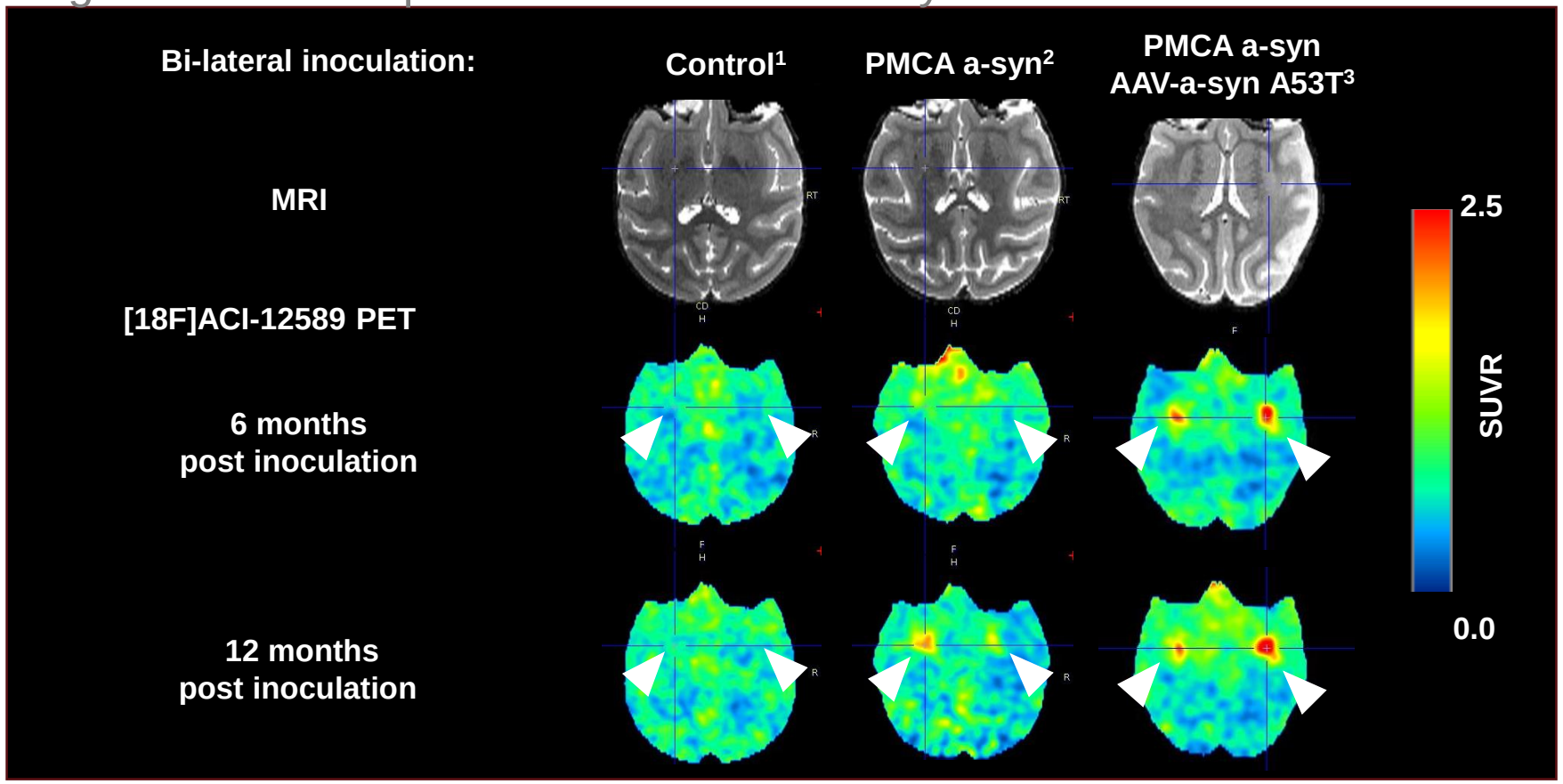
In collaboration with Prof. A. Varrone
Ref.: Smith, Capotosti, et al., Nature Communications 2023

- 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

[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:

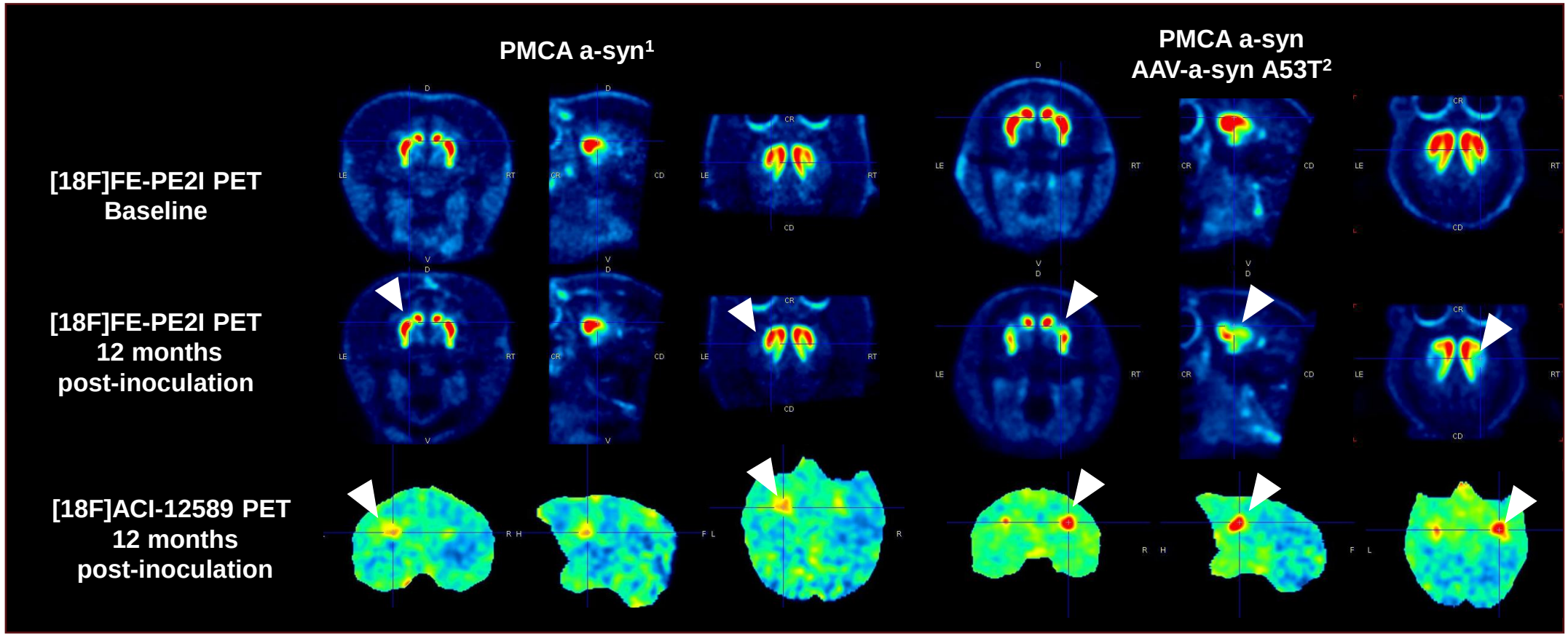
- The higher retention observed in the PMCA-AAV model suggests that the intensity of the PET signal is related to the pathological a-syn load
- A longitudinal increase in [18F]ACI-12589 uptake is observed in two a-syn monkey models

(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 Subtantia Nigra at baseline; (4) Standardized uptake value ratio with whole cerebellum as reference

A-syn PET precedes dopaminergic loss

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

Collaboration with



- 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 Subtantia Nigra

[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

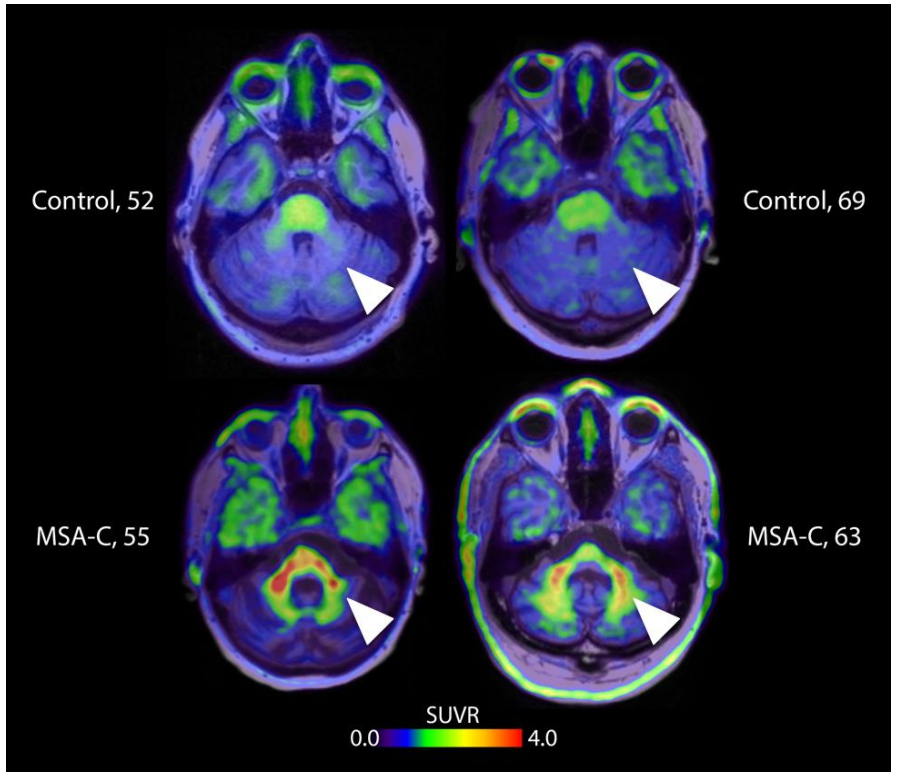
In collaboration with Prof. O. Hansson
Ref.: Smith, Capotosti, et al., Nature Communications 2023

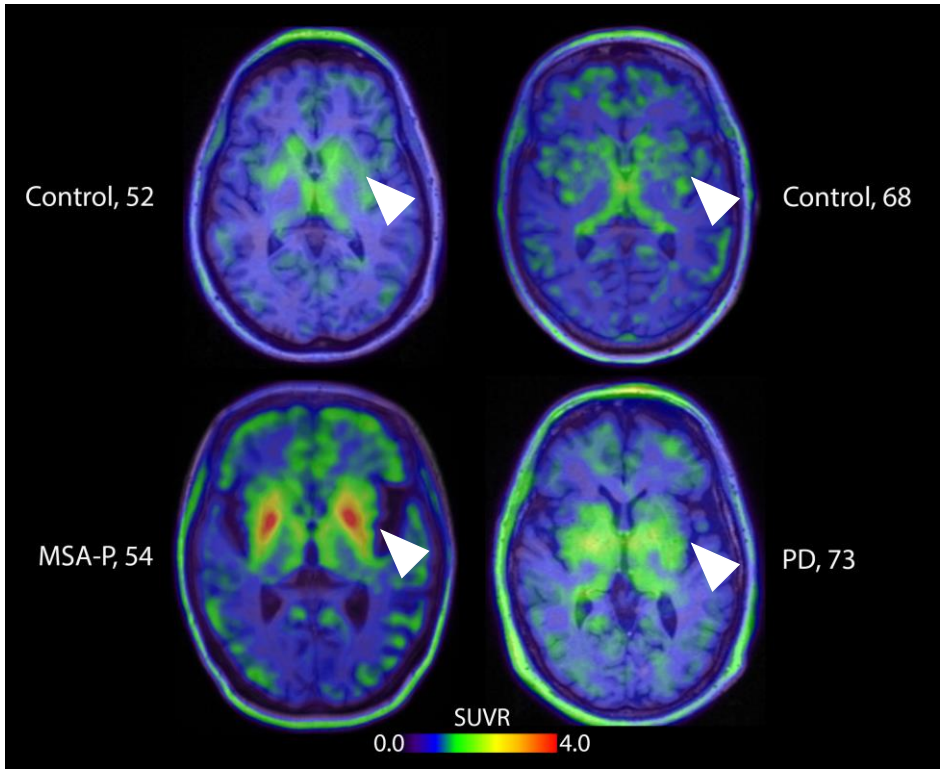
- [18F]ACI-12589 was evaluated in a total of 54 participants; 23 with a-syn-related disorders of which 13 MSA cases
- The initial 25 subjects underwent dynamic 0-90 min scans and the vast majority had arterial blood sampling while following scans were performed with shorter scan time

(1) Positron emission tomography; (2) Alpha-synuclein; (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

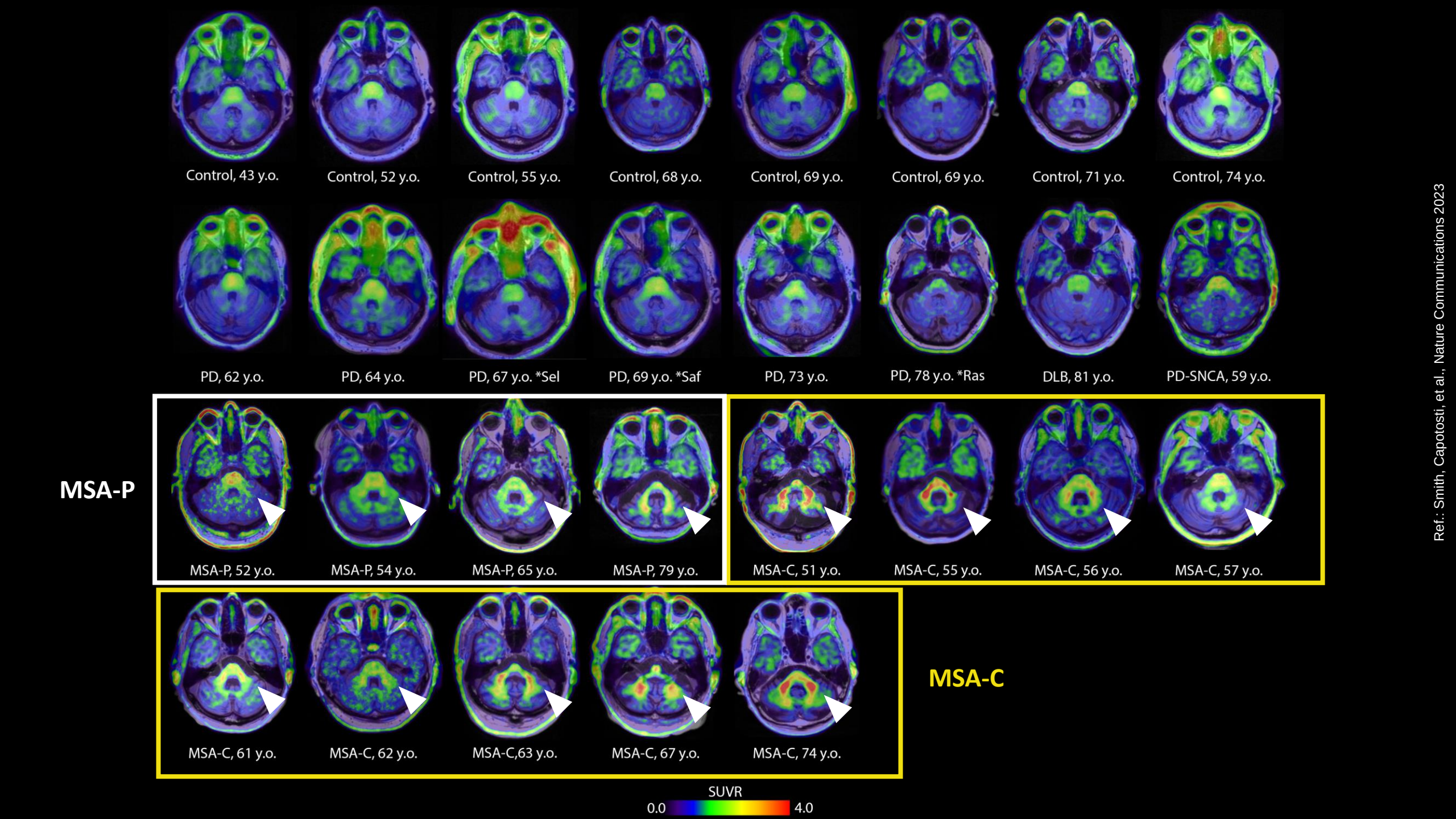
SUVR 60-90 min using occipital cortex as reference region



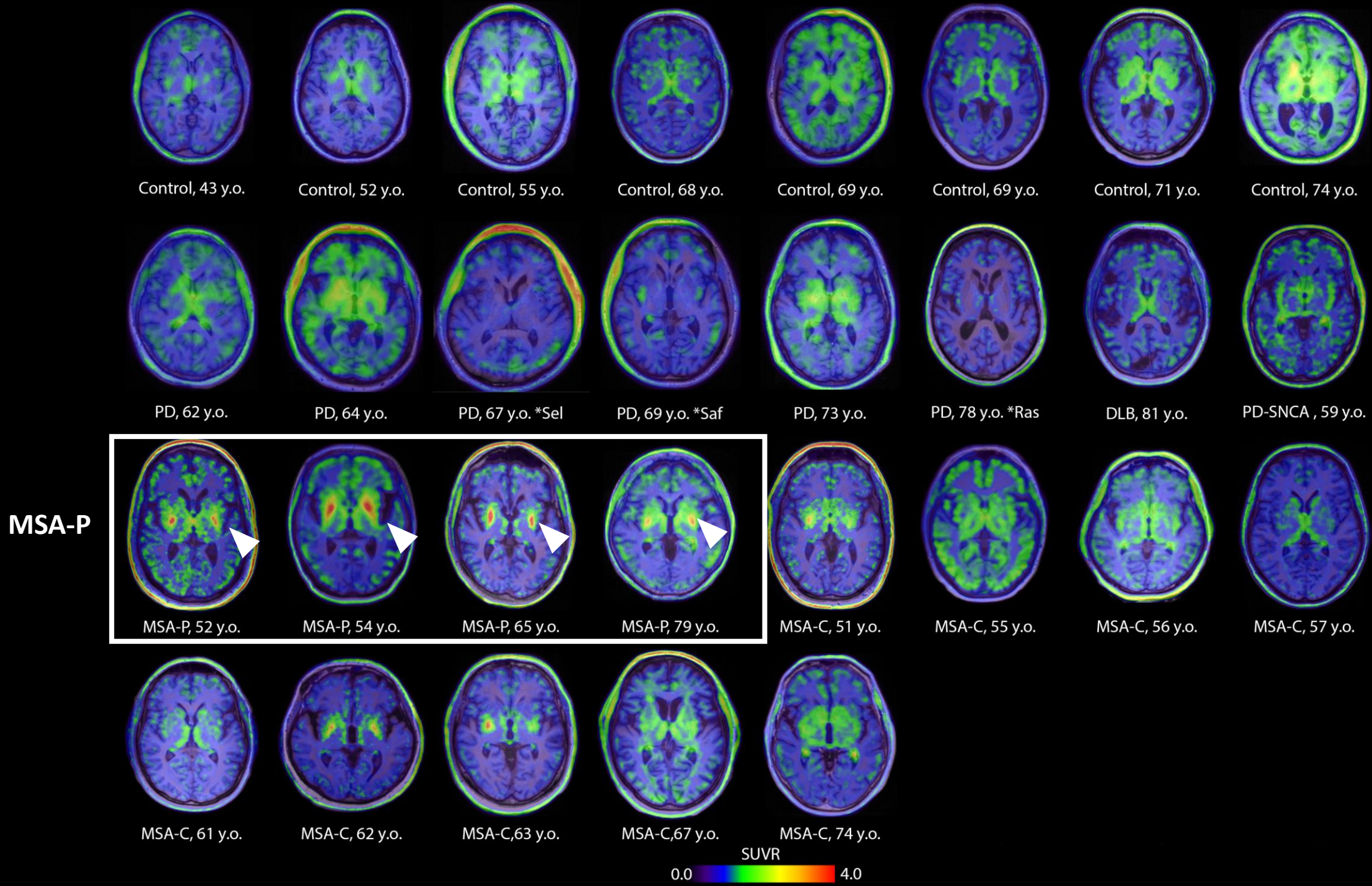


Ref.: Smith, Capotosti, et al., Nature Communications 2023

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



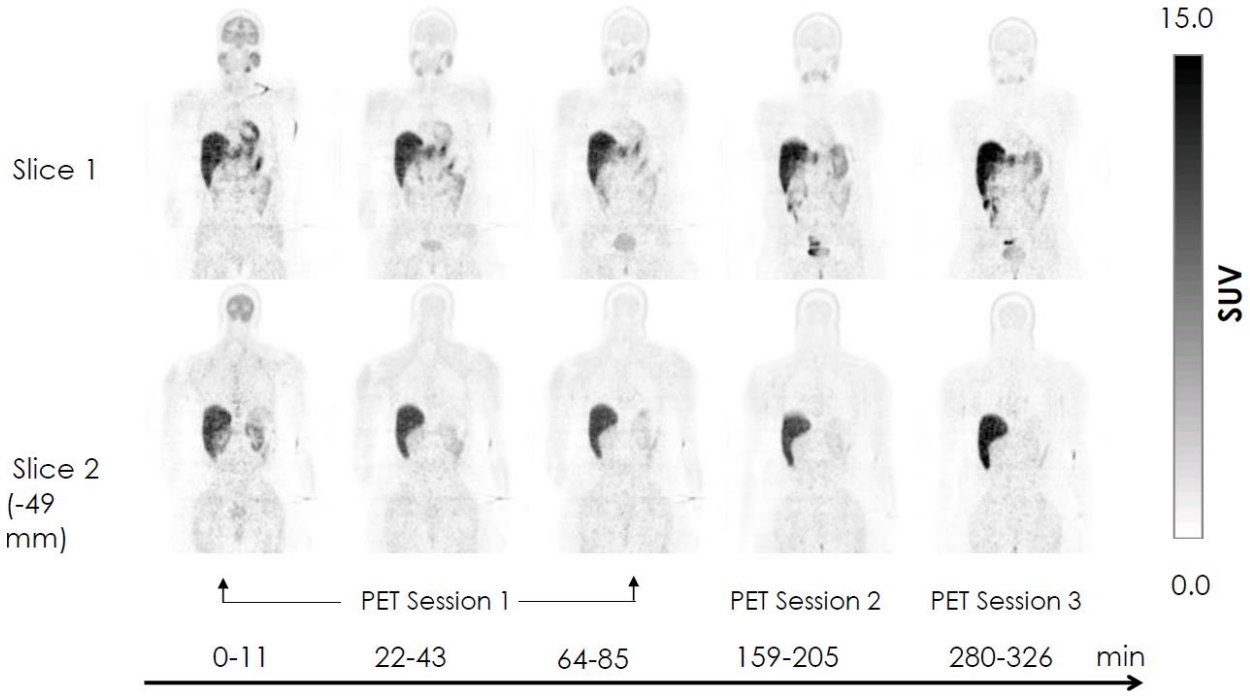
Ref.: Smith, Capotosti, et al., Nature Communications 2023



Ref.: Smith, Capotosti, et al., Nature Communications 2023

[18F]ACI-12589 is ready to be evaluated in longitudinal studies

[18F]ACI-12589 dosimetry in healthy volunteers (3 males and 3 females)



Based on whole-body data of [18F]ACI-12589:

- Elimination occurs mainly via the hepatobiliary route
- Target organ with highest exposure is colon
- The effective dose per 185 MBq (5 mCi) injection is 3.7 mSv for a adult male and 4.09 for an adult female

- [18F]ACI-12589 dosimetry exposure data in line with other 18F-ligands routinely used in clinical practise
- Clinical organ dosimetry data permits several scans per year allowing longitudinal evaluations

[18F]ACI-12589 will improve MSA[1] diagnosis and support precision medicine

Specific & selective

Preclinically, ACI-12589:

- binds specifically and selectively to a-synuclein inclusions in different human synucleinopathy cases
- shows longitudinally increasing uptake in different a-syn[2] monkey models and appearance of PET[3] signal prior dopaminergic loss

First-in-class

- [18F]ACI-12589 is the first tracer detecting pathologic a-synuclein in patients differentiating MSA cases from other synucleinopathies and NDD[4]
- The tracer is ready for evaluation in longitudinal studies

Precision Medicine

[18F]ACI-12589 will:

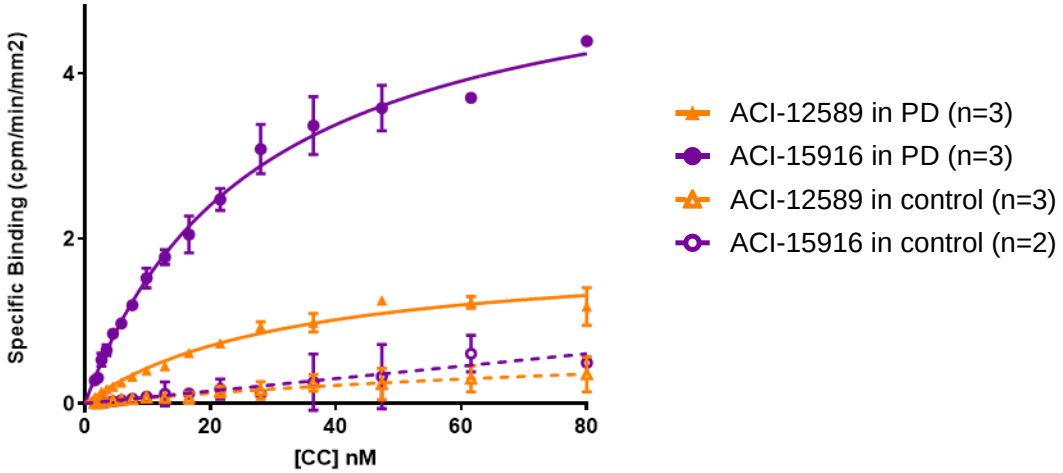
- significantly improve the diagnosis of MSA
- enable Precision Medicine and biomarker-based development in MSA

(1) Multiple system atrophy; (2) Alpha-synuclein; (3) Positron emission tomography; (4) Neurodegenerative disease

ACI-15916: Next generation a-syn[1] tracer for PD[2]

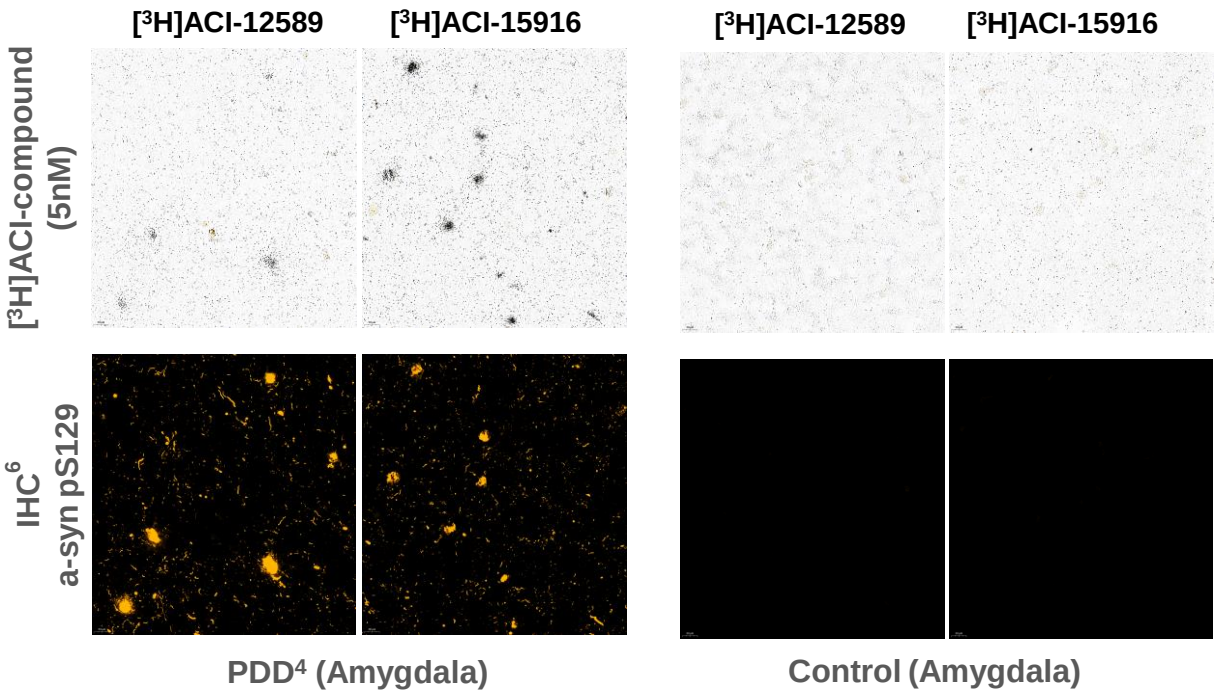
Improved target occupancy on brain tissue from different a-synucleinopathy cases

Saturation binding on total PD brain homogenates or tissue sections



Tracer	ACI-12589	ACI-15916	ACI-15916
Donor	Idiopathic PD#1		Idiopathic PD #2
B_{max} (nM)	80	162	127
K_d (nM)	65	35	18
B_{max}/K_d	**1**	**5**	**7.5**

Target engagement by high resolution autoradiography



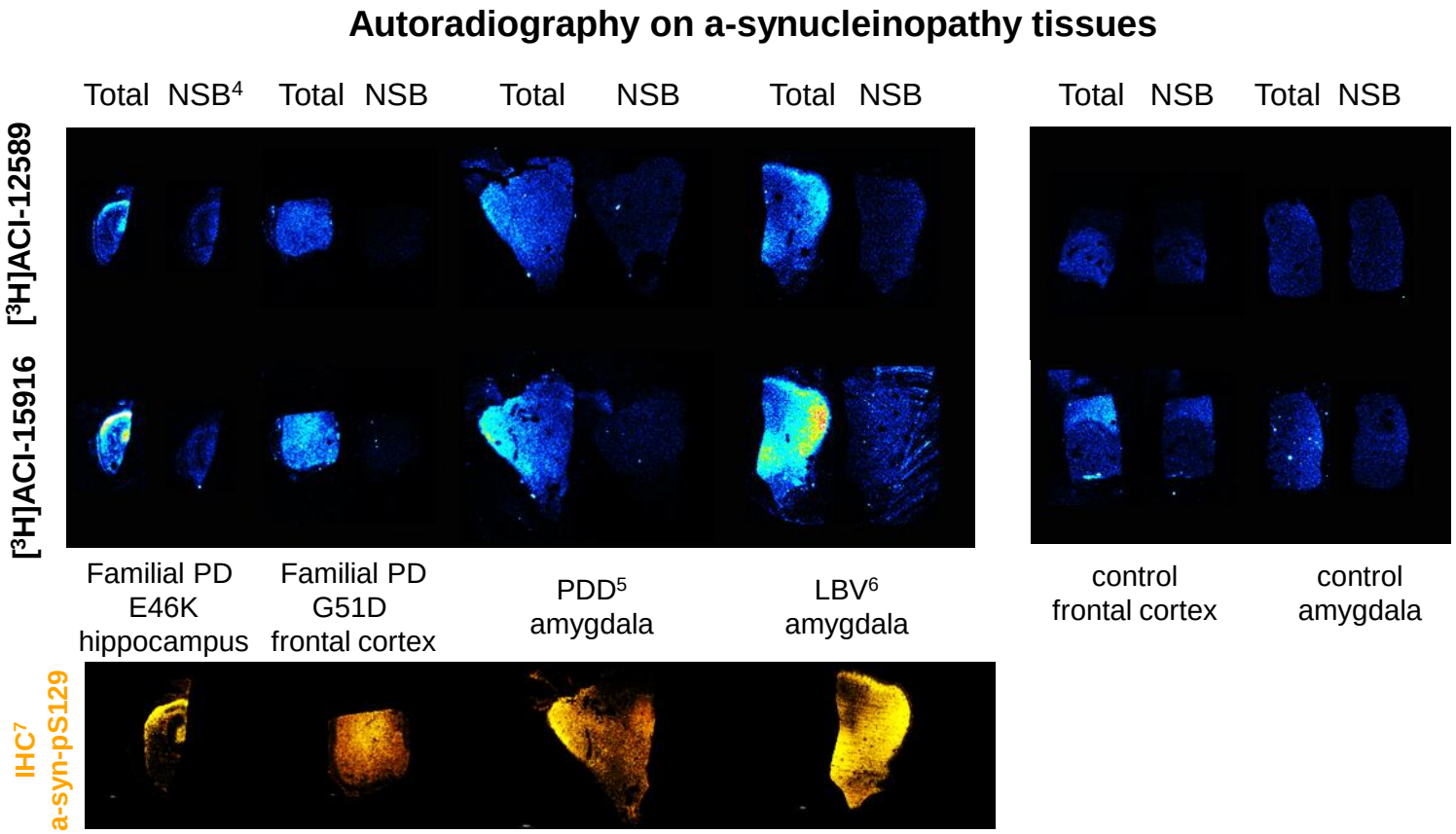
Ref: AC Immune unpublished data

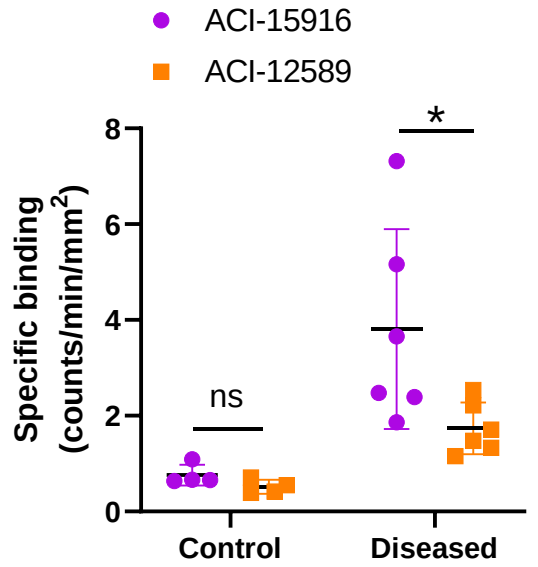
- The newly identified ligand, ACI-15916, shows significantly improved target occupancy on pathological a-syn aggregates in brain homogenates and sections from different a-synucleinopathies

(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

ACI-15916: Next generation a-syn[1] tracer for PD[2]

Specific binding on brain tissue from different a-synucleinopathy cases





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

Ref: AC Immune unpublished data

- ACI-15916 shows significantly improved specific binding to pathological a-syn aggregates in brain sections from different a-synucleinopathies

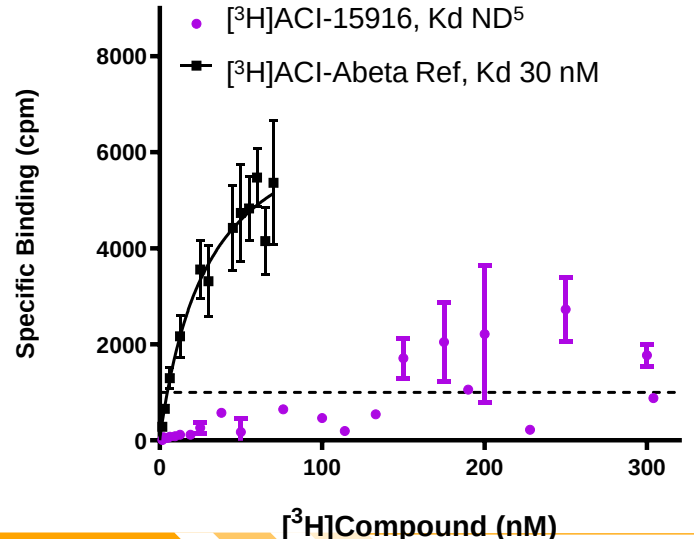
(1) Alpha-synuclein; (2) Positron emission tomography; (3) Parkinson's disease; (4) Nonspecific binding (5) Parkinson's disease with dementia; (6) Lewy body variant of Alzheimer's disease; (7) Immunohistochemistry

AC Immune

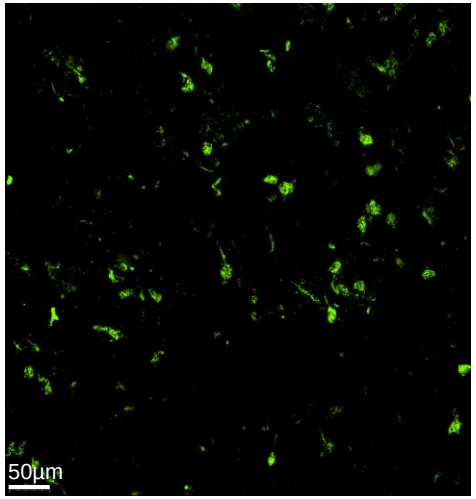
ACI-15916: Next generation a-syn[1] tracer for PD[2]

Selectivity assessment using Alzheimer's disease tissue

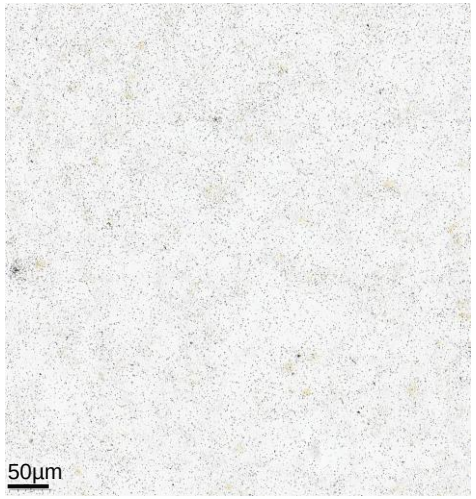
Radiobinding with AD[4] brain homogenates (Frontal Cortex)



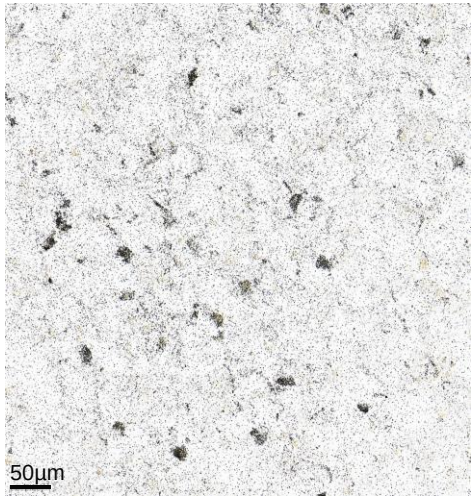
High-resolution ARG[6] on Tau rich AD sections (Entorhinal Cortex)



NFT[7] (Thioflavin S)



[3H]ACI-15916



[3H]PI-2620
Tau reference

Ref: AC Immune unpublished data

- ACI-15916 displays excellent selectivity versus common co-pathologies such as Abeta, 3R and 4R Tau, as well as TDP-43
- ACI-15916 is selective versus common PET tracer off-targets such as MAO-A nor MAO-B

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

ACI-15916: Next generation a-syn[1] tracer for PD[2]

Next-generation a-syn diagnostics

The newly identified [18F]ACI-15916 has the potential to detect synucleinopathies including PD, having:

- significantly improved target occupancy on pathological a-syn
- capability to detect very small aggregates
- excellent selectivity versus potential co-pathologies and no off-target binding *in vitro*
- a pharmacokinetic profile in monkey suitable for its use as brain imaging agent

(1) Alpha-synuclein; (2) Parkinson's disease

Acknowledgements

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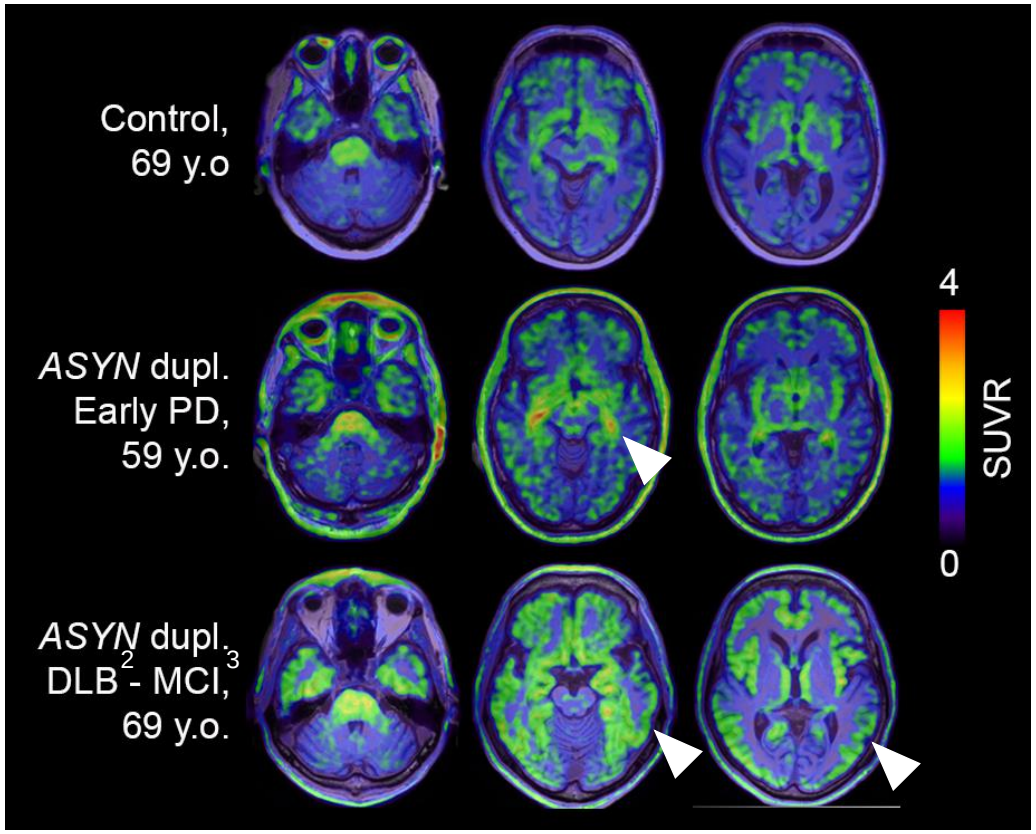
Ronald Melki
Philippe Hantraye
Romina Aron Badin

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

SUVr 60-90 minutes using cerebellar grey as reference region



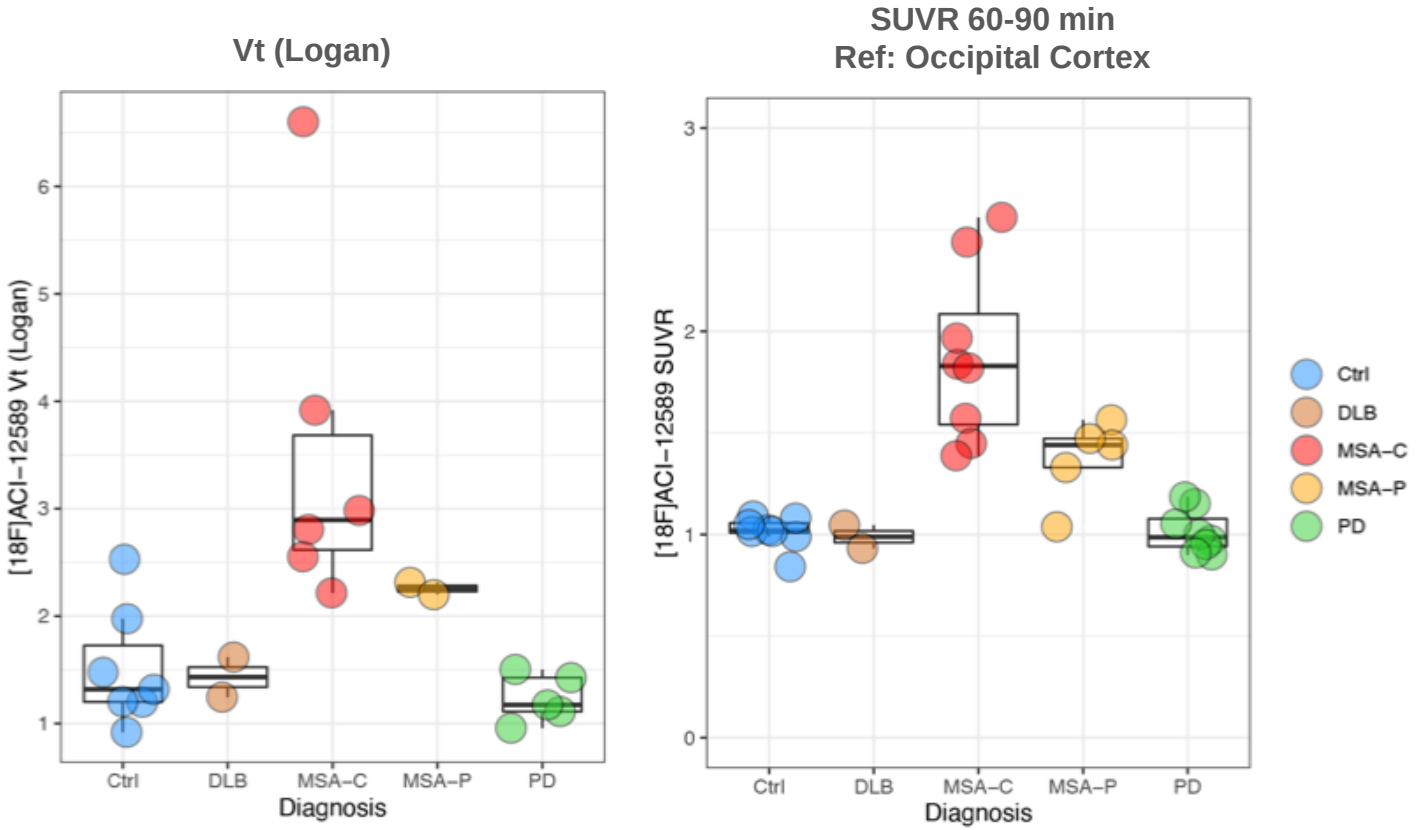
- Signal retention is observed in disease-relevant brain regions in genetic PD cases (SNCA duplication carriers)
- The retention is higher in the more advanced symptomatic case
- Signal distribution pattern is compatible with specificity of the signal for pathological a-syn

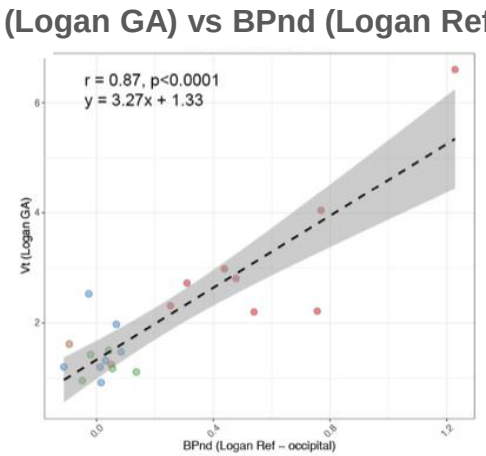
(1) Parkinson's disease; (2) Dementia with Lewy Body; (3) Mild cognitive impairment

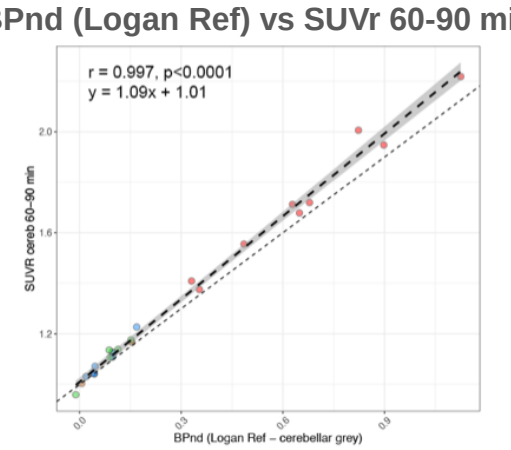
Ref.: Smith, Capotosti, et al., Nature Communications 2023

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

Signal quantification in the cerebellar white matter







Diagnosis: Control DLB MSA-C MSA-P PD

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

Ref.: Smith, Capotosti, et al., Nature Communications 2023

Fabrizio Stocchi
Department of Neurology
University San Raffaele
Rome, Italy

Future Treatment of Parkinson's disease:

Disclosures: Prof Stocchi received consultant honorarium from:

- Chiesi Ltd.
- GlaxoSmithKline Plc.
- Impax Laboratories Inc.
- Lundbeck Ltd
- Teva UK Limited
- UCB Pharma Ltd
- Merck & Co. Inc
- Zambon Pharma
- Novartis AG
- Sunovion
- Neuroderm
- Abbvie
- Britannia
- Lusofarmaco
- Ever pharma
- BIAL pharma
- ROCHE
- BIOGEN
- IRLAB

Decreasing the expression of a-synuclein

- Manipulation of α-syn levels by gene silencing with RNA interference has been shown to be beneficial in normalizing α-syn expression and improve motor function in experimental studies.
- Fine-tuned balance is necessary to avoid nigrostriatal neurotoxicity caused by excess downregulation
- DNA methylation at SNCA intron 1 is a regulator of the α-syn transcription, providing a target for tight of α-syn expression levels.
- Novel clustered regularly interspaced short palindromic repeats technology has been successfully used in fine tuning the downregulation of SNCA expression in stem cell-derived dopaminergic neurons, suggesting a new approach

- McCormack et al. 2010; Takahashi et al. 2015, Kantor et al. 2018

Alpha-synuclein targeting SMEs

Small molecules	Development status
UCB0599 **UCB/Novartis**	Phase 2
ATH434 **Alterity Therapeutics/Takeda**	Phase 2
Anle138b **Modag**	Phase 1b
Mor a-syn small molecule aggregation inhibitors **AC Immune**	Preclinical

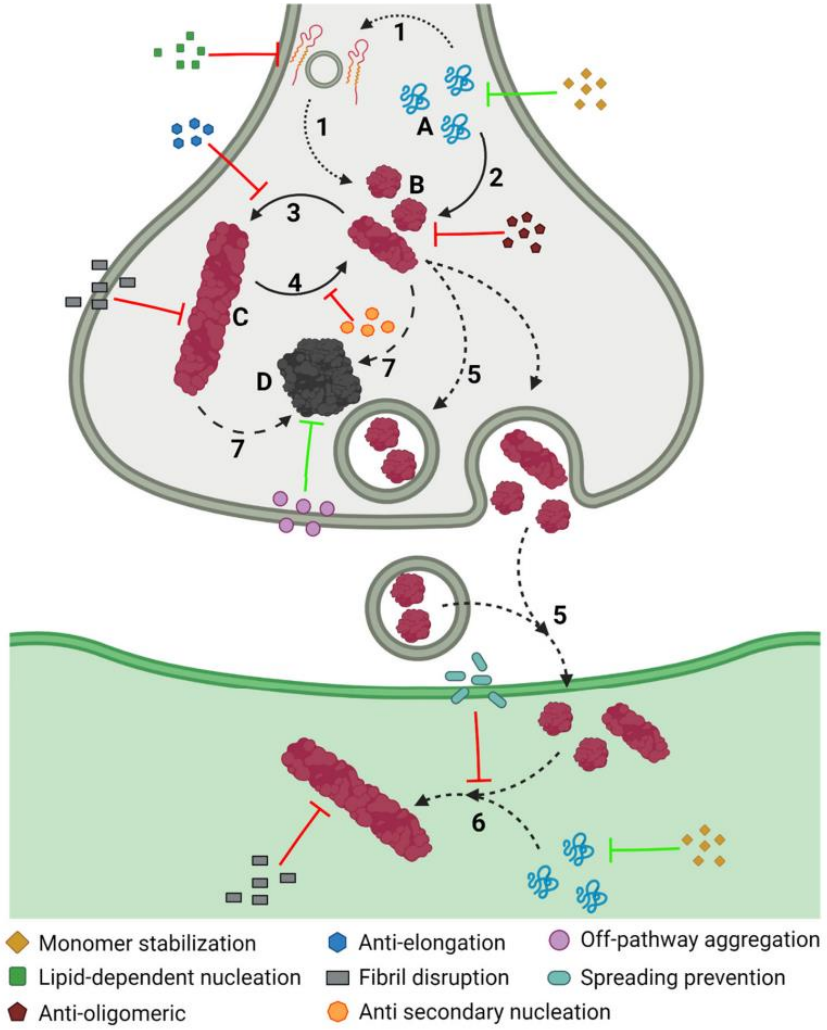


Figure 6. Inhibiting α-Syn aggregation. Schematic representation of the different mechanisms

Peña-Díaz et al., Pharmaceutics, 2023

ORKESTRA study (NCT04658186), with daily oral administration of UCB0599

- UCB0599 is a small-molecule α-synuclein aggregation inhibitor.
- UCB0599 is a cyclic peptidomimetic compound designed to interact with the C-terminal domain of α-synuclein and prevent it from binding to membranes and oligomerizing there.
- UCB0599, aka NPT-200-11, is a second-generation compound, optimized for oral bioavailability and brain entry.
- In phase I/IB study conducted on PD patients UCB0599 was generally well tolerated with no significant safety or tolerability concerns

Smit JW Mov Dis 2022

ATH434 Alterity therapeutics

- ATH434 (formally called PBT434) in preclinical models of Parkinson's disease and shown that it is brain-penetrant, reduces iron accumulation and iron-mediated redox activity, provides neuroprotection, inhibits alpha synuclein aggregation and lowers the tissue levels of alpha synuclein.
- The compound was well-tolerated in a first-in-human oral dosing study in healthy and older volunteers with a favorable, dose-dependent pharmacokinetic profile.
- Phase II study on MSA patients is ongoing

- Finkelstein J Parkinsons Dis. 2022

Anle138b: general inhibitor of protein aggregation

- Anle138b is an oral, brain-penetrant, general inhibitor of protein aggregation. It was identified in a high-throughput screen for small-molecule inhibitors of α-synuclein and prion protein oligomerization. The compound is being developed for treatment of the rapidly progressing synucleinopathy multiple-system atrophy (MSA) and for Parkinson's disease (PD). It could potentially be applied to other synucleinopathies, such as dementia with Lewy bodies (DLB).

Efficacy and Safety of Buntanetap (Annovis BIO) Compared With Placebo in PD (phase II)

- Buntanetap is an orally bioavailable small molecule derived via a biochemical synthetic pathway, which was discovered at the National Institutes of Aging (Bethesda, Maryland).
- Buntanetap suppresses the translation of the mRNAs of APP, tau, αSYN and other neurotoxic aggregating proteins by enhancing the binding of the atypical iron response element (IRE) in those neurotoxic proteins' mRNAs' 5'UTR regions to iron regulatory protein 1 (IRP1) in high iron.
- A treatment strategy that targets toxic species points to the possibility that better clinical outcomes for PD and AD might be achieved by reducing the levels of toxic species found in both

Fang C J Prev Alzheimers Dis. 2023

Small molecules

- Heat shock proteins (HSPs) are small molecular chaperones that serve in protein homeostasis and prevent protein aggregation and toxicity in conditions of cellular stress.
- Several HSPs have been observed as components of Lewy body inclusions, and manipulation of their expression in in-vitro and in-vivo models has been shown to modulate α-syn aggregation

- Sinnige et al. 2020

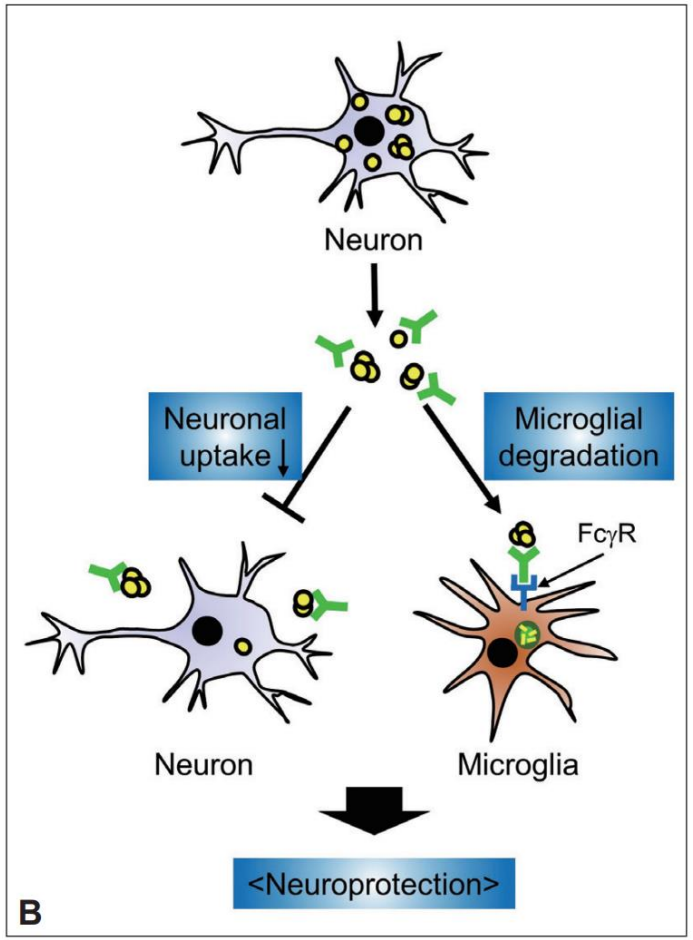
Stimulation of the degradation of extracellular α-syn aggregates

- α-syn extracellular degradation can be stimulated through active and passive immunotherapies

Active immunotherapy	Passive immunotherapy
Immune system stimulation to produce antibodies	Direct administration of antibodies

George S, et al. Immunotherapy in Parkinson's disease: micromanaging alpha-synuclein aggregation. *J Parkinsons Dis*. 2015;5(3):413-424. doi: 10.3233/JPD-150630.

Alpha-synuclein targeting immunotherapies in clinical development



Jun Sung Lee et al., Journal of Movement Disorders 2016

Active immunotherapy	Development status
ACI-7104.056 **AC Immune**	Phase 2
UB-312 **Vaxxinity**	Phase 1

Monocloncal antibodies	Development status
Prasinezumab **Prothena / Roche**	Phase 2
Lu AF82422 **Lundbeck / Genmab**	Phase 2
MEDI-1341 **MedImmune / Takeda**	Phase 1
BAN0805 **BioArctic / AbbVie**	Phase 1
UCB7853 **UCB / Novartis**	Phase 1

Active immunisation for Parkinson's disease: AFFITOPE PD01A/PD03A (ACI-7104.056)

- Novel anti α-syn vaccines are being tested in a phase 1 clinical trial
- The synthetic C-terminal peptides (PD01A and/or PD03A) mimic the peptide sequence of α-syn
- The clinical trial showed induced production of antibodies targeting α-syn and reduced α-syn aggregates
- The antigenic complex KLH-peptide was used to stimulate an immunologic response by B cells, but not by T cells, avoiding an autoimmune response

Mandler M, et al. Next-generation active immunization approach for synucleinopathies: implications for Parkinson's disease clinical trials. *Acta Neuropathol*. 2014;127(6):861-879. doi: 10.1007/s00401-014-1256-4.

Active immunisation: UBITh

- Synthetic T helper peptides
- Linked to target epitopes
- Overcames immune tolerance
- Induces B-cell humoral response
- No T-cell-mediated toxicity

- Data on human study were published by Hui Jing Yu et al. on Movement Disorders Jul 2022

Passive immunisation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Prasinezumab in Early-Stage Parkinson's Disease

G. Pagano, K.I. Taylor, J. Anzures-Cabrera, M. Marchesi, T. Simuni, K. Marek, R.B. Postuma, N. Pavese, F. Stocchi, J.-P. Azulay, B. Mollenhauer, L. López-Manzanares, D.S. Russell, J.T. Boyd, A.P. Nicholas, M.R. Luquin, R.A. Hauser, T. Gasser, W. Poewe, B. Ricci, A. Boulay, A. Vogt, F.G. Boess, J. Dukart, G. D'Urso, R. Finch, S. Zanigni, A. Monnet, N. Pross, A. Hahn, H. Svoboda, M. Britschgi, F. Lipsmeier, E. Volkova-Volkmar, M. Lindemann, S. Dziadek, Š. Holiga, D. Rukina, T. Kustermann, G.A. Kerchner, P. Fontoura, D. Umbricht, R. Doody, T. Nikolcheva, and A. Bonni, for the PASADENA Investigators and Prasinezumab Study Group*

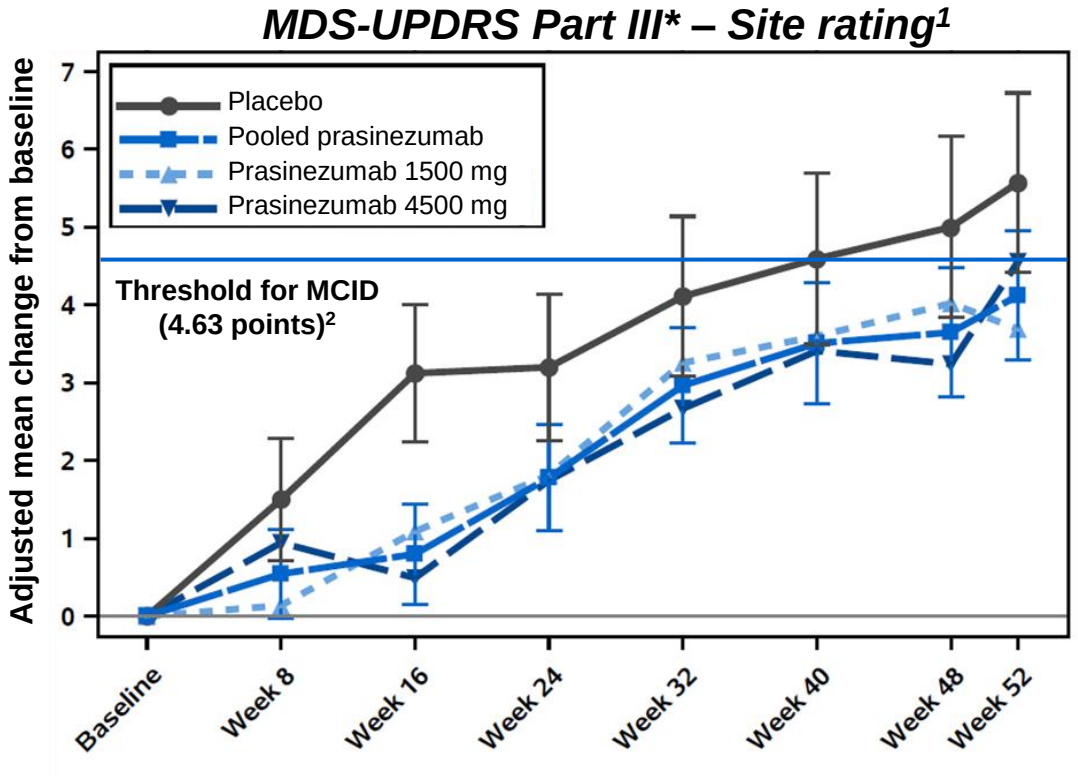
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Cinpanemab in Early Parkinson's Disease

A.E. Lang, A.D. Siderowf, E.A. Macklin, W. Poewe, D.J. Brooks, H.H. Fernandez, O. Rascol, N. Giladi, F. Stocchi, C.M. Tanner, R.B. Postuma, D.K. Simon, E. Tolosa, B. Mollenhauer, J.M. Cedarbaum, K. Fraser, J. Xiao, K.C. Evans, D.L. Graham, I. Sapir, J. Inra, R.M. Hutchison, M. Yang, T. Fox, S. Budd Haeberlein, and T. Dam, for the SPARK Investigators*

Prasinezumab reduced clinical decline in motor signs compared to placebo based on MDS-UPDRS Part III score



Pooled: –1.44, 80% CI=(–2.84, –0.05); **–25.9%**
Prasinezumab 1500 mg: –1.88, 80% CI=(–3.49, –0.27); **–33.8%**
Prasinezumab 4500 mg: –1.02, 80% CI=(–2.64, 0.61); **–18.2%**

CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MAO-B, monoamine oxidase B; MCID, Minimal Clinically Important Difference; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; MMRM, mixed-effect model repeated measures; PD, Parkinson's disease.
* Patients who started symptomatic PD treatment contribute until the last visit before symptomatic PD treatment is started. Bars represent 80% CI. Estimates are based on an MMRM with the following covariates: MAO-B inhibitor at baseline (yes/no), treatment, week, age <60 versus ≥60, sex, DaT-SPECT putamen binding ratio (contralateral to most clinically affected side), baseline MDS-UPDRS corresponding endpoint. Pooled-dose analysis is a pre-specified exploratory analysis. 4500 mg for ≥65 kg; 3500 mg for <65 kg. Data readout correct based on snapshot from January 2020.
1. Pagano G, et al. *Eur J Neurol.* 2021; 21:Suppl 1 (OPR-104). Presented at virtual EAN 2021. 2. Pagano G, et al. *N Engl J Med.* 2021; In submission.

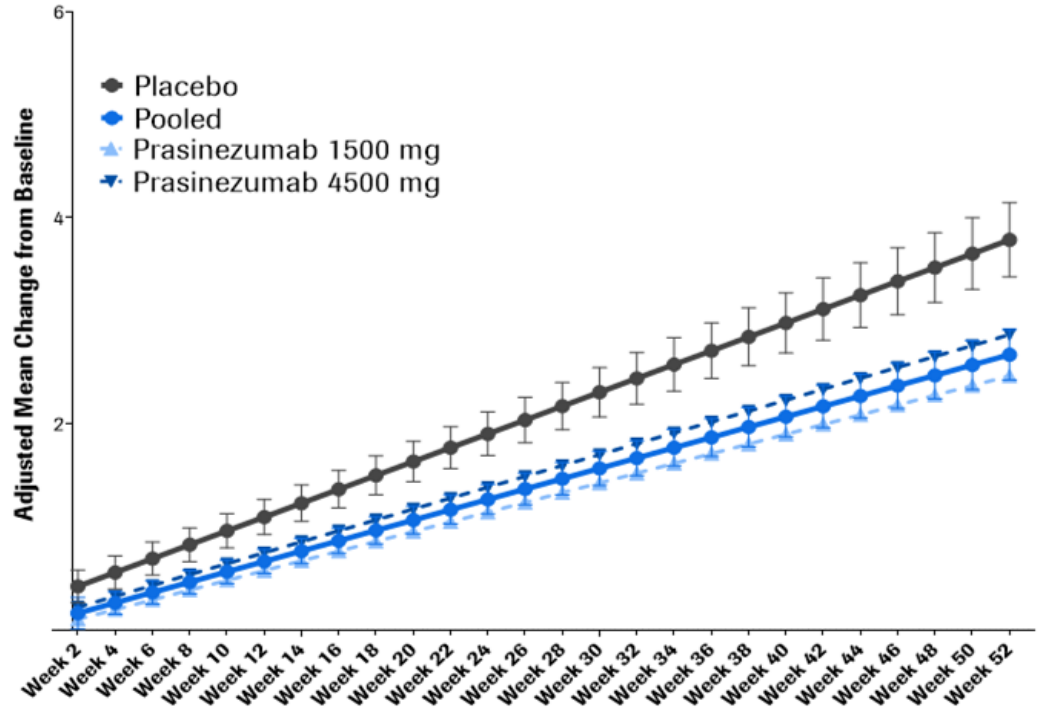
Prasinezumab reduced clinical decline confirmed by digital measures of progression (slope analysis)

Digital measures included in the Roche Parkinson's Disease Mobile Application v2

PASSIVE MONITORING		
Bradykinesia and Activities of Daily Living		
Gait	Arm Swing & Tremor	Mobility & Sociability
Daily	Daily	Daily

ACTIVE TESTS									
Bradykinesia			*Tremor/ Bradykinesia*	*Tremor*			*Rigidity/ Postural Instability*		*Cognition*
Draw A Shape	Dexterity	Hand Turning	Speech	Phonation	Postural Tremor	Rest Tremor	Balance	U-Turn	Cognitive Test (SDMT)
Bradykinesia Days (Every 2nd Day)			Alternating		Tremor and Stability Days (Every 2nd Day)				Fortnightly

Digital PASADENA Motor Score[1]



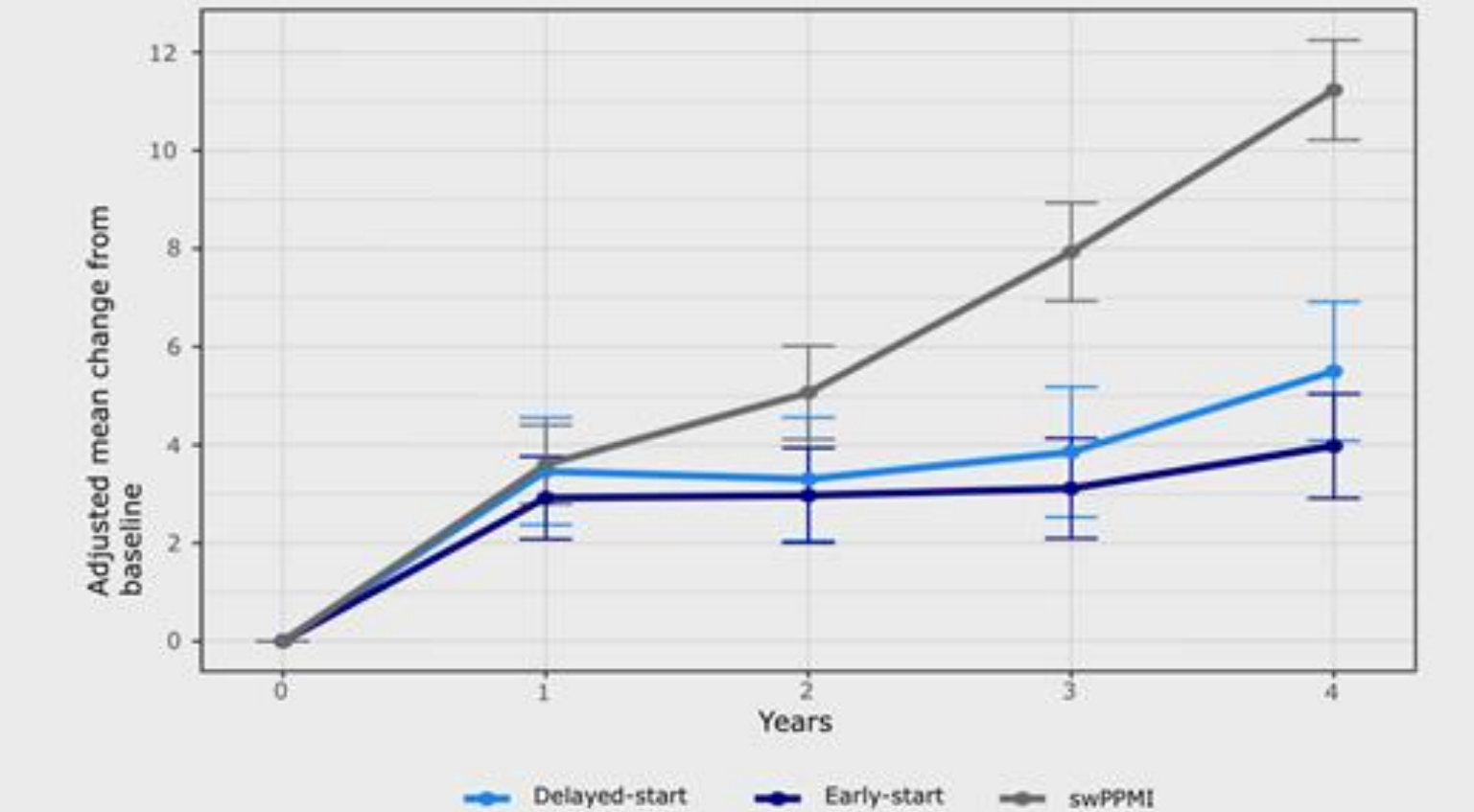
Pooled: –0.030, 80% CI=(–0.050, –0.010); **–25.0%**
Prasinezumab 1500 mg: –0.040, 80% CI=(–0.063, –0.017); **–30.3%**
Prasinezumab 4500 mg: –0.029, 80% CI= (–0.052, –0.006); **–21.5%**

CI, confidence interval; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; SDMT, Symbol Digit Modalities Test.
Pooled-dose analysis is a pre-specified exploratory analysis. 4500 mg for ≥65 kg; 3500 mg for <65 kg.

•The digital PASADENA motor score was built from 80% bradykinesia features and 20% resting tremor features using blinded data from 150 PASADENA patients prior to unblinding.

•1. Horvath K, et al. *Mov Disord.* 2015; 21:1421–1426.

Adjusted mean change from baseline in MDS-UPDRS Part III in OFF state
Prasinezumab versus PPMI coort, Parkinson's Progression Markers Initiative; RWD, real-world data



Number of Patients					
Delayed-start	94	93	83	83	75
Early-start	177	175	149	147	143
swPPMI	303	215	185	182	180

Pagano G. et al. Nature Neurology 2024

UCB7853 UCB/Novartis

UCB7853 is an α-synuclein antibody

A phase I: Safety and Pharmacokinetics Study of UCB7853 in Healthy Study Participants and Study Participants With Parkinson's Disease (PD) has been completed

Lu AF82422 (Lundbeck)

Lu AF82422 is an anti-aSyn human IgG1 mAb, which binds all known forms of aSyn, including aggregated and/or C-terminal truncated aSyn.

The anti-alpha-synuclein antibody Lu AF82422 was safe and well tolerated in a FIH-SAD study in healthy subjects and patients with PD

L. Buur, J. Wiedemann, abstract at MDS 2022

A phase II study on MSA patients has been conducted in Japan in 2022/2023

ABBV-0805

- ABBV-0805 is a humanized monoclonal antibody targeting α-synuclein
- On April 20 2022, BioArctic announced that AbbVie had terminated its collaboration on α-synuclein antibodies, including ABBV-0805 (press release). BioArctic said it is looking for ways to continue development.

MEDI1341/TAK341

- high-affinity monoclonal antibody to a C-terminal epitope on monomeric and aggregated α-synuclein, originally developed by AstraZeneca.
- Safety concern
- Takeda plan to run a study on MSA

Active versus passive immunisation: Pros and Cons

- **Pros**
- Long lasting immune response
- Large interdose intervals
- Sc/im administration

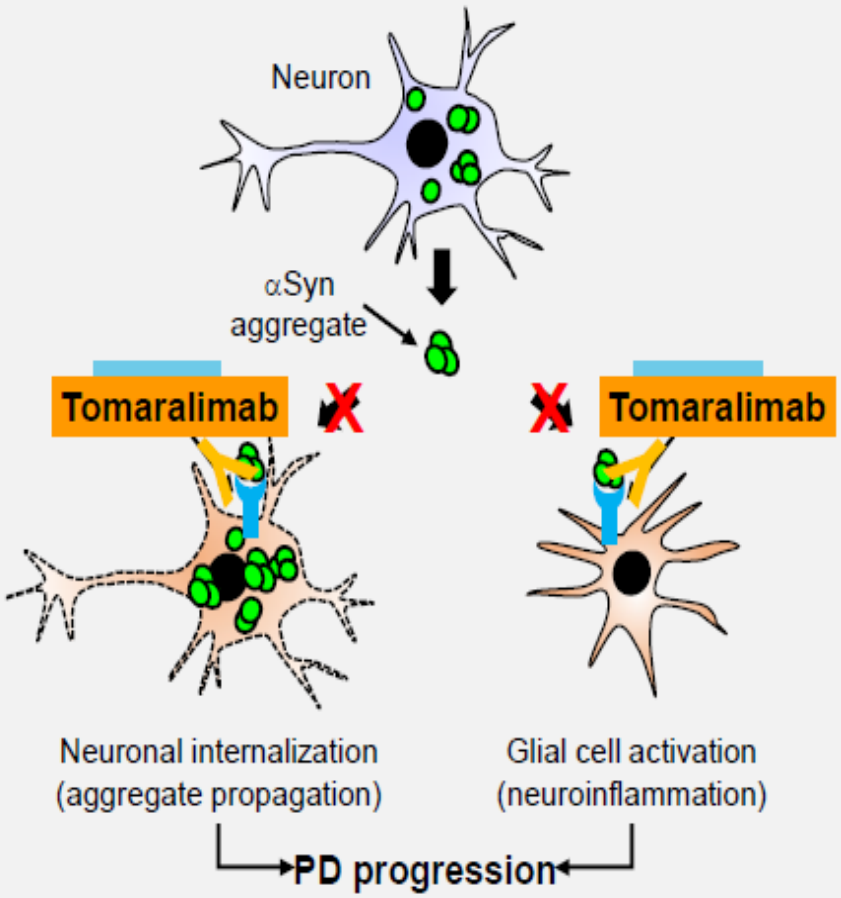
- **Cons**
- Possible immune tolerance
- Robust immune response
- Avoid T.cell mediated toxicity

BIIB122/DNL151 phase IIb in PD (LUMA)

- Increased LRRK2 kinase activity is thought to impair lysosomal function and drive Parkinson's disease (PD) pathogenesis. Inhibition of LRRK2 kinase activity is a promising new approach to treat PD with a LRRK2 mutation and sporadic PD.
- DNL151 is a potent, selective, CNS-penetrant LRRK2 kinase inhibitor
- Oral administration
- The phase II LUMA study is ongoing

- Jennings D et al. Movement Disorders 2023

Solving the mechanism of αSyn aggregate propagation and identification of Toll-like receptor 2 (TLR2) as a receptor for the aggregates



Elucidation of pathogenic roles of extracellular αSyn aggregates

- Exocytosis of αSyn aggregate from neuronal cells
- Transfer of extracellular αSyn aggregates to neurons (propagation) and induction of glial cell activation (neuroinflammation)
- PNAS (2009), Nature Reviews Neurology (2014)

Identification of TLR2 as a receptor for extracellular αSyn aggregates

- Regulation of PD pathologies by TLR2 in *in vitro* and *in vivo* experimental systems
- Inhibition of aggregate propagation and neuroinflammation by TLR2 antibody *in vivo*
- Nature Communications (2013), Cell Reports (2015), Molecular Neurodegeneration (2018)

TLR2 and aggregate propagation are drug targets for Parkinson's disease

NM-101 (Tomaralimab) is a humanized IgG4 monoclonal antibody to the human TLR2. (Neuramedy)

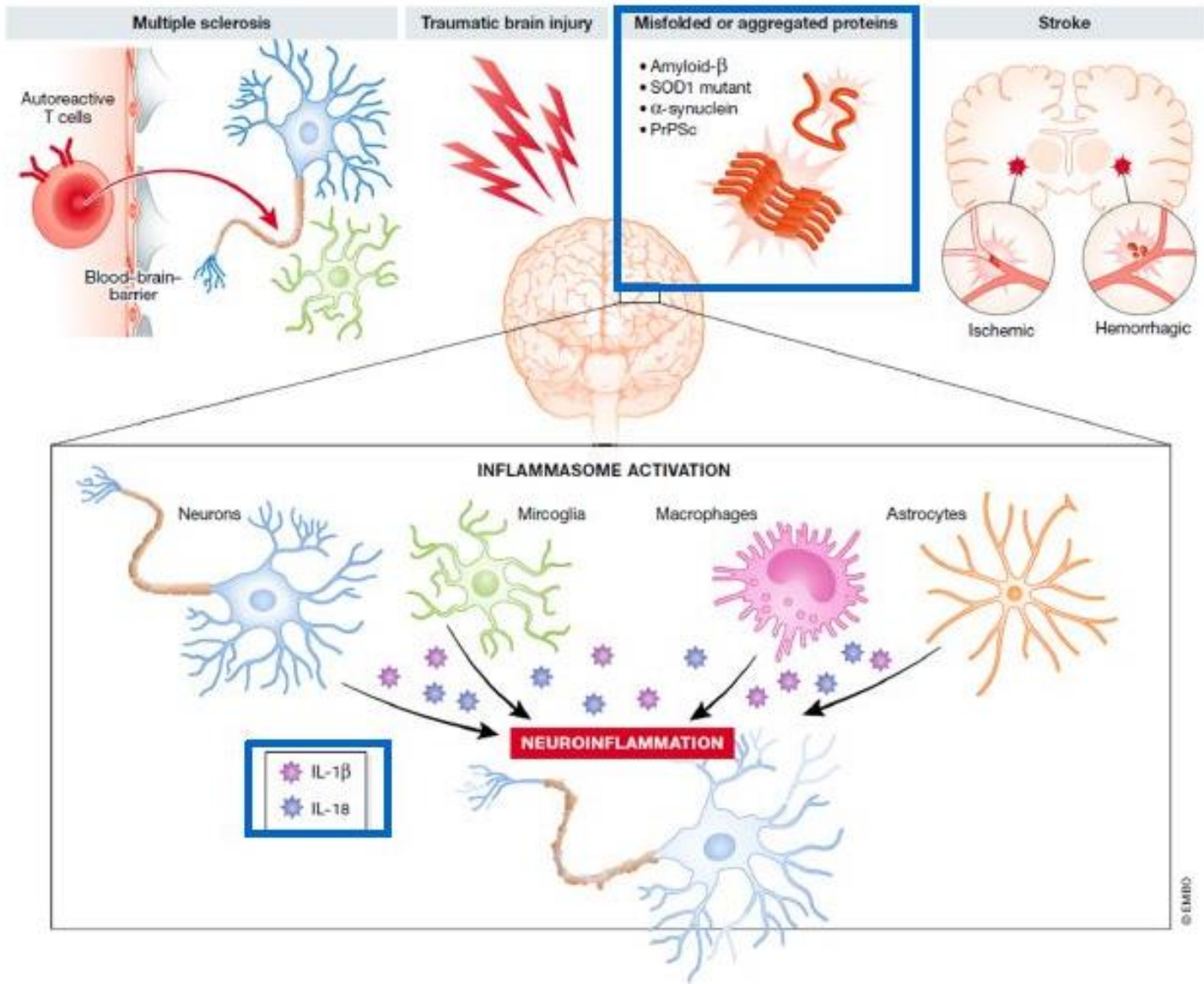
NLRP3 inflammasome

Role in neuroinflammation

Inflammasomes can be activated in the CNS in response to accumulation of misfolded or aggregated proteins in the brain (e.g., alpha-synuclein in Parkinson's disease).

Inflammasome activation results in caspase-1-mediated cleavage of pro-IL-1b and pro-IL-18, and the subsequent release of the mature cytokines.

High levels of IL-1b and IL-18 can be detected in many neurodegenerative conditions and are considered to be crucial for the establishment of a chronic inflammatory environment, leading to neuronal dysfunction and eventually neurodegeneration.



Voet et al. 2019, *EMBO Mol Med*

Scientific rationale for NLRP3 inhibition in PD

- Post mortem, in vivo and preclinical evidence suggest a key role of NLRP3 inflammasome/microglia activation in PD
- Preclinical evidence suggest that NLRP3 inhibition may be beneficial in PD patients
- **Inzomelid** (Inflazome/Roche) is an inhibitor of NLRP3 which may reduce neurodegeneration of dopaminergic system and Alfa-Syn aggregation leading to slow down disease progression in PD

GBA parkinsonism

The GBA gene encodes the protein glucocerebrosidase (GCase), a lysosomal hydrolase, which converts glucosylceramide to ceramide and glucose.

The accumulation of undegraded substrates by compound heterozygous or homozygous GBA mutations has been linked to the lysosomal storage disorder Gaucher’s disease (GD).

Goker-Alpan et al. J Med Genet. 2004; Neudorfer et al. QJM Mon J Assoc Phys 1996

BIAL BIA 28-6156 activator of the GCase enzyme

- BIA 28-6156 is the first activator of the GCase enzyme to have been tested in clinical studies. It is designed to target the GCase enzyme to increase activity and improve glycosphingolipid metabolism in the lysosome. Preclinical studies have shown that BIA 28-6156 easily crosses the blood-brain-barrier and accesses the GCase enzyme within the brain and central nervous system. BIA 28-6156 is under development as a novel, first-in-class drug compound for the potential treatment of patients with GBA-AP.

Surgical approaches to disease modification in Parkinson disease

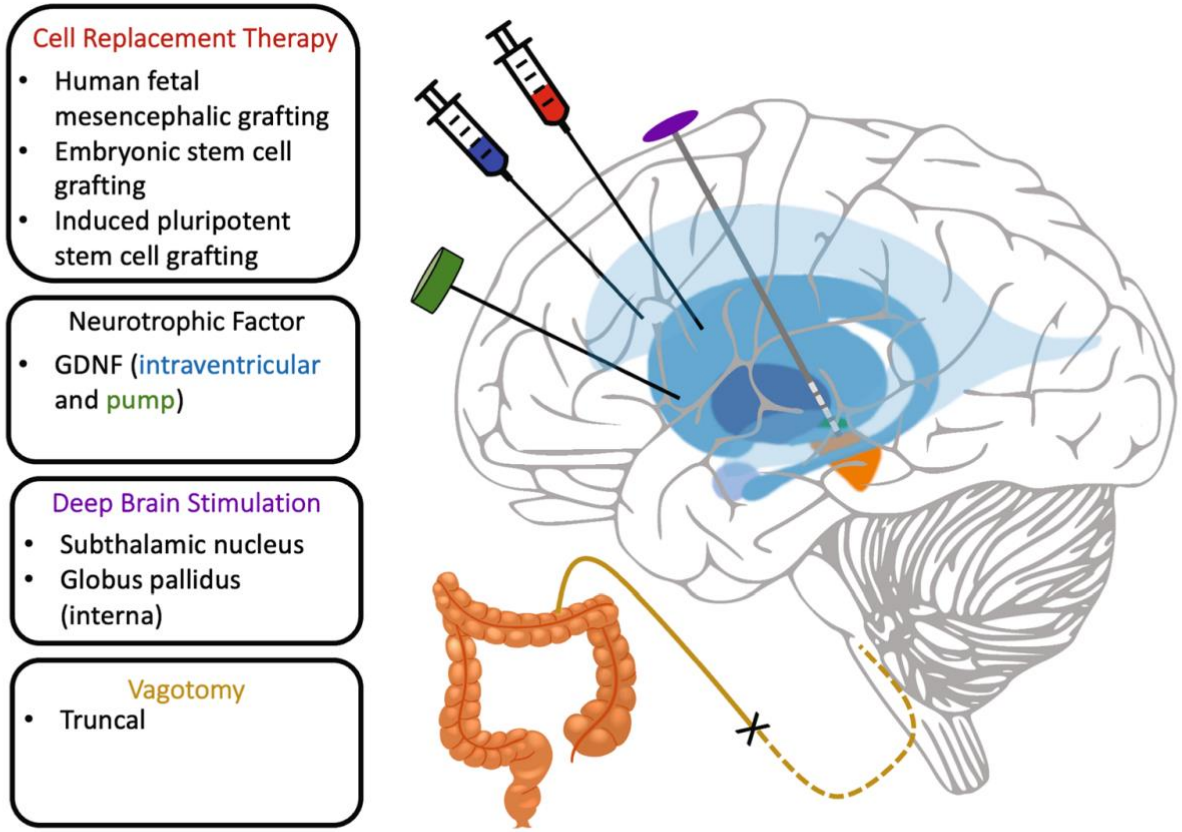


Fig. 1 Surgical methods of disease modification. Disease-modifying surgical strategies include cell replacement therapy, infusion or gene therapy of dopamine neurotrophic growth factors (both intraventricular and intraparenchymal administration), early subthalamic deep brain stimulation, and abdominal vagotomy.

Rahimpour, et al., npj Parkinson's Disease, 2022

Gene therapies

- Gene therapy is a rapid evolving, genome editing technology aiming to treat a disease by genetically modifying populations of cells that are either directly functionally impaired or capable of relieving disease symptoms.
- The technology is based on the use of a vector to carry DNA, RNA, antisense oligonucleotides or DNA- or RNA-editing enzymes into specific cells to modulate gene expression.
- Increasing clinical evidence of viral vector-based gene therapy approaches is available in PD

- Borel et al. 2014; Haggerty et al. 2020; Han et al. 2019; Hudry et al. 2019

Gene therapy clinical trials in PD: main targeted approaches

- restoring dopamine synthesis,
- neuroprotection
- genetic neuromodulation
- addressing disease-specific pathogenic variants (pathogenic GBA variants).

Stem Cells

- Bluerock is performing a phase I trial with human derived stem cells neurones
- Phase II studies with neurones implanted in the striatum of PD patients will start early 2024
- The prestudy selection is ONGOING

Current non-pharmaceutical disease-modifying aproaches

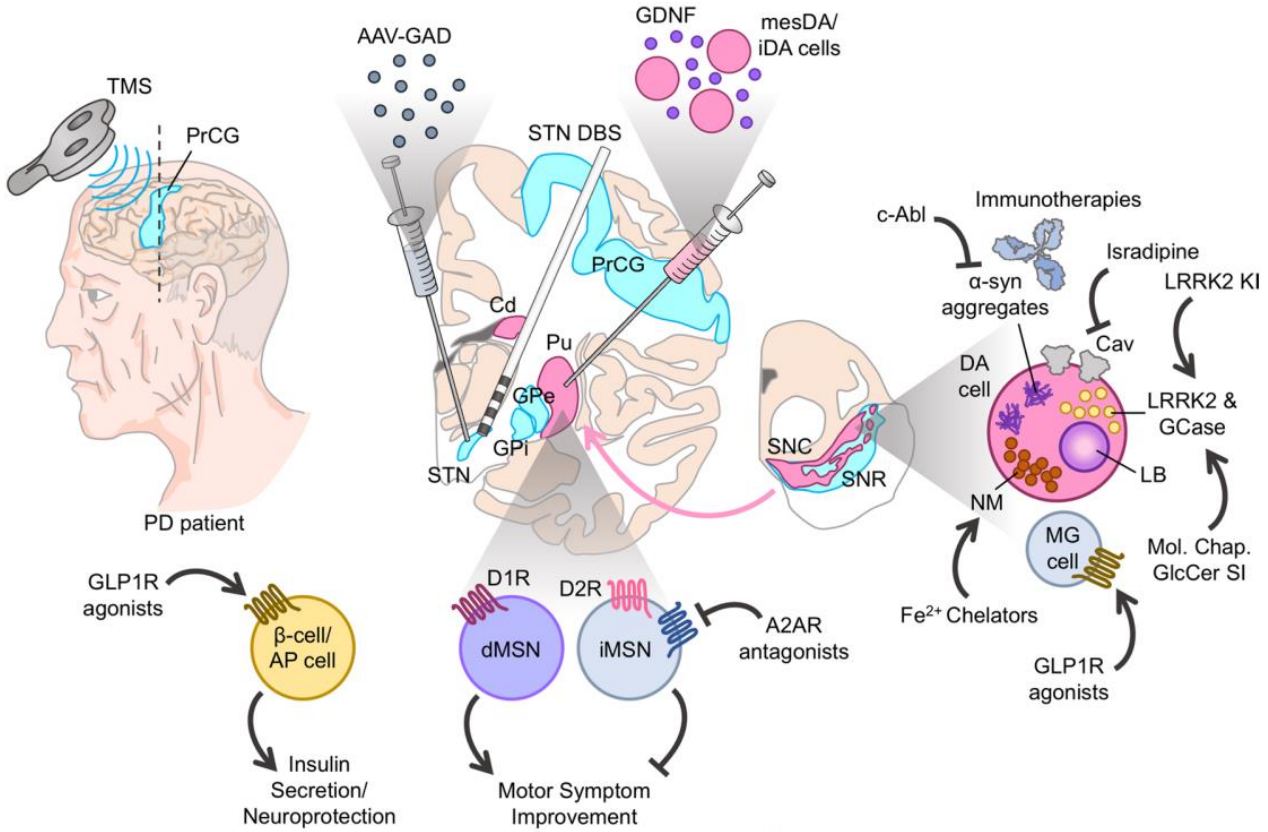


Fig. 1 Potential neuroprotective mechanisms of novel targeted therapies in Parkinson's disease.

AAV adeno-associated virus, *AP* area postrema, *A2AR* adenosine A2A receptor, *Cd* caudate nucleus, *DA cell* dopaminergic cell, *DBS* deep brain stimulation, *dMSN* direct pathway medium spiny neurons, *D1R* dopamine D_1 receptor; *D2R* dopamine D_2 receptor; *GAD* glutamate decarboxylase; *GCase* glucocerebrosidase, *GDNF* glial cell-line derived neurotrophic factor, *GLP1R* glucagon-like peptide 1 receptor, *GPe* globus pallidus externa, *GPi* globus pallidus interna, *iMSN* indirect pathway medium spiny neurons; *KI* kinase inhibitor, *LB* lewy body, *LRRK2* leukine-rich repeat kinase 2, *MG* microglia, *NM* neuromelanin; *PrCG* pre-central gyus, *Pu* putamen; *SNC* substantia nigra pars compacta, *SNR* substantia nigra pars reticulata, *STN* subthalamic nucleus, *TMS* transcranial magnetic stimulation

Ntetsika et al., Molecular Medicine, 2021

CONCLUSION

- Different approach are under evaluation to achieve disease modification and neuroprotection in Parkinson’s disease
- Ongoing studies involve:
- - active and passive immunisation
- - immunomodulation and treatment of inflammation
- - Gene therapy
- - Cells replacements

Morphomer® small molecules targeting alpha-synuclein for the treatment of Parkinson's disease

Elpida Tsika, PhD | ADPD 2024 | March 2024

AC Immune

Disclaimer

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Conflict of interest disclosure

Elpida Tsika is an employee of AC Immune entitled to stock options.

Funding

Grand from the Michael J. Fox Foundation for Parkinson's Research

Parkinson’s disease

Pathological deposition of alpha-synuclein

Most common neurodegenerative movement disorder
Affects ~1% of the population over 65 years

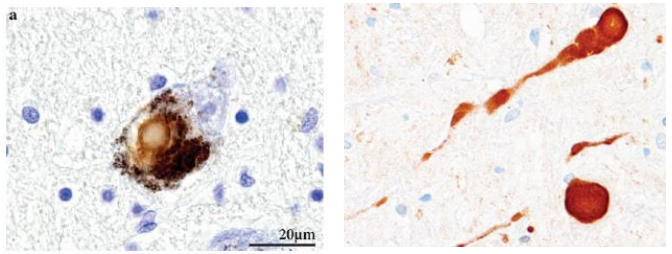
Etiology
5-10% genetic, 90-95% idiopathic, unknown cause

Cardinal motor symptoms
Tremor, rigidity, bradykinesia

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

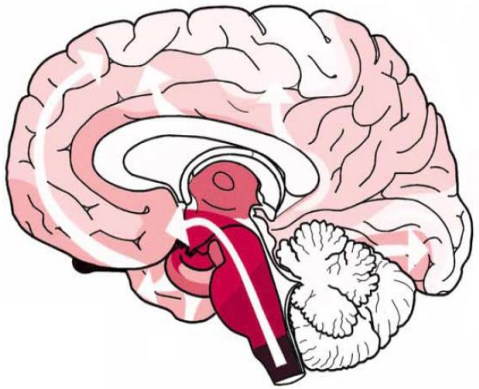
Pathological hallmarks
Neuron loss, alpha-synuclein aggregates – Lewy bodies

Main component of Lewy bodies: Alpha-synuclein



Halliday *et al.* 2011

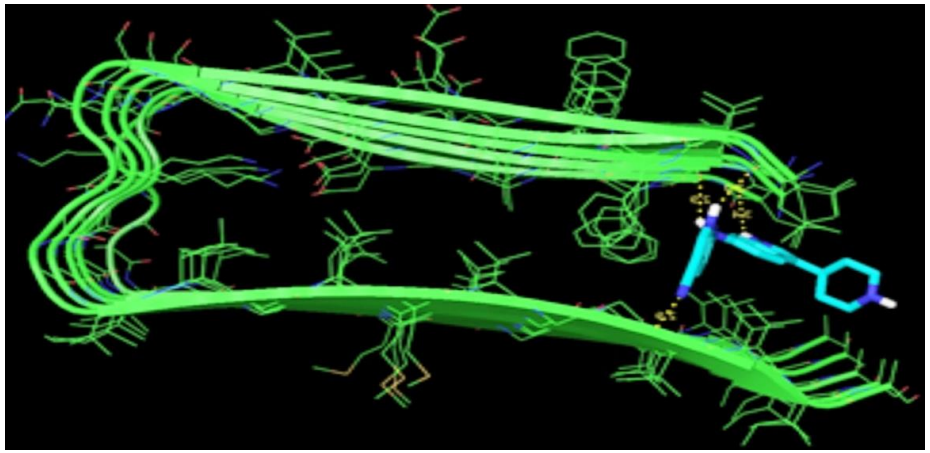
Progression of pathology



Braak *et al.* 2003

Proprietary Morphomer® platform

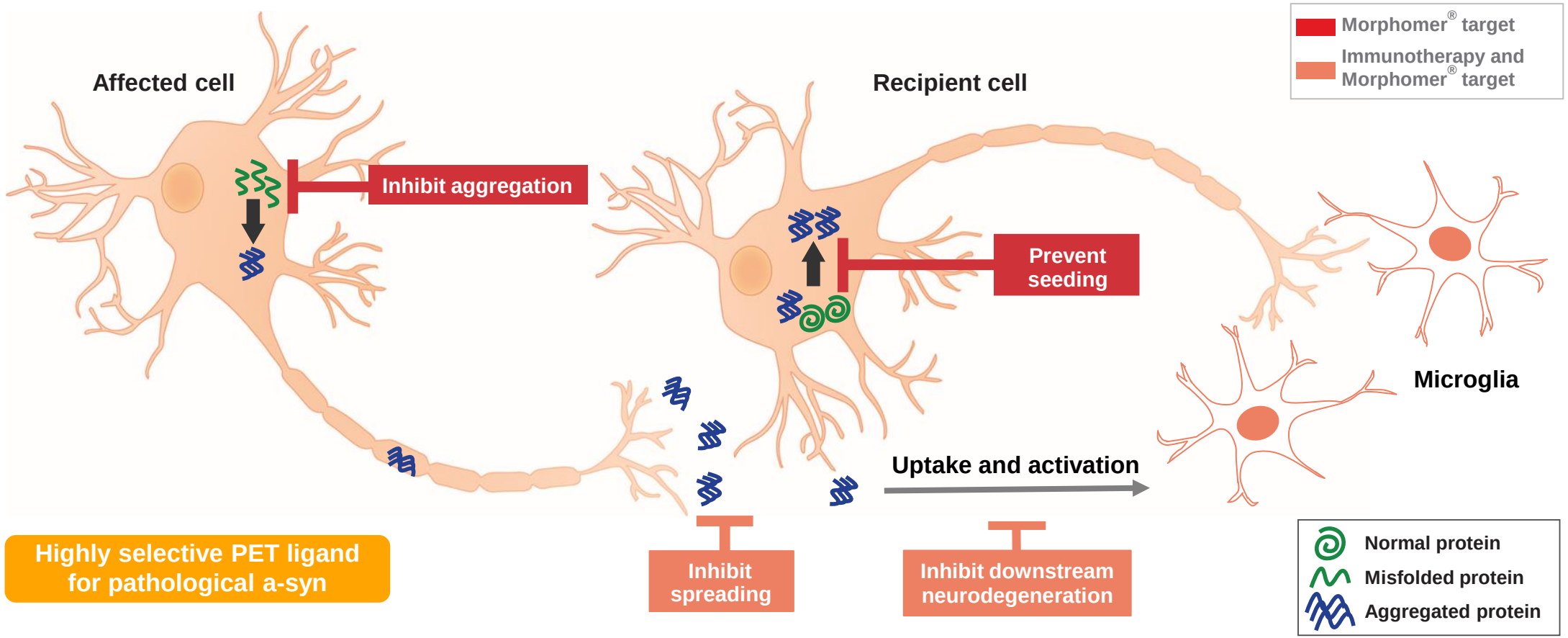
Targeting alpha-synuclein aggregation with small molecules



- Robust library of conformation-specific, non-peptidic small molecules with desirable CNS[1] properties constructed and continually refined and expanded over many years
- Comprehensive screening, rational design and early validation processes rapidly generate highly specific hit compounds
- Clinically validated with two diagnostic and one therapeutic candidate in clinical development

(1) Central nervous system

A-syn[1]-targeting Morphomer® designed to stop disease progression

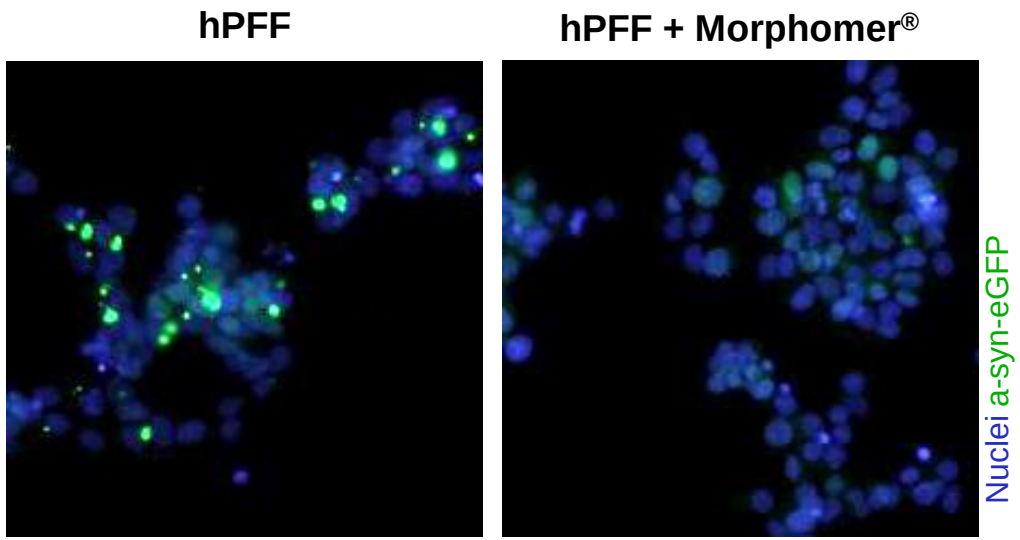


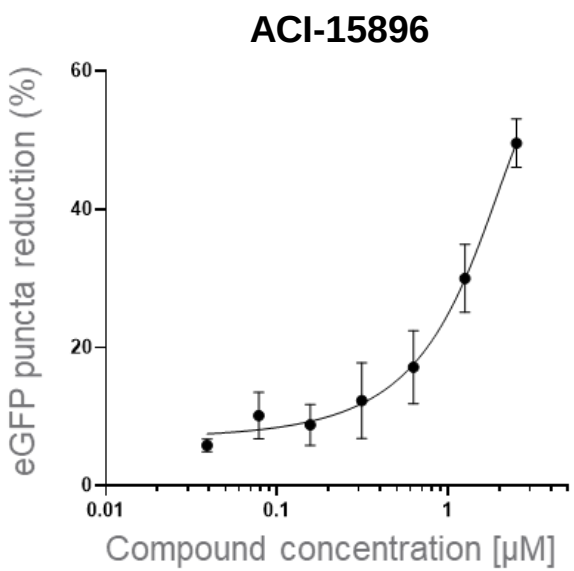
- Targeting aggregation and seeding intracellularly
- Combining with inhibition of extracellular spreading for full control of disease
- Synergizing with the a-syn PET tracer program enabling precision medicine

(1) Alpha-synuclein

Inhibition of pathological a-syn aggregation

ACI-15896 in hPFF[1]-seeded HEK[2] cells overexpressing human a-syn with eGFP[3] reporter





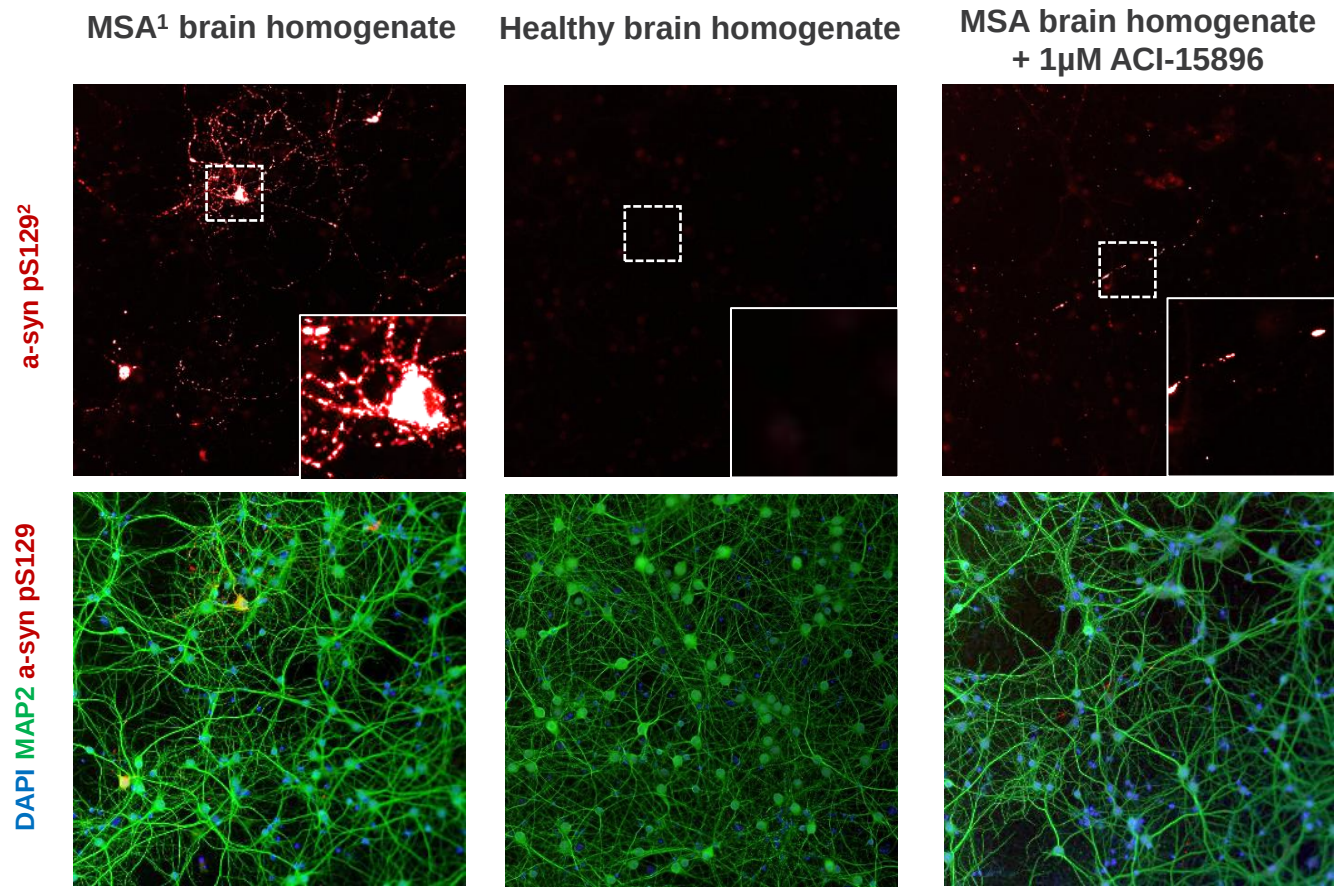
AC Immune unpublished data

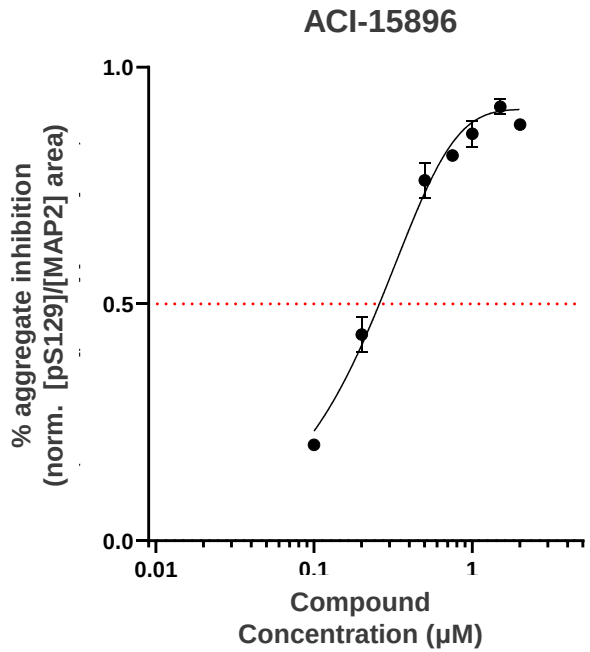
- PFF addition to HEK-a-syn-eGFP cells[4] leads to accumulation of detergent-insoluble, intracellular aggregates
- Treatment of cells with ACI-15896 results in reduction of intracellular aggregates

(1) Human preformed fibrils; (2) Human embryonic kidney; (3) Enhanced green fluorescent protein; (4) Cell line provided by Prof. Outeiro, University Medical Center Goettingen

Inhibition of pathological a-syn aggregation in neurons

Evaluating ACI-15896 in primary neurons seeded with MSA[1]-derived brain material





Ait-Bouziad et al. Synuclein 2022

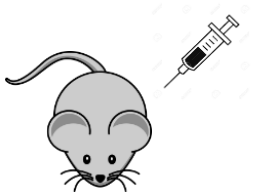
- Rat primary neurons seeded by brain-derived a-syn develop pS129[2]-positive inclusions
- ACI-15896 treatment reduces burden of intracellular a-syn aggregates with IC_{50} in nanomolar range

(1) Multiple system atrophy; (2) Phospho-Serine 129

Evaluation of potency in a model of Parkinson's disease

a-syn hPFF[1] model on the M83 line

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



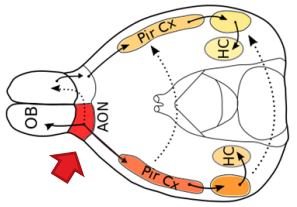
Human A53T a-syn expressed in neurons under the PrP promoter

Unilateral hPFF inoculation & dietary administration of compound

14 weeks in-life

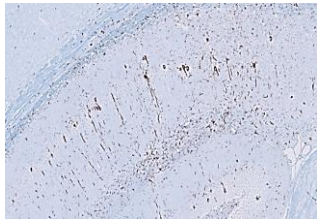
Started dosing 48h following surgeries

Projections from injection site to interconnected brain areas



Injection site

a-syn pS129[2] IHC[3]



Group	Inoculum	Treatment
A	PBS	Vehicle (normal chow)
B	hPFF	Vehicle (normal chow)
C	hPFF	100mg/kg ACI-15896
D	hPFF	60mg/kg ACI-15896

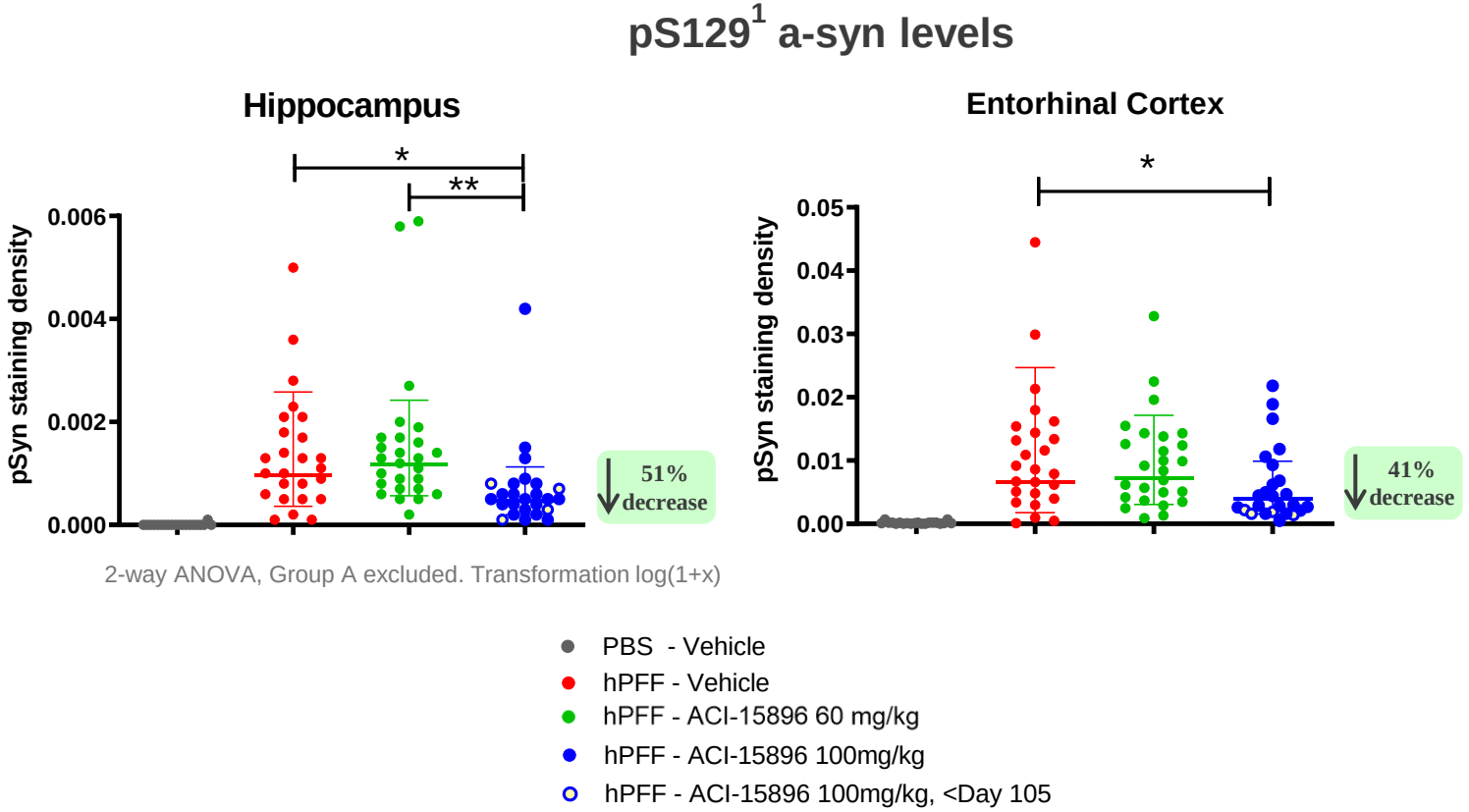
Tsika et al. ADPD™ 2023

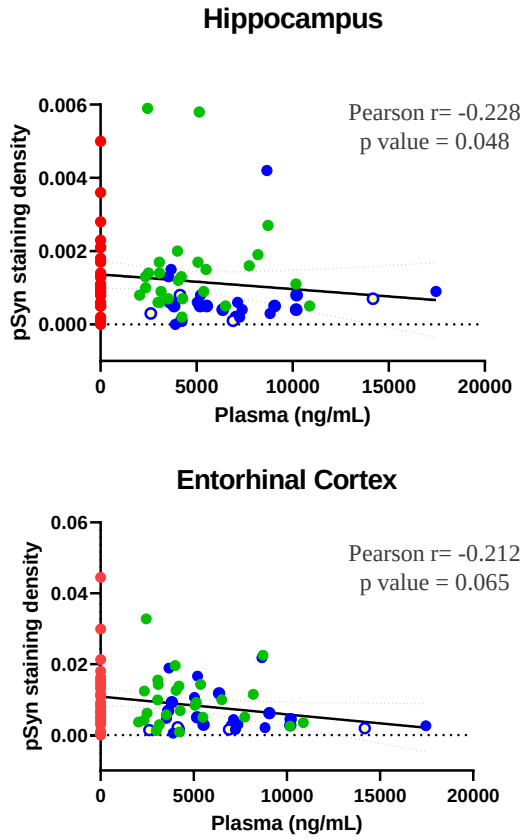
- Two treatment doses administered via medicated chow
- Used therapeutic paradigm by starting treatments 48h post-inoculation of pathological a-syn

(1) Human preformed fibrils; (2) Phospho-Serine 129; (3) Immunohistochemistry

Inhibition of aggregation in a model of Parkinson's disease

ACI-15896 inhibits the formation of pathological a-syn aggregates





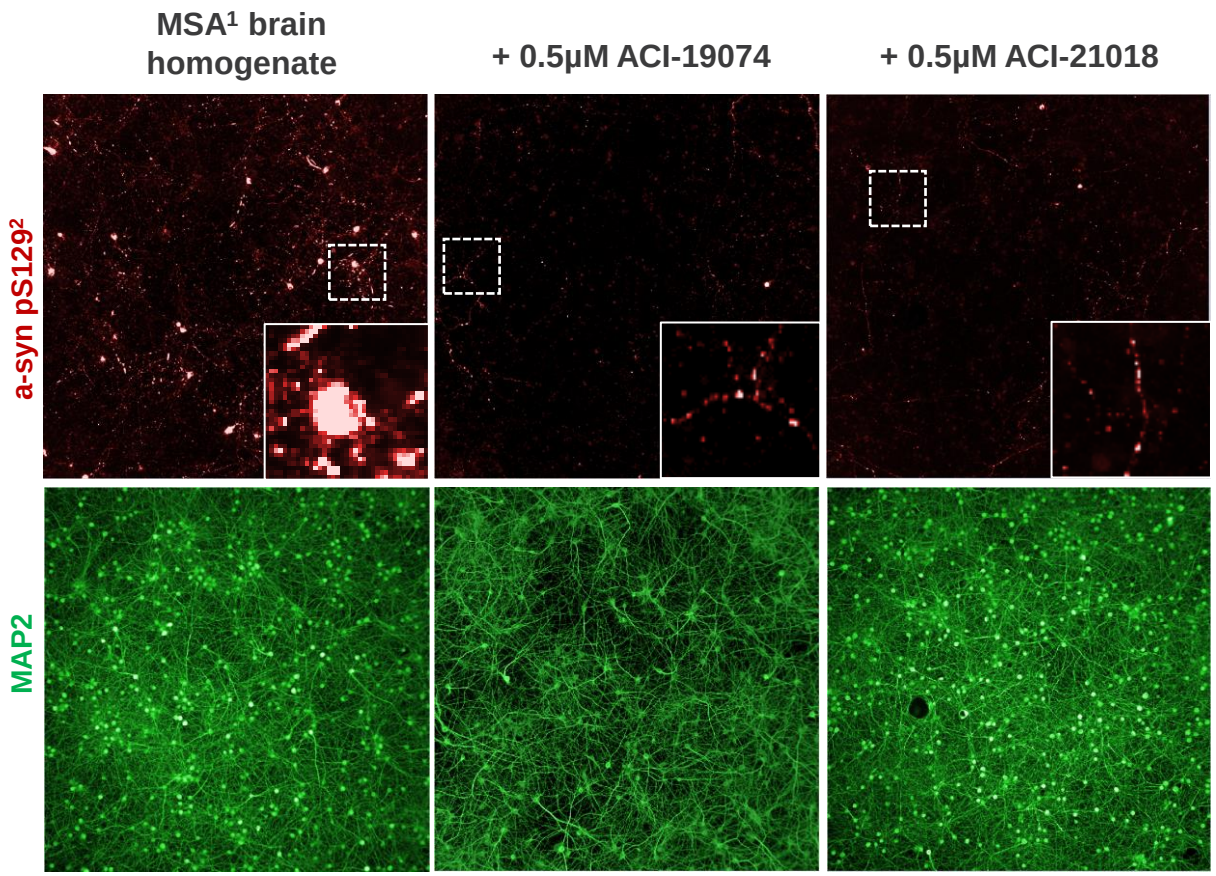
Tsika *et al.* ADPD™ 2023

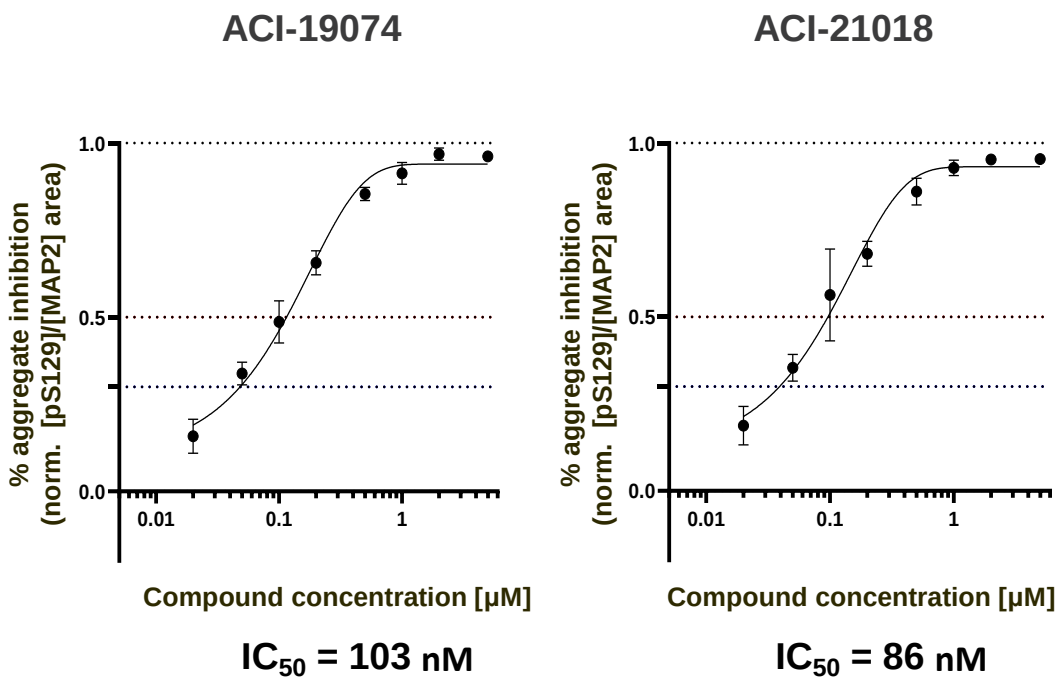
- Dose-dependent effect on pathological a-syn with ACI-15896 treatment
- Significant decrease of 41% and 51% in contralateral entorhinal cortex and hippocampus, respectively

(1) Phospho-Serine 129

Evaluating compounds in the neuronal seeding assay

Improved potency to inhibit of a-syn aggregation in MSA[1]-derived seeded neurons



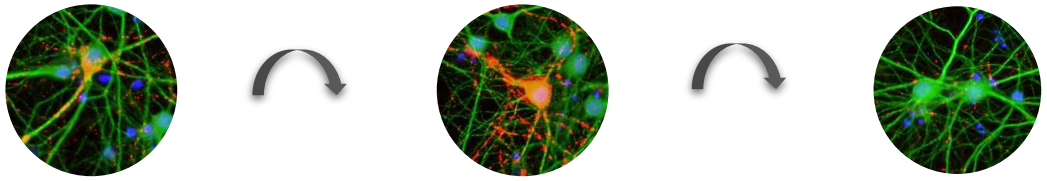


- Rat primary neurons seeded by brain-derived a-syn develop pS129-positive inclusions
- Compound treatment reduces burden of intracellular a-syn aggregates with IC_{50} in nanomolar range

(1) Multiple system atrophy; (2) Phospho-Serine 129

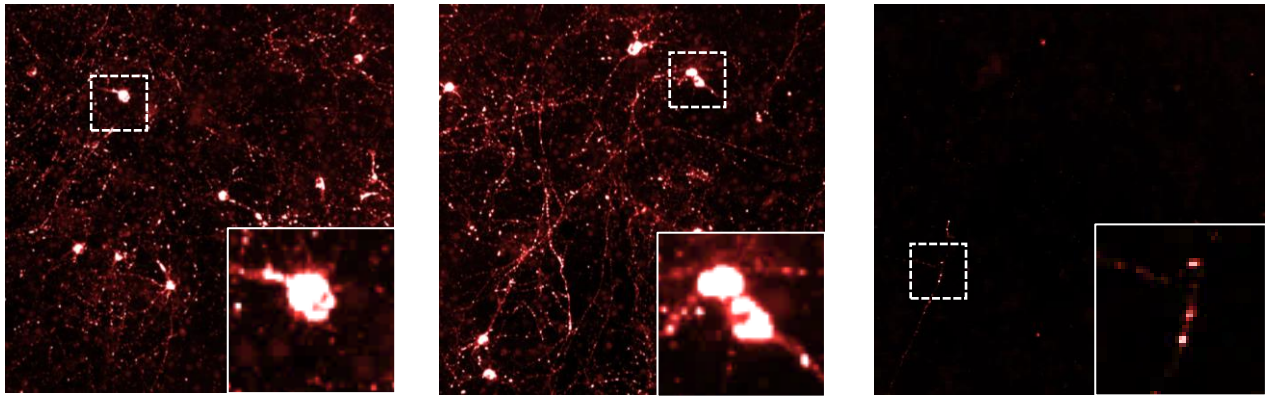
Evaluating compounds in seed amplification neuronal assay

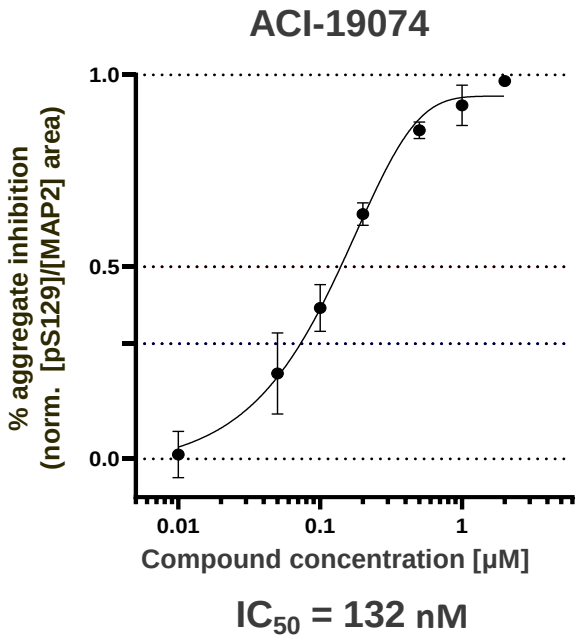
Potent inhibition of aggregation mediated by neuron-amplified MSA[1]-derived material



1st generation aggregates	2nd generation amplified aggregates	2nd generation amplified aggregates + 2µM ACI-19074

a-syn pS129[2]





AC Immune unpublished data

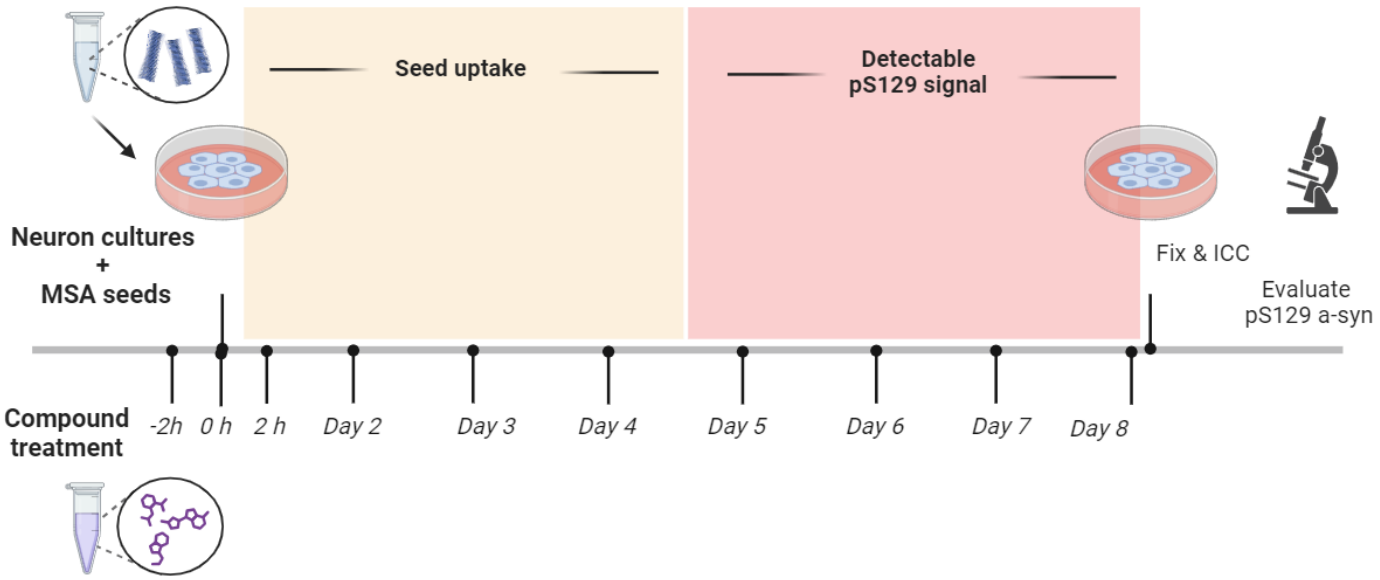
- Aggregates resulting from MSA material passaged twice in neurons maintain their seeding capacity and serve as a model for pathology propagation
- nM potency is maintained independent of using brain-derived or 2nd generation seeds

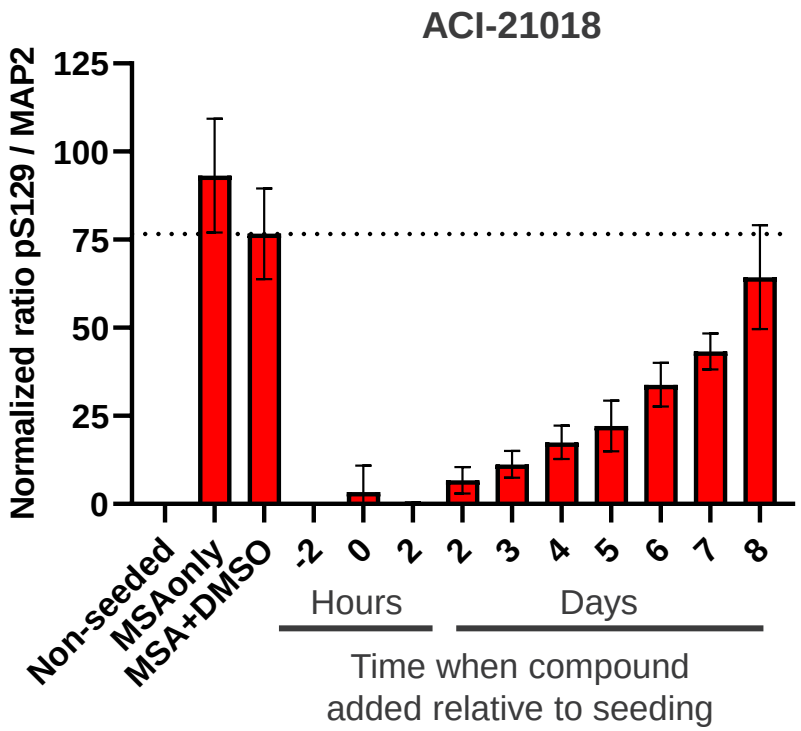
(1) Multiple system atrophy; (2) Phospho-Serine 129

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

Delayed treatment effect in primary neurons

Experimental timeline





AC Immune unpublished data

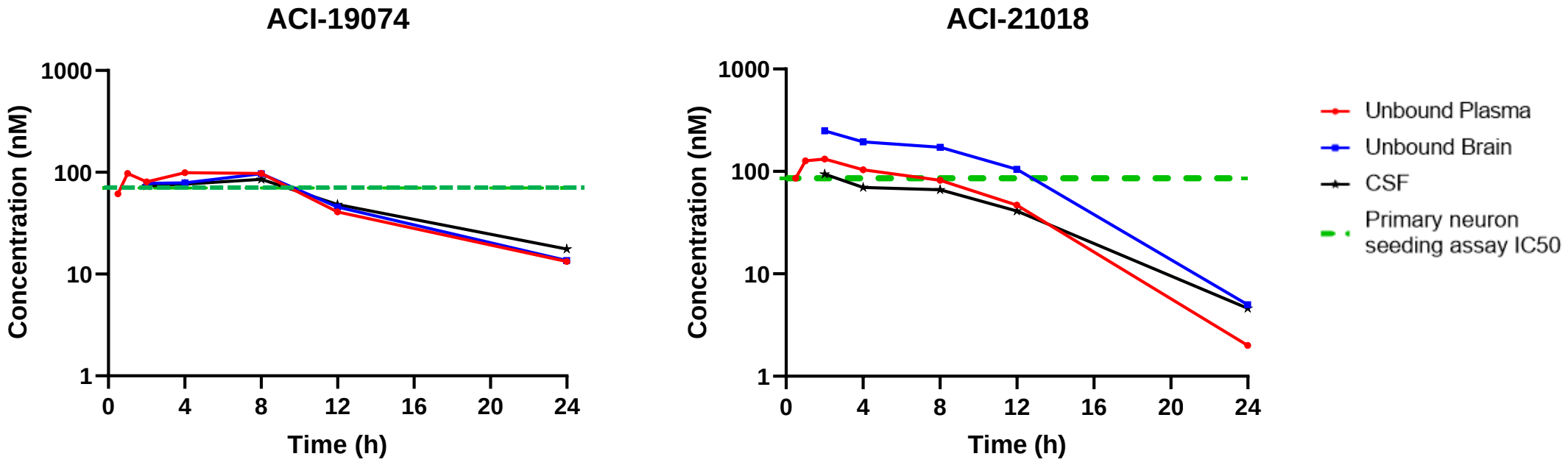
- Reduction of aggregate burden even when compound treatment delayed by several days after seeding
- Demonstrates compound treatment prevents *de novo* aggregation intracellularly

(1) Multiple system atrophy

Evaluating *in vivo* pharmacokinetics

Achieve exposure levels in CNS above the *in vitro* efficacious concentration

PK profiles after single 20 mg/kg p.o. administration vs potency *in vitro*



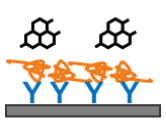
AC Immune unpublished data

- Compounds have nM potency *in vitro* and favorable pharmacokinetic properties
- Target engagement achieved up to 8 hours after single dose of 20mg/kg

Target engagement on PD[1]-derived aggregates

Using Surface Plasmon Resonance (SPR)

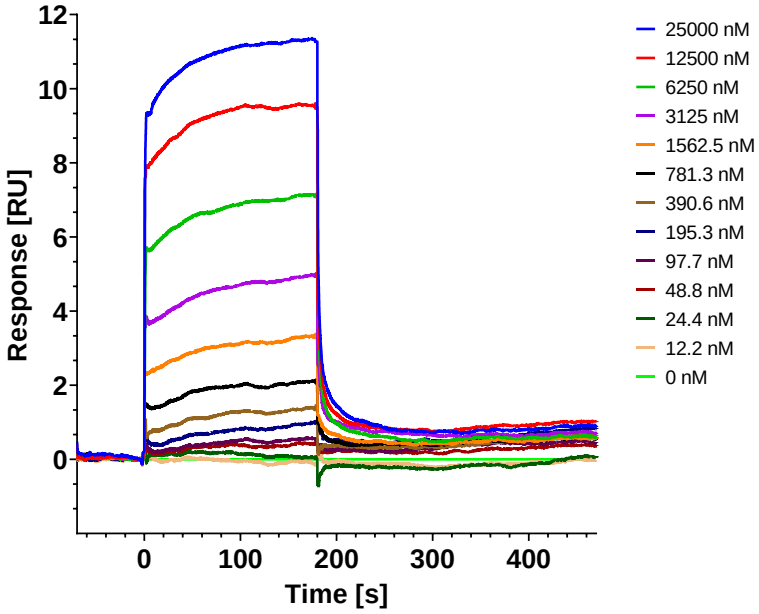
SPR setup:



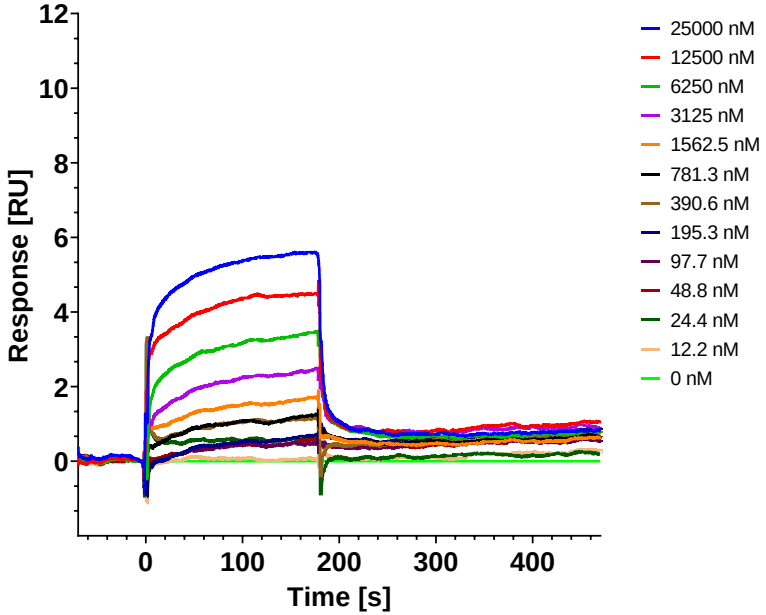
Morphomer®
a-syn aggregates
10D2 a-syn mAb
Sensor chip

ACI-21018

Parkinson's disease



MSA[2]



- ACI-21018 demonstrates binding to a-syn aggregates derived from PD as well as MSA patient brain tissue

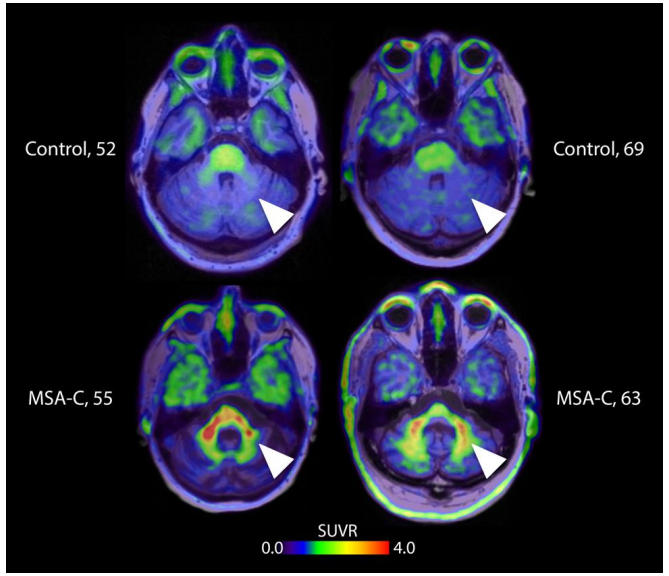
(1) Parkinson's disease; (2) Multiple system atrophy; (3) Surface Plasmon Resonance

AC Immune unpublished data

Common binding site of ACI-21018 and a-syn PET[1] tracer, ACI-12589

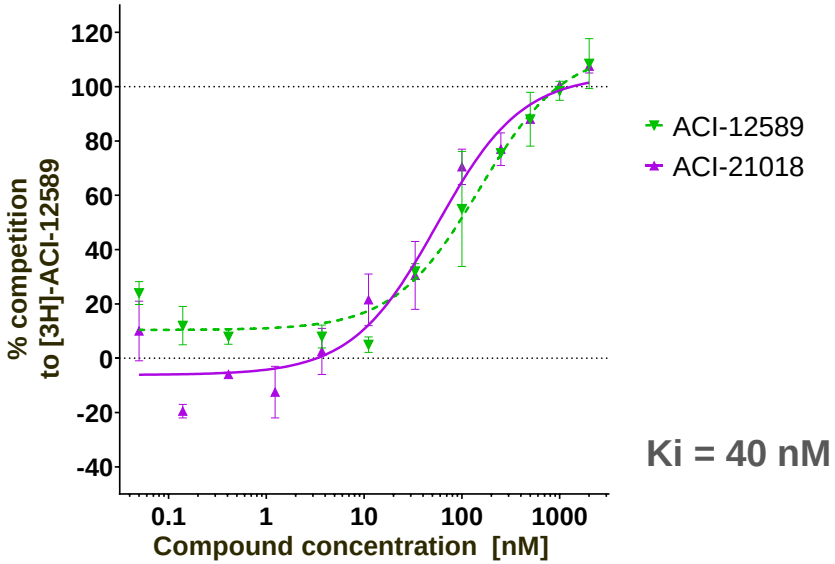
Accelerating and de-risking clinical development in MSA[2]

ACI-12589
PET signal in MSA patients



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

Competition radiobinding



AC Immune unpublished data

Common binding site with an a-syn PET tracer provides two key clinical endpoints:

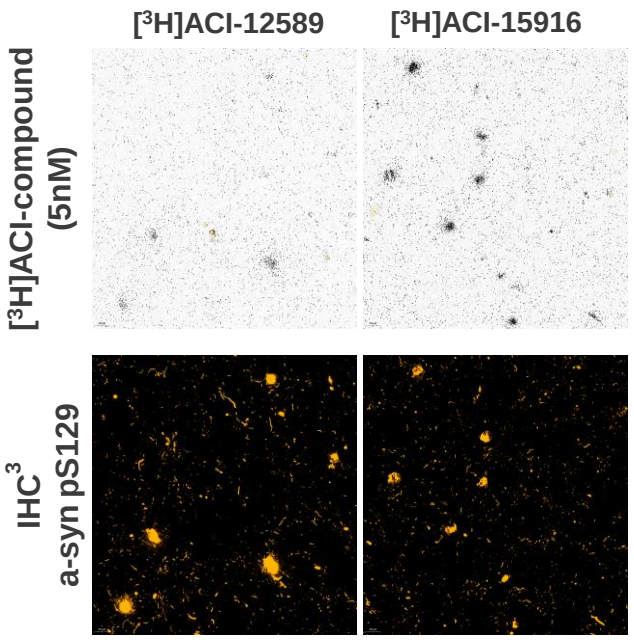
- Target engagement: PET scan with drug on-board in target occupancy study for dose selection
- Pharmacodynamic biomarker: PET scan after drug washout to evaluate effect on pathology

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

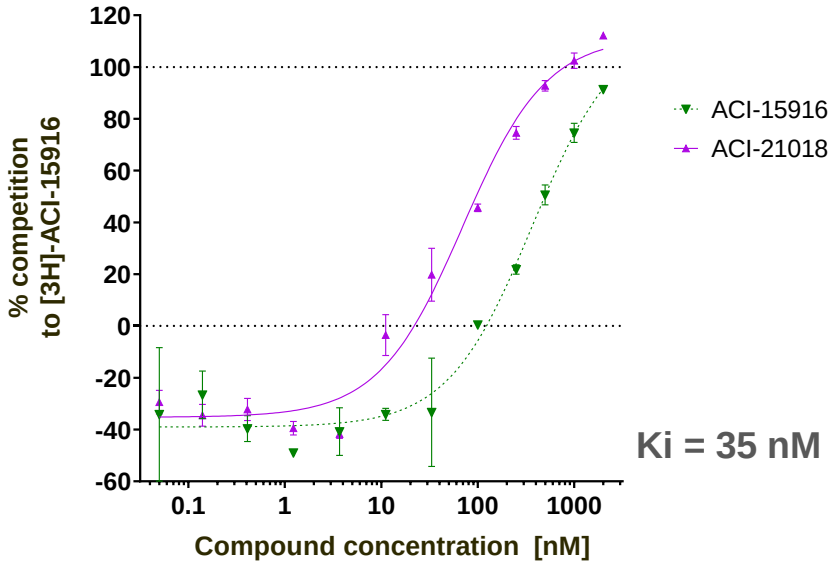
Common binding site with next generation a-syn tracer, ACI-15916

Accelerating and de-risking clinical development in PD[1]

Target engagement by high resolution autoradiography



Competition radiobinding



AC Immune unpublished data

- Shared binding site with the next generation PET candidate, ACI-15916, having the potential to detect synucleinopathies including Parkinson's disease
- Tracer will be used for target engagement and as pharmacodynamic biomarker in studies for PD

(1) Parkinson's disease; (2) Parkinson's disease dementia; (3) Immunohistochemistry

Conclusions

First-in-class

- Morphomer® a-syn therapeutics are first-in-class, orally active, CNS penetrant small molecules that target pathological intracellular a-syn

Precision medicine

Morphomer® a-syn therapeutics:

- Demonstrate target engagement on PD and MSA-derived a-syn aggregates
- Common binding site with AC Immune's PET tracers enables precision medicine & accelerated development

Reduction of pathology

- Proven efficacy by reducing a-syn pathology in a model of Parkinson's disease

Lead optimization

- Identified compounds with improved potency and affinity for pathological a-syn currently being tested *in vivo*

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Marie Kosco-Vilbois

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NETHERLANDS BRAIN BANK

Banner Health

MIAMI MILLER SCHOOL of MEDICINE

Brain Endowment Bank

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

VacSYn : a biomarker-based Phase 2 clinical trial to evaluate ACI-7104.056, a novel active immunotherapy for Parkinson's disease

Nuno Mendonça, MD | ADPD 2024 | March 2024

AC Immune

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Disclosures

Nuno Mendonça is an employee of AC Immune entitled to stock options.

Global prevalence of Parkinson’s disease on the rise

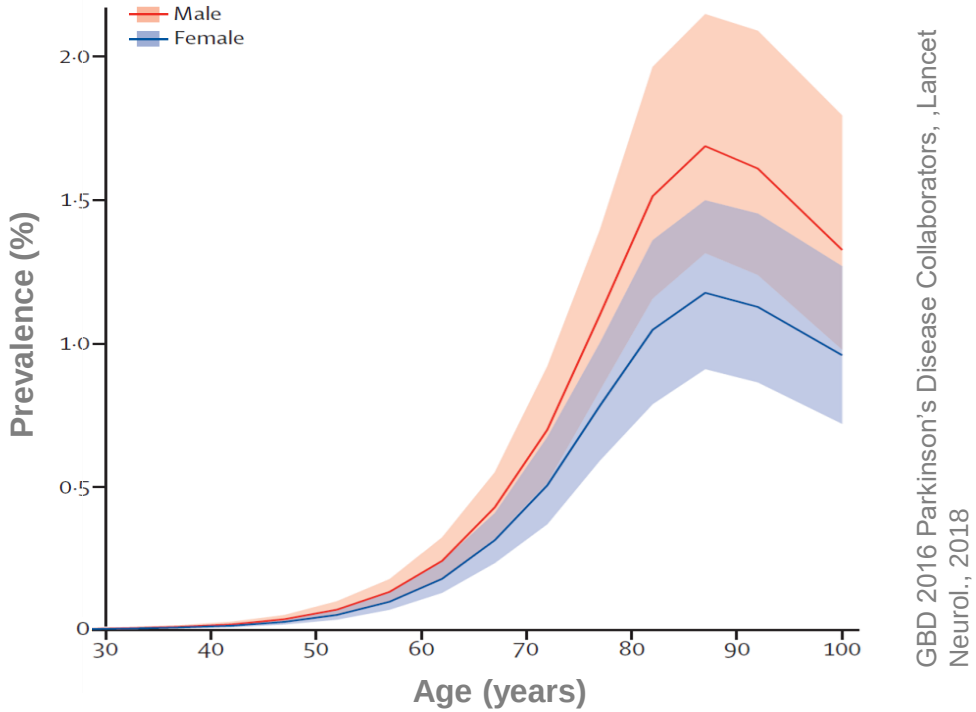
Prevention the best avenue to long-term preservation of function

>6 Million people living with Parkinson’s[1] globally

20-50% of people over age 80 living with LATE[2,3]

>8 Million people living with NeuroOrphan diseases[4]

Global prevalence of Parkinson’s disease, by age and gender



- Parkinson's disease prevalence rises with an aging population
- PD prevention through combination of earlier diagnosis with disease-modifying therapies

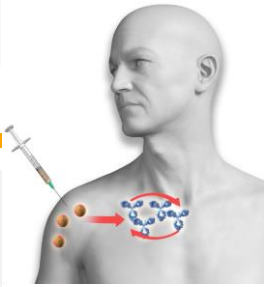
(1) Source: Michael J Fox Foundation; (2) Limbic-predominant age-related TDP-43 encephalopathy; (3) Nelson et al. Brain 2019; (4) in the USA - National Institute of Neurological Disorders and Stroke

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)

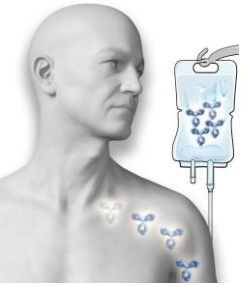


Active immunotherapy

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 NDDs[2]

(1) Amyloid-related imaging abnormalities; (2) Neurodegenerative diseases

Broad and robust pipeline in neurodegenerative diseases

Driven by validated proprietary technology platforms for sustained growth

Clinical Stage Programs

CLASS	PRODUCT CANDIDATE	INDICATION	Discovery	Preclinical	PHASE 1	PHASE 2	PHASE 3	News	Partner
Active Immunotherapy	**ACI-24.060** *(anti-Abeta)*	AD[1] treatment						data H1 '24[3] data H2 '24	
		AD treatment (*Down syndrome*[2])							
	ACI-7104.056 *(anti-α-syn*[4]*)*	PD[5], α-synucleinopathies						data H2 '24	
	ACI-35.030 *(anti-pTau)*	AD treatment							janssen
Small Molecule Morphomer®	**Tau-PET**[6] **tracer**	AD diagnostic							Life Molecular Imaging
		PSP[7] diagnostic							
	α-syn-PET tracer	α-synucleinopathies (e.g. MSA[8])							
	Tau aggregation inhibitor	Rare Tauopathies treatment							Lilly
		AD treatment							
Monoclonal antibody	**Semorinemab*** *(anti-Tau)*	AD treatment (*mild-to-moderate*)							
	Crenezumab* *(anti-Abeta)*	AD prevention							

(1) Alzheimer's disease; (2) Down syndrome-related Alzheimer's disease; (3) Refers to expected readouts from the ABATE Phase 1b/2 trial of ACI-24.060 in patients with AD; (4) alpha-synuclein; (5) Parkinson's disease; (6) Positron emission tomography; (7) Progressive supranuclear palsy; (8) Multiple system atrophy; * licensed to Genentech (a member of the Roche Group) until April 19, 2024

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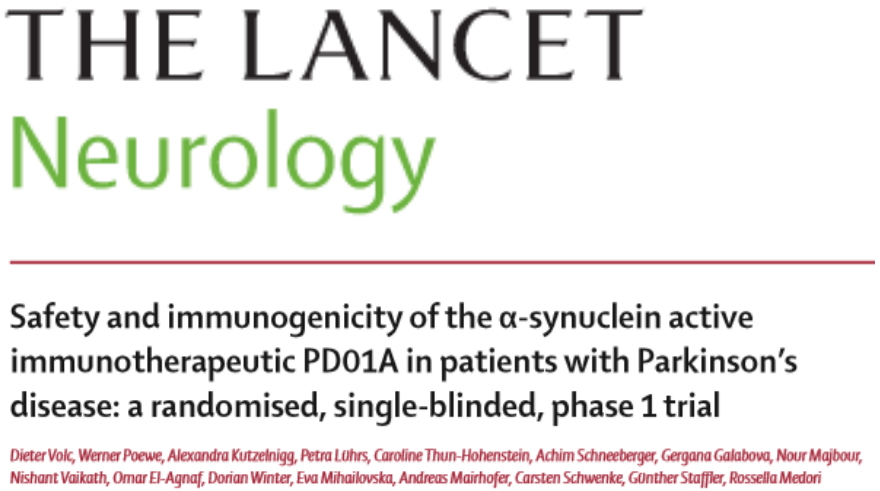
Anti-a-syn ACI-7104-based active immunotherapy is clinically validated[1]

Phase 1 results support best-in-class profile

1. Safe and well tolerated with no safety concerns noted in patients followed for more than 3.5 years
2. Induced strong and boostable antibody responses
3. Evidence of target engagement: 50% reduction in pathological (oligomeric) α-syn[2] in the CSF[3]
4. UPDRS III[4] scores correlated with reductions in oligomeric α-syn



Please visit for more details poster P0996 / #1513 presented by Guenther Staffler

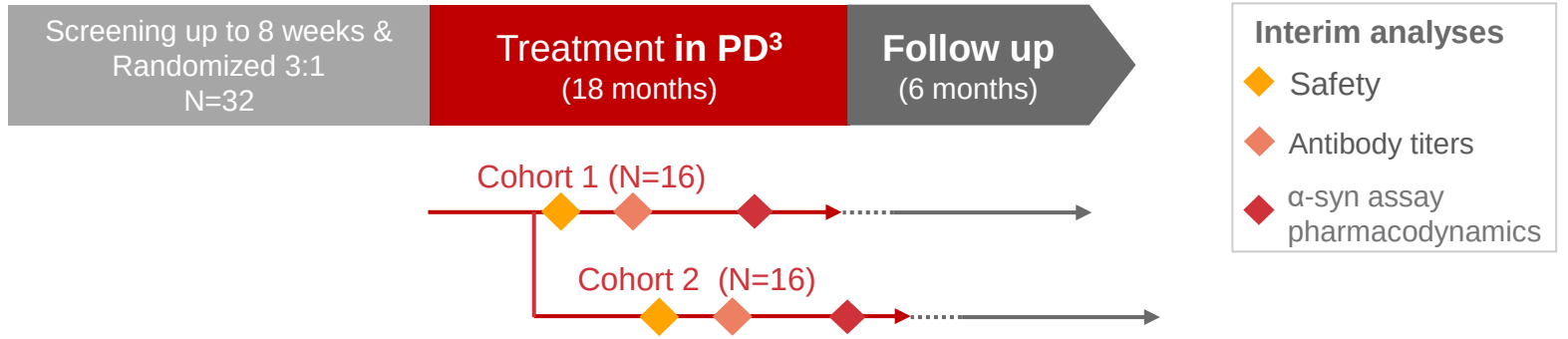
(1) Volc *et al.*, Lancet Neurol. 2020; (2) Alpha-synuclein; (3) Cerebrospinal fluid; (4) Unified Parkinson's Disease Rating Scale

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 a-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

(1) Parkinson's disease; (2) Pharmacokinetics and 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

VacSYn an adaptive biomarker-based Phase 2 study of ACI-7104 in early PD

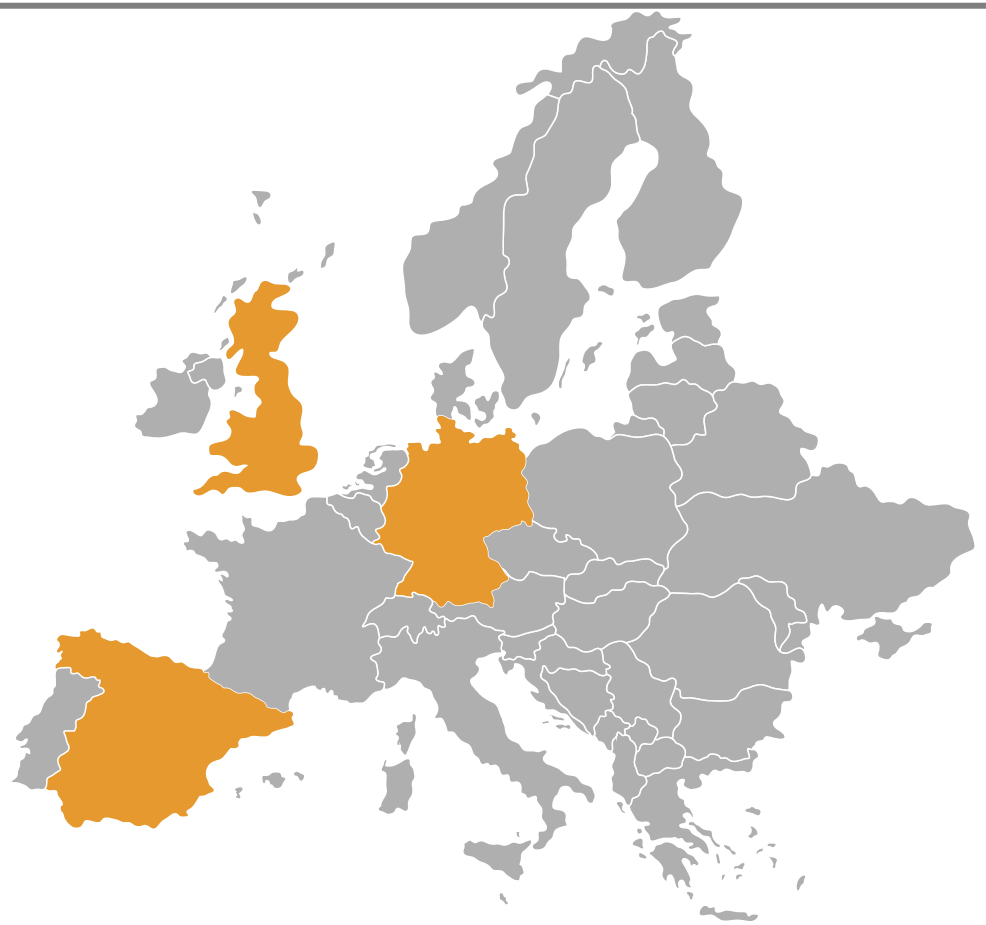
Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Aged ≥40 to ≤75 years
- Diagnosis of clinically established early PD (confirmed by DaT-SPECT)
- ≤ 2 years from time of onset motor symptoms
- H&Y Stage I to II
- Monotherapy treatment with L-Dopa at 300 mg per day or treatment naïve

Key Exclusion Criteria

- carriers of certain familial PD gene mutations
- Parkinsonian syndrome other than idiopathic PD
- Significant CNS disease

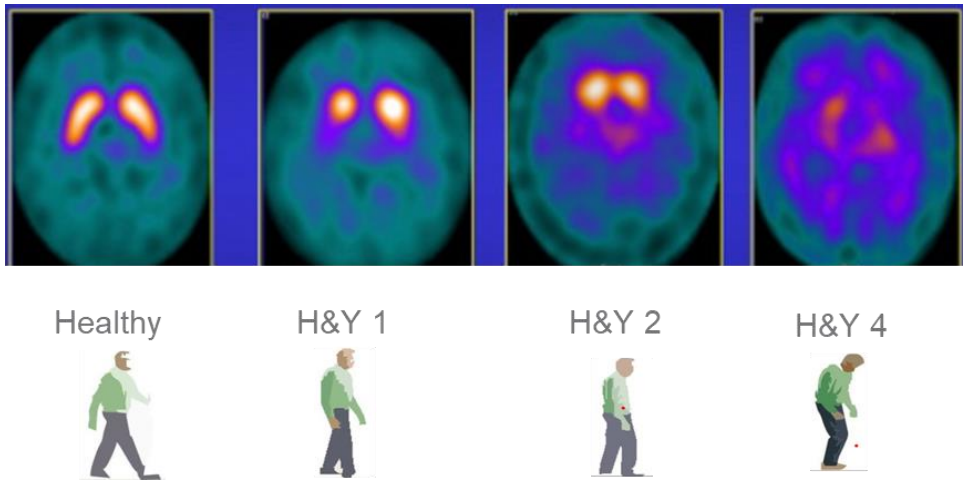


- Enrolment status: 26 patient from sites in Spain (14), Germany (2) and UK (10)

Baseline characteristics of VacSYn trial

Variable	Total
Total number of patients, n	26
Age (years), mean (std)	62.2 (7.34)
Sex, n (%)	
Male	16 (61.5%)
Female	10 (38.5%)
PD Treatment, n (%)	
treatment-naïve	9 (34.62%)
on L-Dopa 300mg/day	17 (65.38%)
Hoehn and Yahr stage, n (%)	
Stage I	8 (30.7%)
Stage II	18 (69.23%)
MDS-UPDRS scores, mean (std)	
Part 1: Non-motor experiences of daily living	4.00 (2.859)
Part 2: Non-motor experiences of daily living	4.52 (3.084)
Part 3: Motor examination	23.00 (10.253)
DaTSCAN type, n (%)	
Type 1	9 (34.62%)
Type 2	9 (34.62%)
Type 3	8 (30.77%)

DaTSCAN type vs Hoehn and Yahr stage



Adapted from A .Antonini, *et al.* 2004

For more details, please attend:

presentation by ***Dymitr Kostrica*** *on* ***March 9th, 2024***

Advances in PD and LBD drug development symposium

Blinded Treatment-Emergent Adverse Events (TEAE) summary[1]

1. **No deaths**
2. **No other serious TEAEs**
3. **No TEAEs leading to discontinuation from the study**
4. **Most common TEAEs were injection site reactions (e.g. redness, itching)**
5. **All TEAEs mild or moderate in severity**

Up to the present date, no significant risks, either known or anticipated, were associated with ACI-7104.056

(1) Cut-off date: March 1st, 2024

Conclusions

Clinical trial	▪ Phase 2 study in early PD subjects based on innovative two-part trial design
Adaptability	▪ Approach designed for early de-risking and simultaneously allowing acceleration with rapid entry into a pivotal clinical phase
Patient selection	▪ Targeting early PD population
Safety status	▪ Good safety and tolerability profile with no safety concerns identified thus far
Progress update	▪ Finishing randomization to Part 1 scheduled for March 2024

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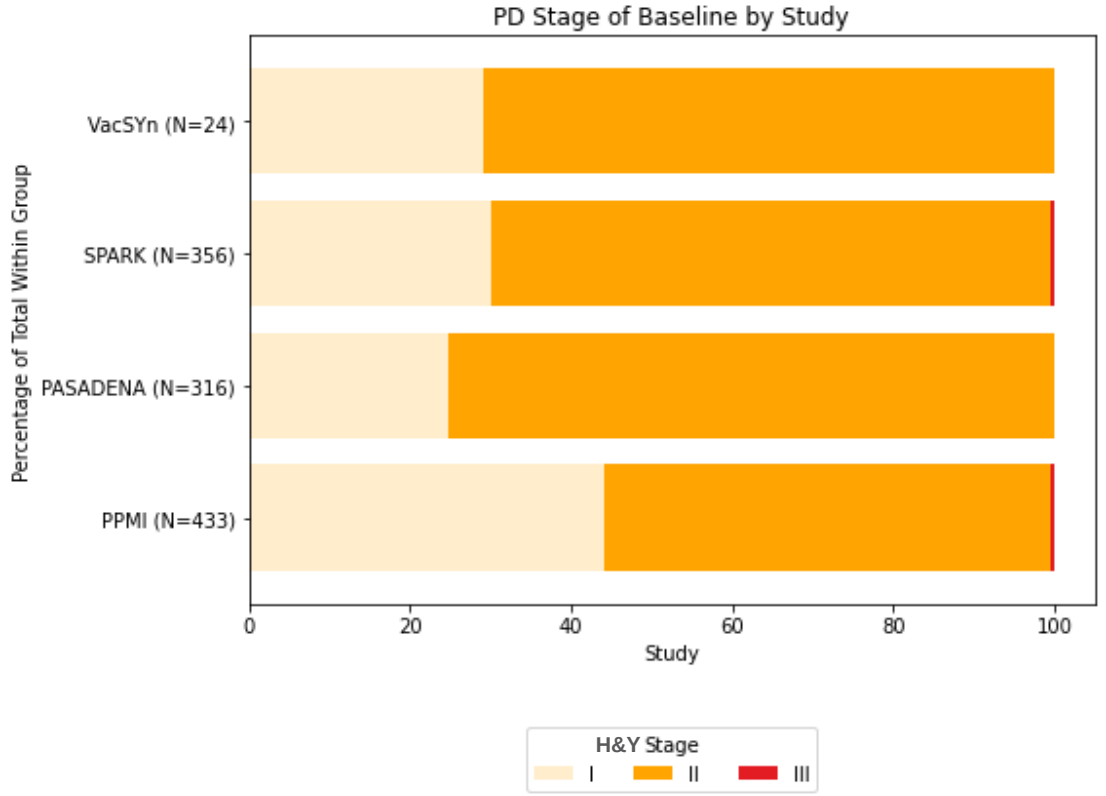
Andrea Pfeifer

We want to thank the study participants, their families for their participation and commitment, as well as all Investigators and Site personnel for their active participation and support.

AC Immune

VacSYn baseline characteristics consistent with population earlier than PPMI[1] and in line with recent PD[2] trials



- PPMI[1] natural history cohort leveraged for optimal design of the VacSYn study
- Selected population has a measurable and predictable rate of progression over a 1-year period

(1) PPMI - Parkinson's Progression Markers Initiative; (2) Parkinson's disease.

Q&A session

AC Immune