
AC Immune
Industry Symposium
From Treatment to Prevention
in Parkinson's Disease
Wednesday, March 18th, 2026
Hall A1, 8:40 – 10:40 am

Agenda

From Treatment to Prevention in Parkinson's Disease

Wednesday, March 18, 2026
Hall A1 · 08:45 – 10:20

08:40 – 08:45	**Introduction** *Andrea Pfeifer*
08:45 – 09:00	**Shifting treatment to prevention: lessons learned from Alzheimer's disease** *Catherine J. Mummery*
09:00 - 09:25	**Targeting α-synuclein in Parkinson's disease: pathophysiology and supporting evidence** *Werner Poewe*
09:25 - 09:40	**Misfolding of α-synuclein as fluid biomarker measured with the iRS platform of betaSENSE** *Klaus Gerwert*
09:40 - 10:05	**Stabilizing the progression of Parkinson's disease: Interim results of the VacSYn trial of ACI-7104.056** *Günther Staffler*
10:05 - 10:20	**Intracellular targeting of α-synuclein with Morphomer small molecules** *Francesca Capotosti*
10:20 - 10:35	**Discussion and Q&A** *Panel chaired by Catherine Mummery and Andrea Pfeifer*
10:35 – 10:40	**Closing remarks** *Andrea Pfeifer*

UKDTN
Dementia Trials Network

Shifting treatment to prevention: lessons learned from Alzheimer's disease

Prof Cath Mummery

Director, UK Dementia Trials Network

Disclosures

- Advisory board/ consultancy: AC Immune, Biogen, Roche, WAVE, IONIS, Prevail, Lilly, Eisai, Alector, Neurimmune, Novartis, Switch, Voyager, Alnylam, Denali, Arrowhead, Helicon,
- Commercial grants: BRAPIDD ultrafast MRI study, Biogen
- Non-commercial grants: NIHR UK Dementia Trials Network; Alzheimer's Society; Rosetrees
- Speaker for sponsored events: Biogen, Roche, EISAI, IONIS, Lilly
- Therapeutic evaluation board member: Washington University DIAN-TU Next Gen trials

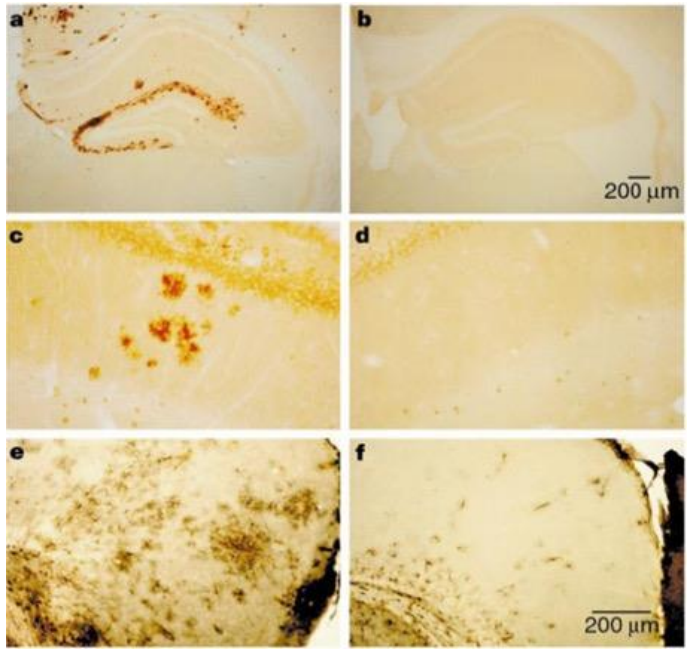
First demonstration of CNS amyloid clearance - active immunisation

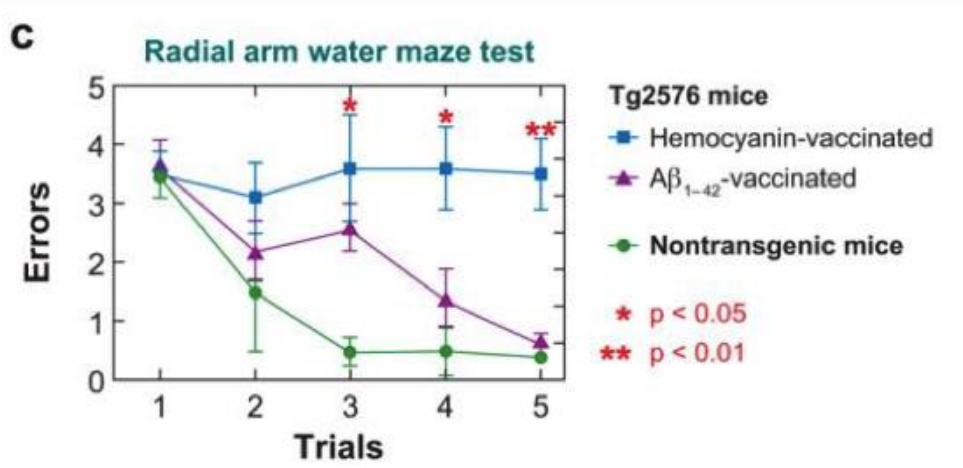
PBS-treated Aβ-vaccinated

Aβ plaques

Dystrophic neurites

Astrocytosis GFAP





2001: Vaccination with β-amyloid: AN1792 phase II trial in mild to mod AD

-> Trial terminated 2002

Schenk et al, 1999
Immunization with amyloid-β attenuates Alzheimer-disease-like **pathology** in the PDAPP mouse *Nature* **400**, 173–177

Anti-amyloid passive immunotherapy

A long road with many negative trials - patient selection; dose; design

but now 2 licensed DMTs

June 2021
Aducanumab FDA accelerated approval in early AD

July 2023
Lecanemab full FDA approval in early AD

July 2024
Donanemab full FDA approval in early AD

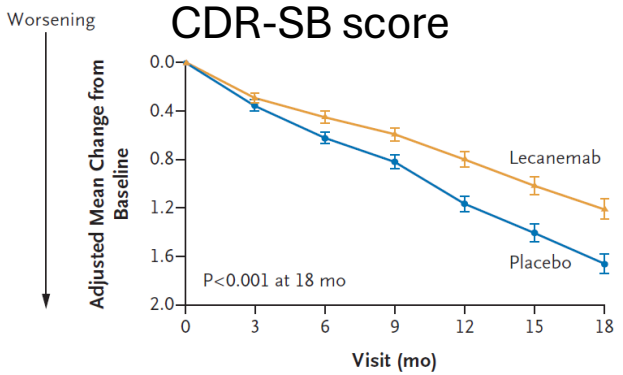
Aug 2024
Lecanemab MHRA approval in early AD

Oct 2024
Donanemab MHRA approval in early AD

The first evidence of disease modification in AD

Significant reduction in amyloid; modest benefit in slowing of cognitive decline

CLARITY[1]

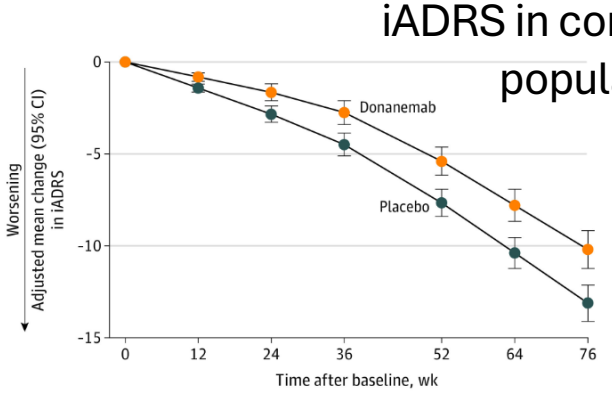


No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

LS mean difference at 18 months: -0.45[1]

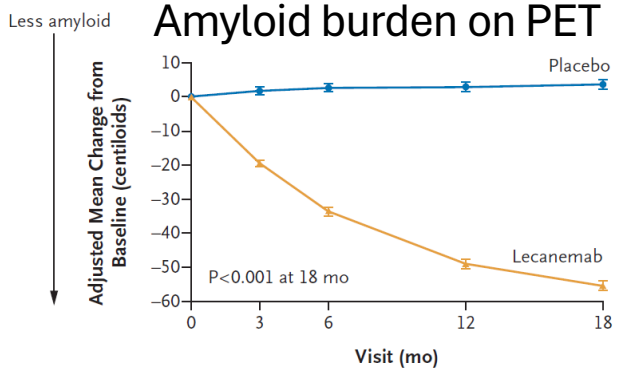
27% slowing by lecanemab at 18 months[2]

TRAILBLAZER-ALZ 2[3]



No. of participants							
Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

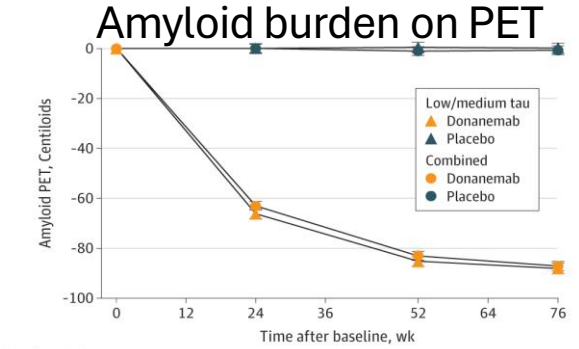
22% slowing by donanemab at 76 weeks[3]



No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

Mean <30 Centiloids for lecanemab at 18 months[1]

Difference of -59.1 Centiloids at 18 months[1]



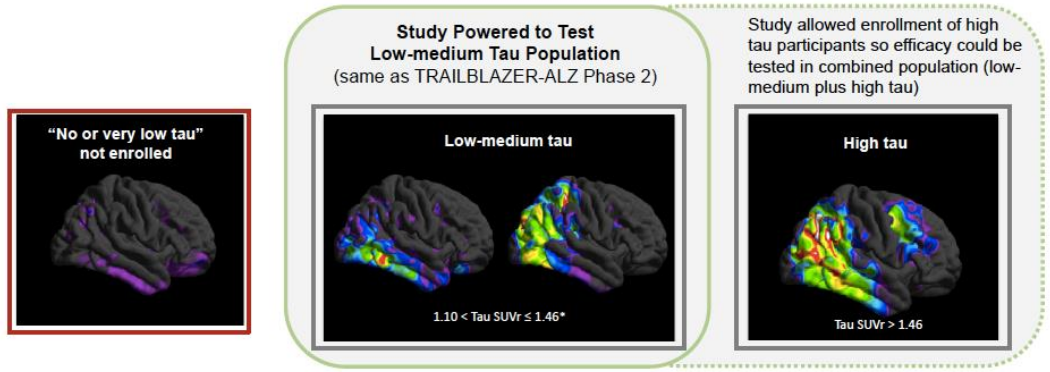
No. of participants				
Low/medium tau				
Donanemab	525	521	463	433
Placebo	556	552	498	470
Combined				
Donanemab	765	760	670	614
Placebo	812	805	729	690

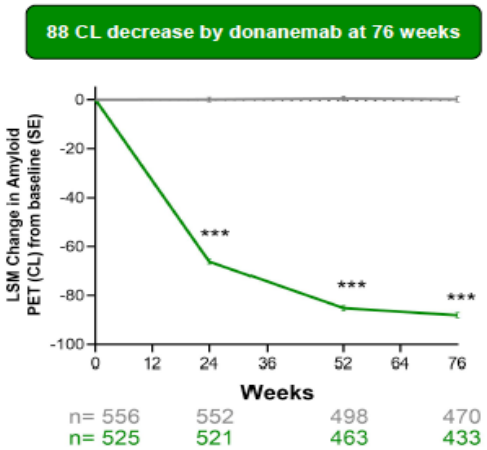
87 CL decrease by donanemab in combined tau population at 76 weeks[3]

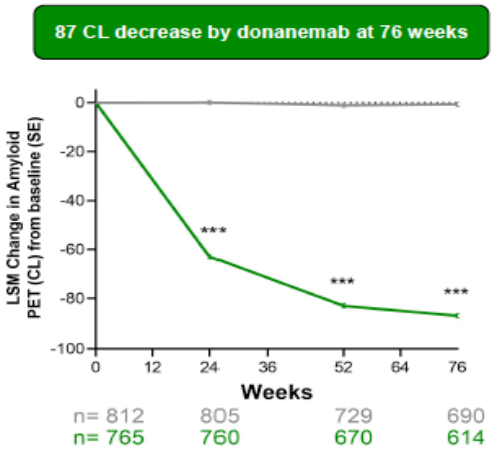
•AD/PD, Alzheimer's and Parkinson's Diseases; CDR, clinical dementia rating; CL, centiloid; iADRS, integrated Alzheimer's Disease Rating Scale; CTAD, Clinical Trials on Alzheimer's Disease; LS, least squares; PET, position emission tomography; SB, sum of boxes; SE, standard error.

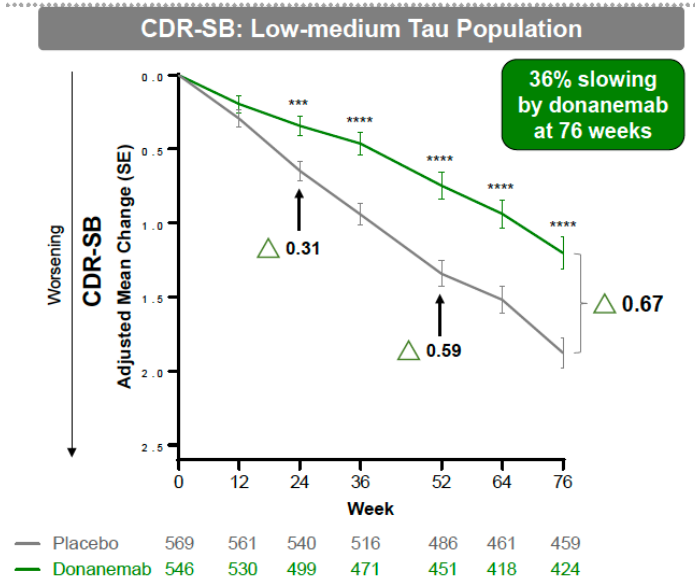
•1. van Dyck C, et al. N Engl J Med. 2023;388:9–21; 2. van Dyck C, et al. Presented at CTAD 2022, San Francisco, CA, USA; 3. Sims J, et al. *JAMA* 2023;330:512–527.

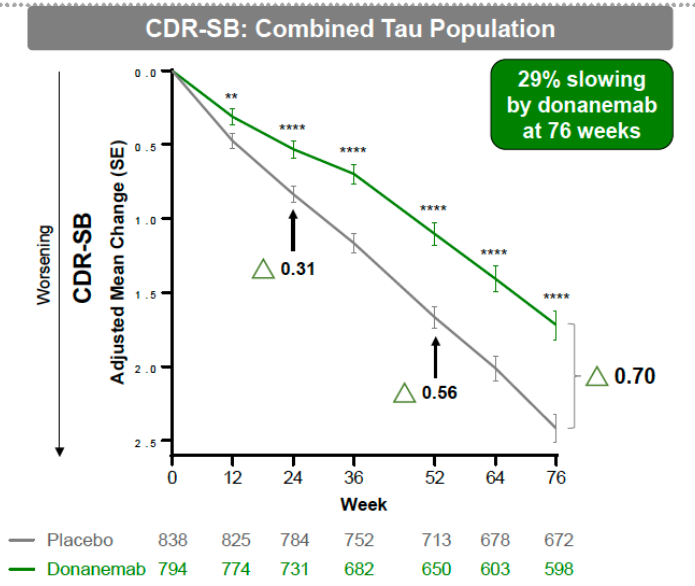
Evidence suggests that treating earlier is better











Sims J et al ., *JAMA Neurology*; 2023

Effects of anti-amyloid therapies in AD at post-mortem

Pathology

- motheaten and reduced amyloid plaques
- activated microglia
- some relative reduction in tau accumulation

BUT

- cases progressed clinically
- at PM, all at Braak stage V/VI

-> tau accumulated in spite of amyloid removal

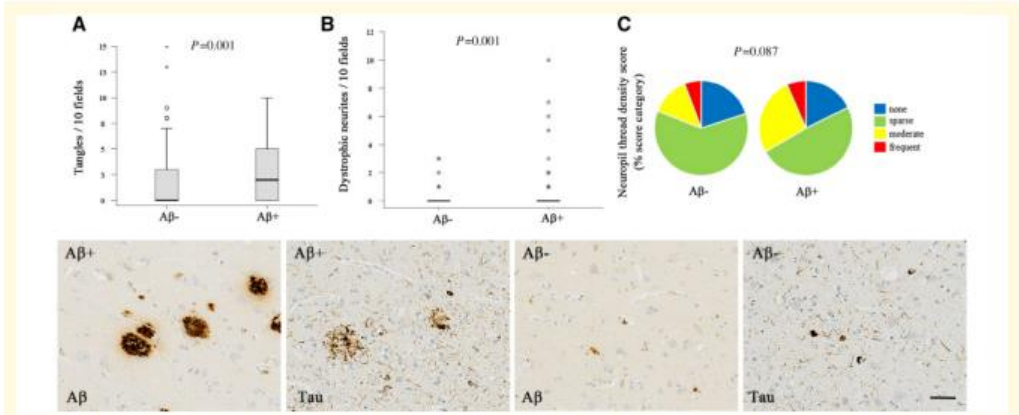
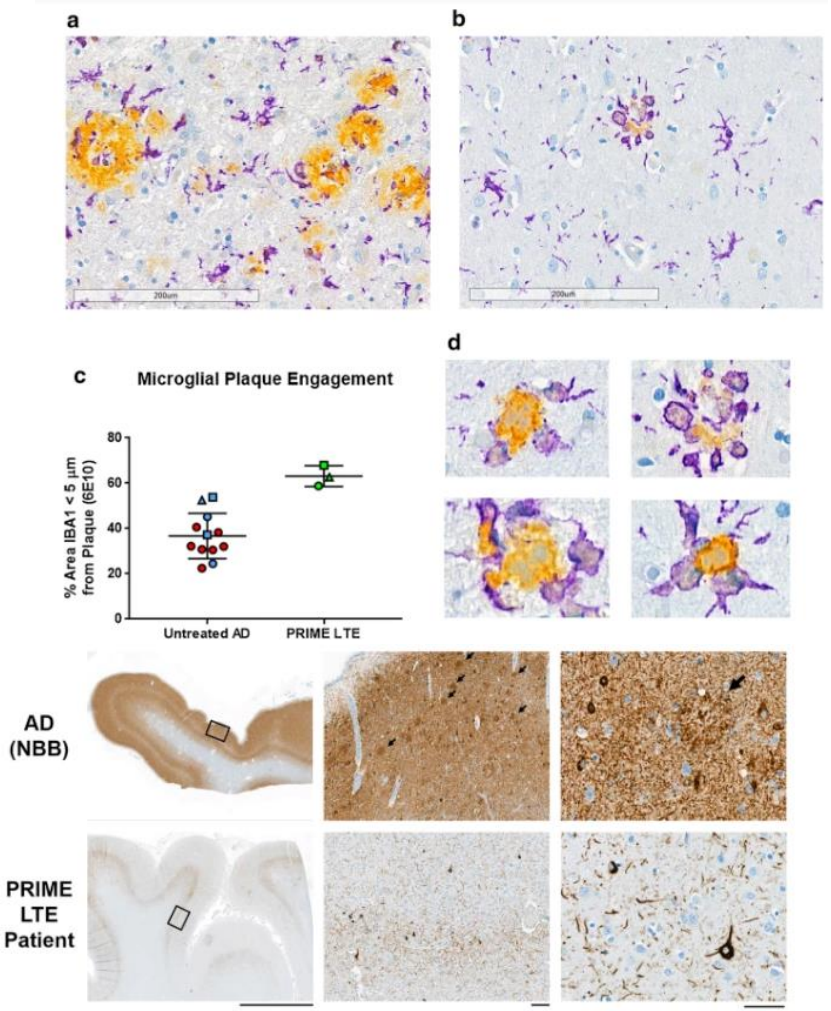


Figure 4 The effect of amyloid-β removal was quantified for each of the different histological features of intraneuronal tau accumulation (tangles, dystrophic neurite clusters and neuropil threads) by comparing cortical regions with amyloid-β plaques remaining (Aβ+) to regions with amyloid-β plaques removed (Aβ−). There were significantly fewer tangles and dystrophic neurite clusters in the regions where amyloid-β plaques had been removed in response to the amyloid-β immunotherapy; not significant for neuropil threads. Scale bar = 50 μm.

Persistent neuropathological effects 14 years following amyloid-β immunization in Alzheimer's disease

James A.R. Nicoll,[1,2] George R. Buckland,[1] Charlotte H. Harrison,[1] Anton Page,[3] Scott Harris,[4] Seth Love,[5] James W. Neal,[6] Clive Holmes[1,7] and Delphine Boche[1]



Acta Neuropathologica (2022) 144:145–153
https://doi.org/10.1007/s00401-022-02433-4

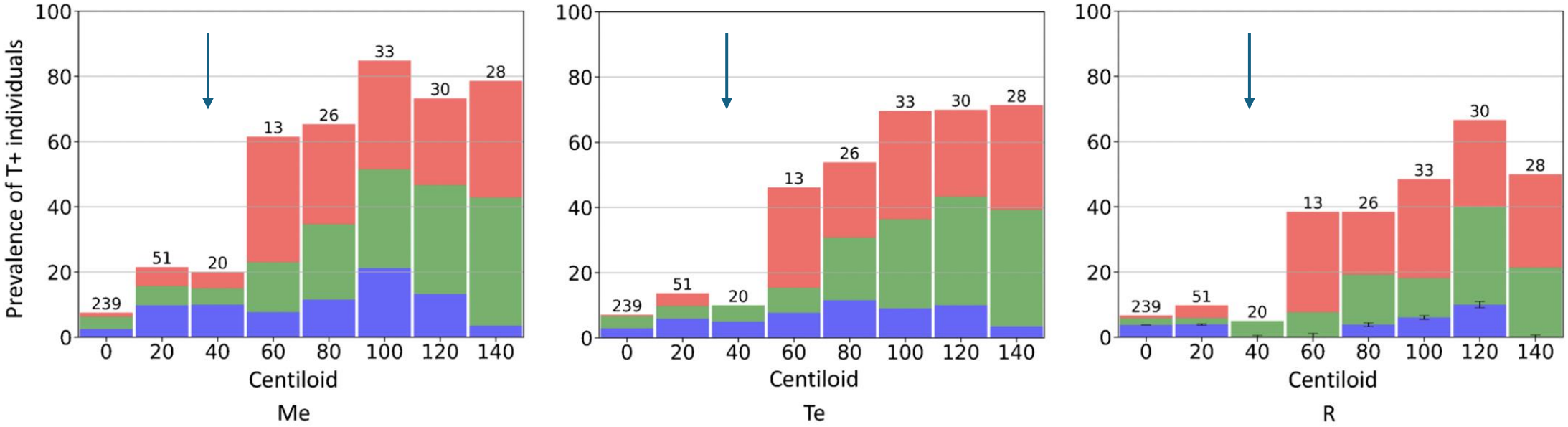
CASE REPORT

Alzheimer disease neuropathology in a patient previously treated with aducanumab

Edward D. Plowey[1] · Thierry Bussiere[1] · Raj Rajagovindan[1] · Jennifer Sabalusky[1] · Stefan Hamann[1] · Christian von Hohn[1] · Carmen Castrillo-Viguera[1] · Alfred Sandrock[1] · Samantha Budd Haeberlein[1] · Christopher H. van Dyck[2] · Anita Huttner[3]

Tau / amyloid interaction: clues on when to intervene?

- ? 40-60 centiloids is point of disconnect - ‘cataustrophe’*
  with dramatic acceleration in spread of tau

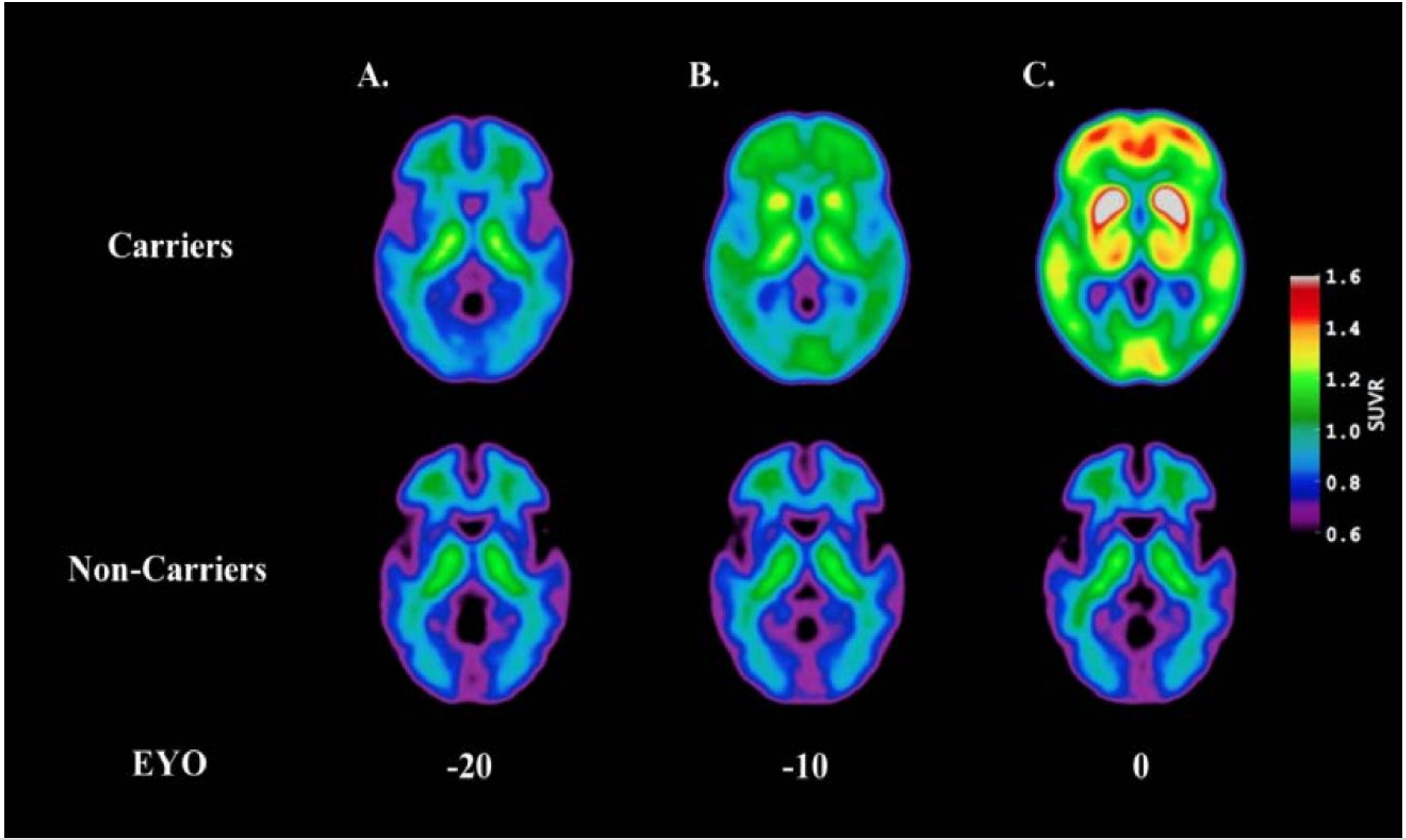


Me – mesial temporal
Te – temporoparietal
R – rest of the neocortex

CU: blue, MCI: green, AD: red

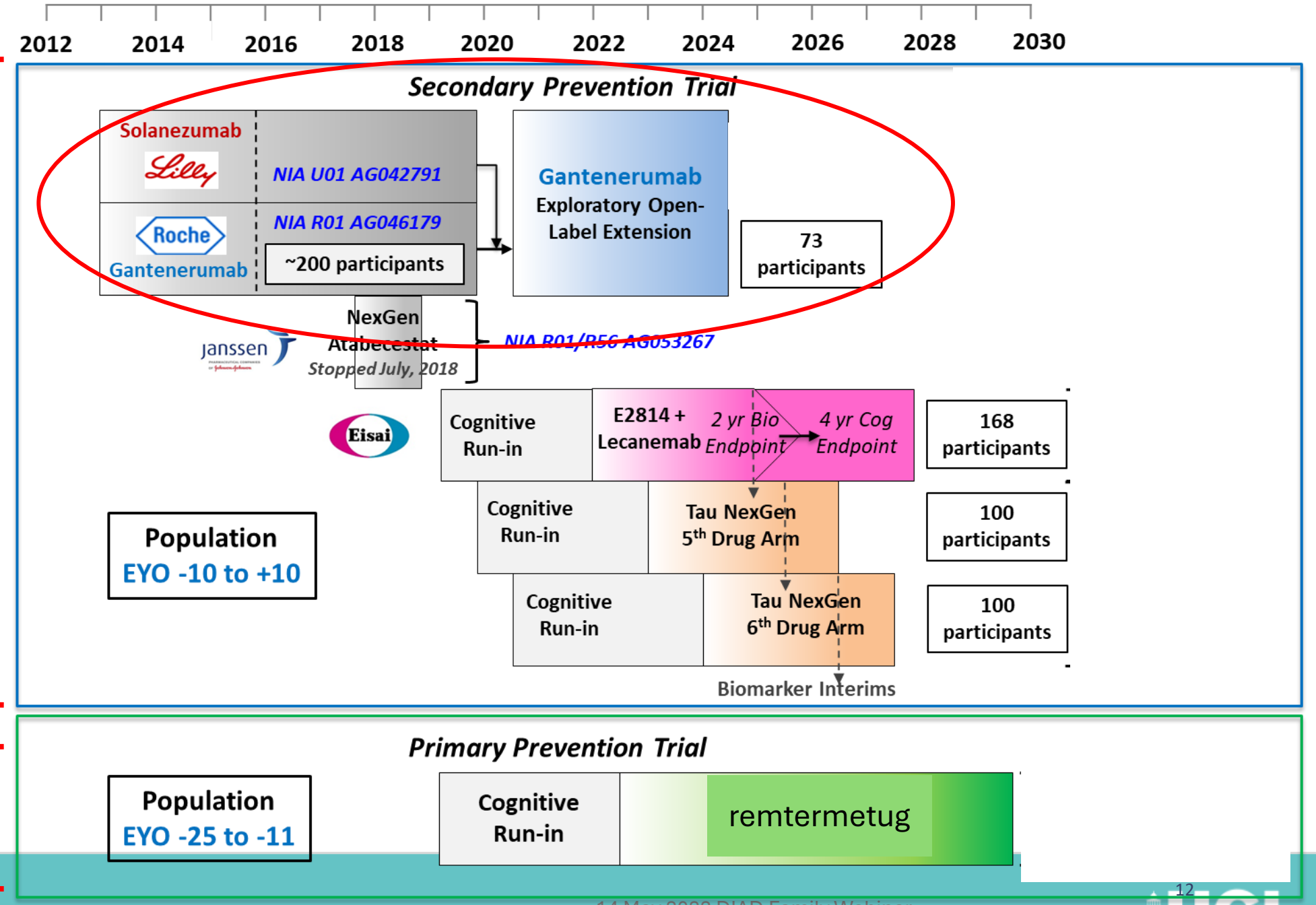
Tau tracer – MK-6240

ADAD: an exemplar for prevention trials

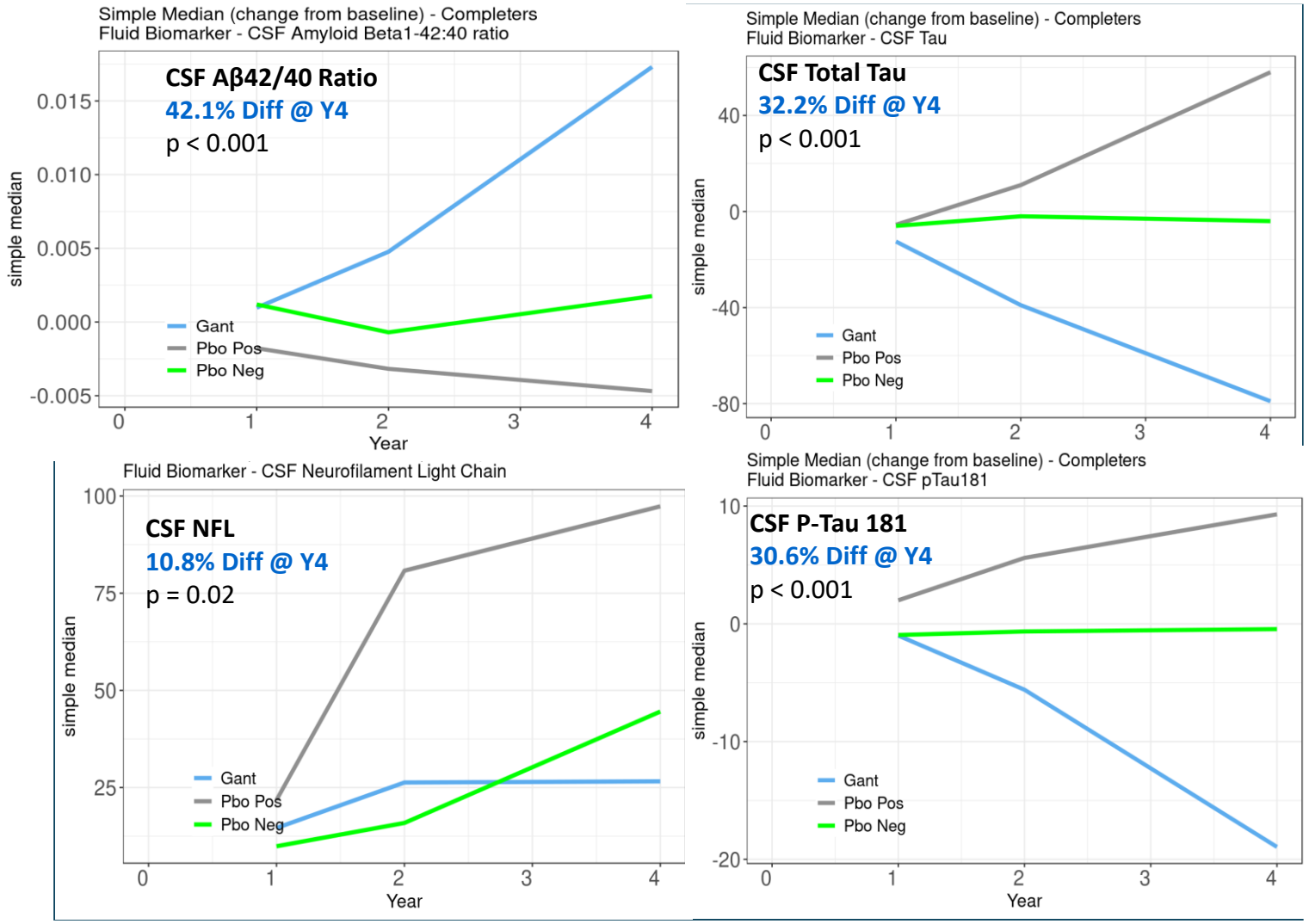


•Courtesy of Tammie Benzinger and Tyler Blazey

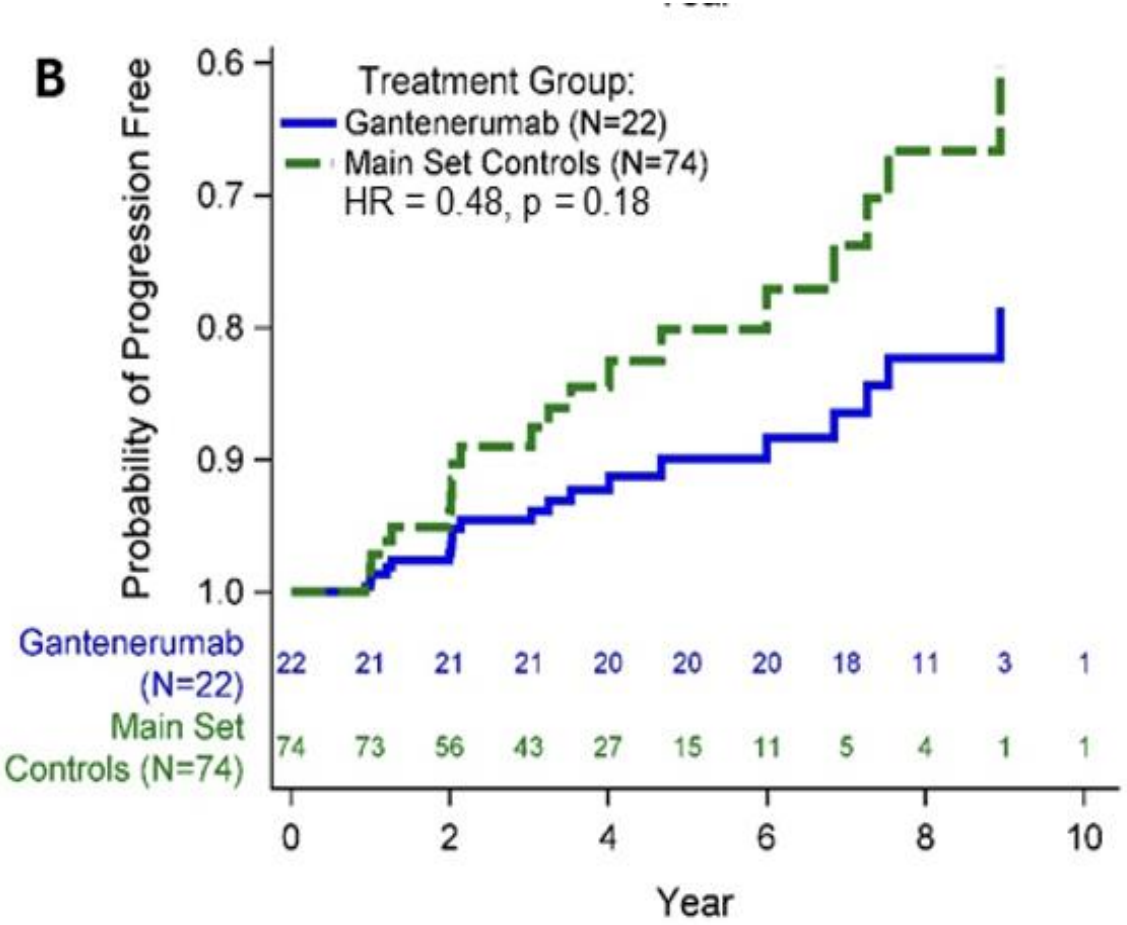
DIAN-TU ADAD Trial Platform



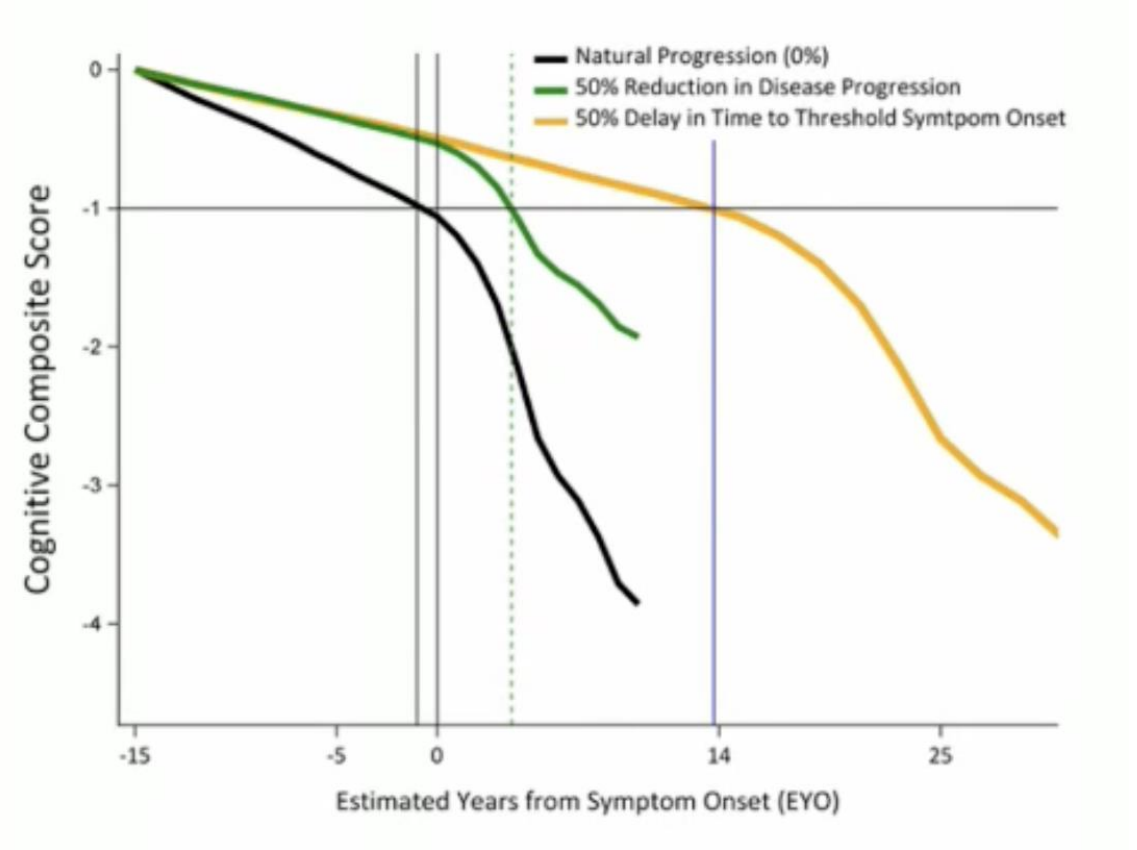
Biomarker changes gantenerumab vs placebo at 4 years



Treatment of ADAD at risk with gantenerumab > 10 years



50% reduction in risk of progression to symptomatic over 10 years



May translate into 5 - 15 years delay in onset

Bateman, Randall J et al. Lancet Neurology, Volume 24, Issue 4, 316 - 330

Secondary prevention in AD

Pathology present; prevent symptom onset

Key requirements:

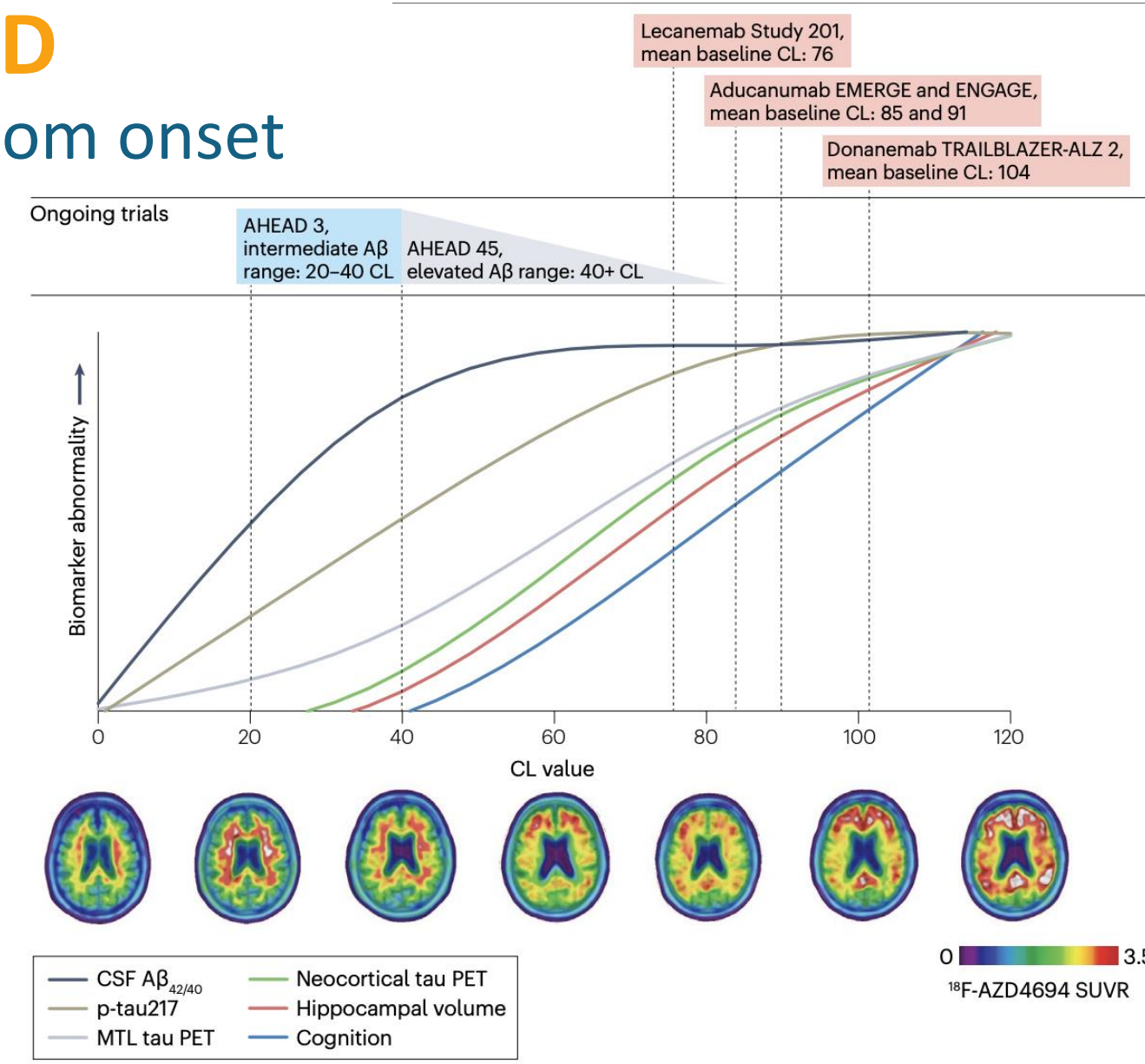
- Able to detect pathology pre-symptomatically
- Need to be able to predict symptom onset
- Enough time to alter trajectory
- Treatment able to slow or stop downstream effects

Challenges:

- Identification and staging harder => heterogeneity
- Recruitment more challenging
- Outcome measures: progression slower and variable
- Duration: long, expensive trials if cognitive measures - surrogates needed

Ongoing trials in preclinical AD/ADAD

AHEAD 3-45; DIAN-TU; Trailblazer ALZ 3



Plasma biomarkers:

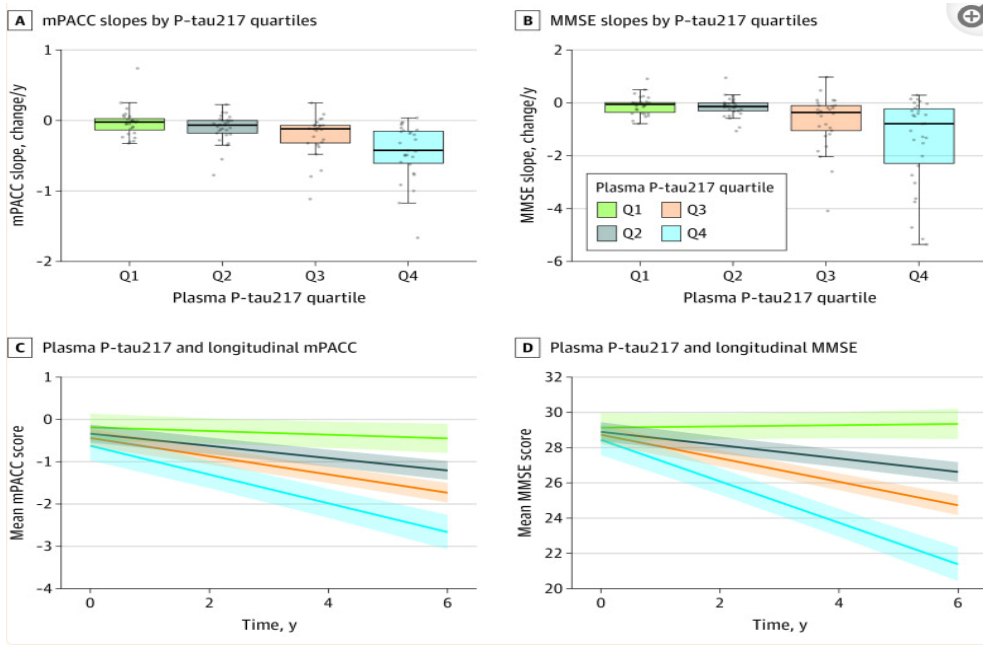
Biological identification; predicting symptom onset

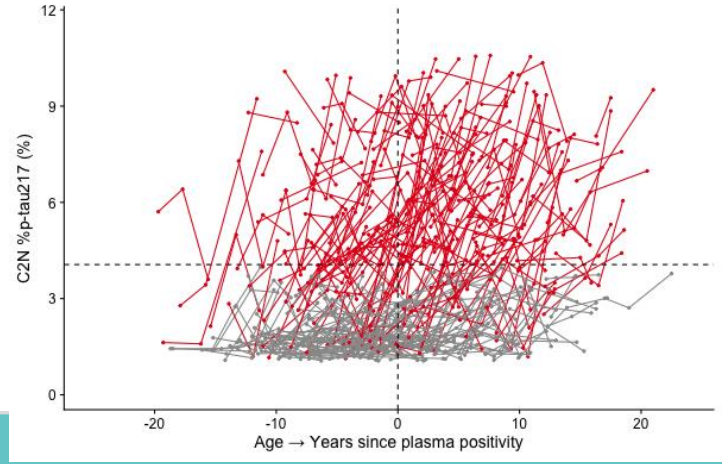
PET (amyloid and tau) gold standard
however,
expensive and limited resource

Scaleable markers crucial for preclinical AD

- **eg plasma ptau 217 'amyloid bothering tau'**
  detects early change - potential to enrich recruitment
  - may predict progression to symptoms
    - higher levels correlate with more rapid cognitive deterioration
    - clock models suggest can predict individual risk

  - used in trials; clinical roll out continues

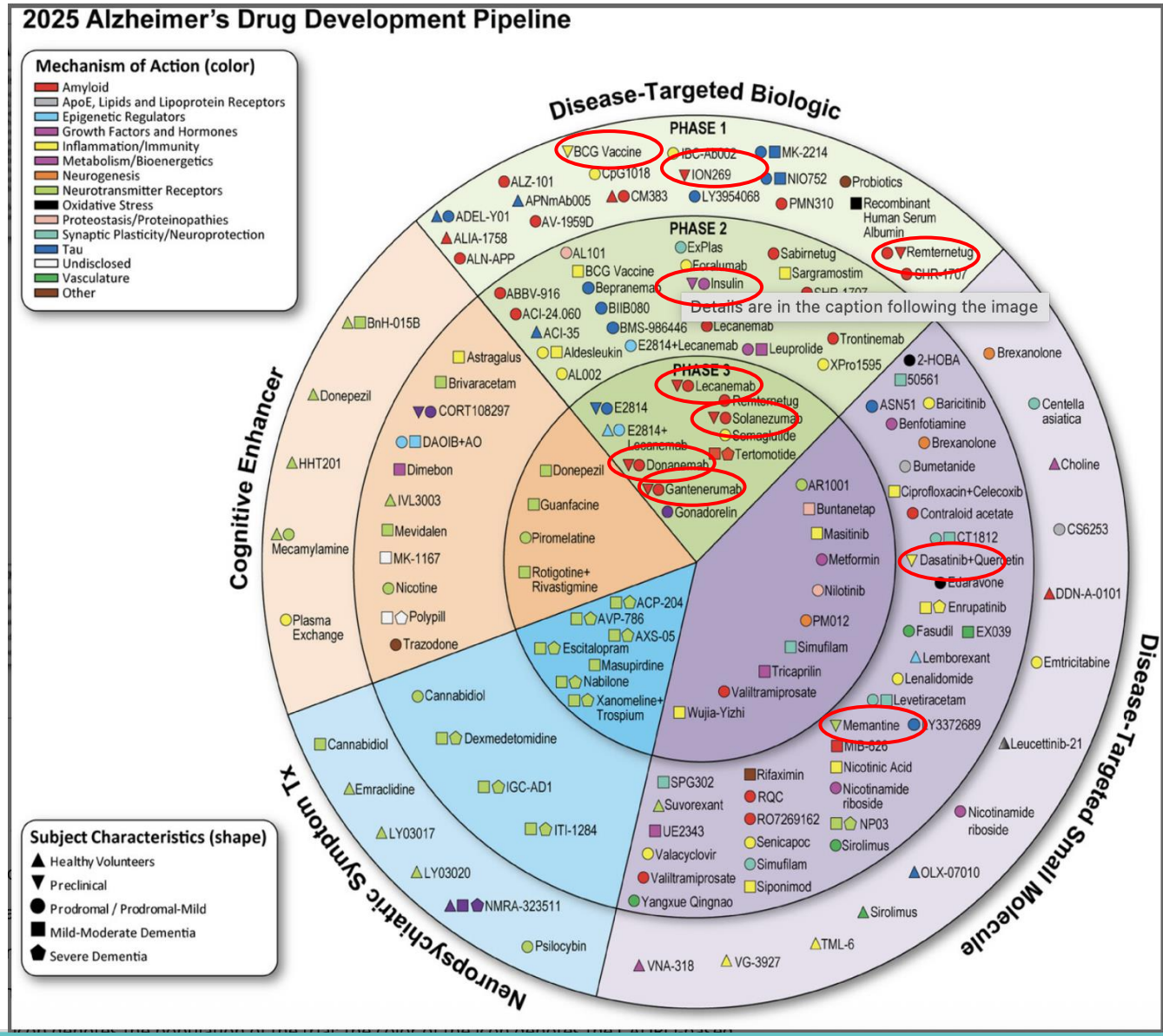




Petersen et al, Nature Medicine 2026; Mattsson-Carlgren et al JAMA Neurology 2023

Drug properties for prevention trials

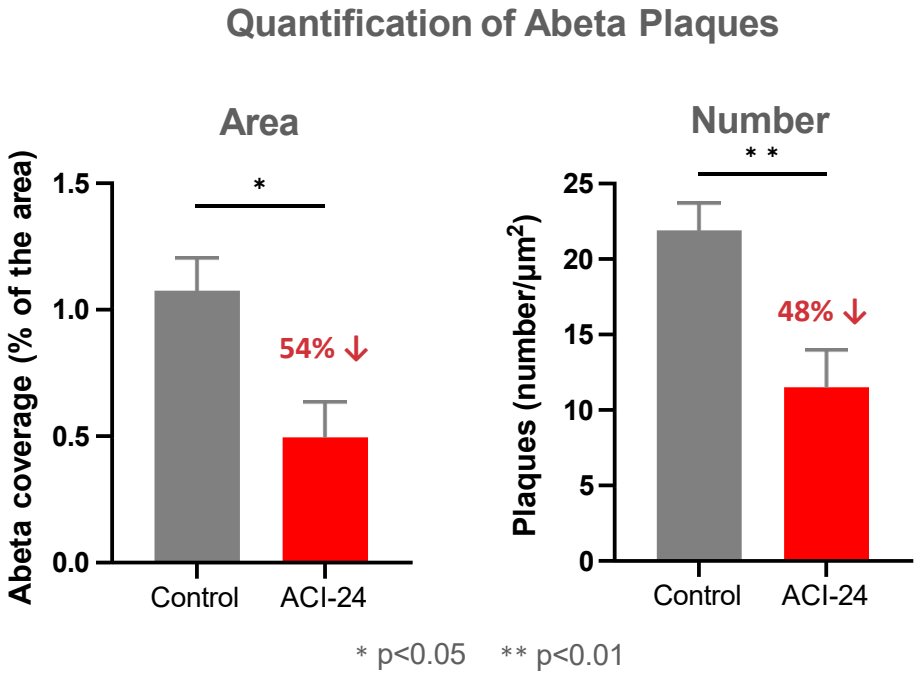
- **Safety**
  - Risk benefit balance changes in at risk population
  - Some SFx likely to be less problematic eg ARIA
- **Low burden of administration**
  - Oral ideal
  - S/C self-administered infrequent dosing
  - IV/IT very infrequent; home dosing
- **Potential for implementation in the community**
- **Potential MOAs in prevention**
  - **Immunotherapy**
    - **passive - current trials**
    - **active - eg ABATE**
  - Gene silencing ASO/siRNA - APP, ApoE
  - Small molecules eg GSM



Active immunotherapy II: Phase 1b/2 (ABATE) ongoing in AD/DS

ACI-24 reduces Abeta plaque burden

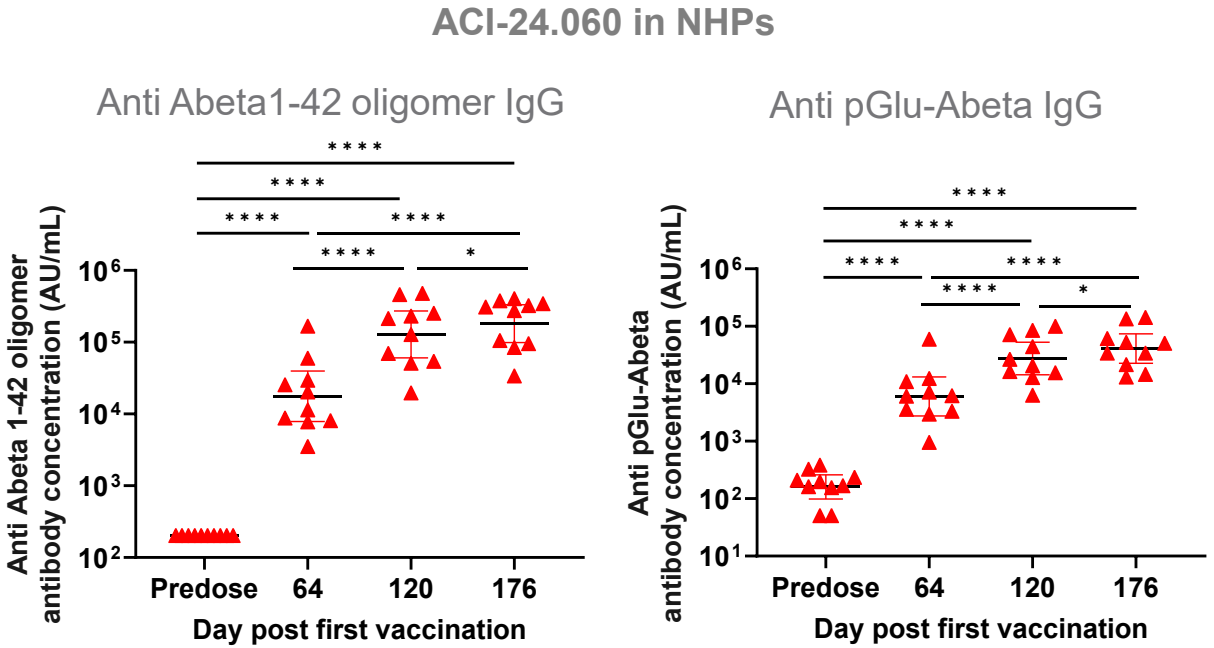
Significant Abeta plaque reduction *in vivo* in preclinical APPxPS1 model[1]



* p<0.05 ** p<0.01

Ref: Njavro, *et al.*, Cells 2023

ACI-24 shows a strong immune response against Abeta



* p<0.05 **** p<0.0001

- ACI-24 treatment significantly reduces Abeta plaque burden in aggressive APPxPS1 mode
- Sustained, boostable IgG response against Abeta oligomers and pyroglutamate Abeta

(1) Alzheimer's disease mouse model: APPxPS-1 double transgenic mice

Lessons from AD trials, moving towards prevention

- **Right drug:**
  - Low burden, safe and appropriate mechanism
  - Demonstrates target engagement
- **Right time:**
  - Early intervention - preserve brain function; prevent neuronal damage
  - Stage of disease appropriate to target
- **Right participant:**
  - Pathology specific identification - biomarkers crucial
  - Genetic forms of disease can inform future therapies in sporadic AD
- **Right Trial:**
  - Appropriate dose modelling in early phase
  - Right monitoring; right schedule for safety and efficacy
  - Screening methods with scaleable markers and new methods of recruitment
- **Right Outcome Measures:**
  - Early phase mechanistic; later phase real world
  - Current primary outcome measures cognitive and functional: biological surrogate?
  - Meaningful to patients

Cummings et al., Alz Res & Therapy 2019

UKDTN
Dementia Trials Network

Acknowledgements and Thanks:

Biomedical Research Centre, UCLH
Dementia Research Centre, UCL
Leonard Wolfson Experimental Neurology Centre, NHNN

NIHR | National Institute for Health and Care Research

UCL

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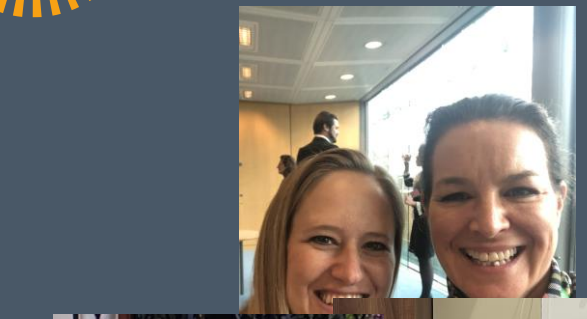




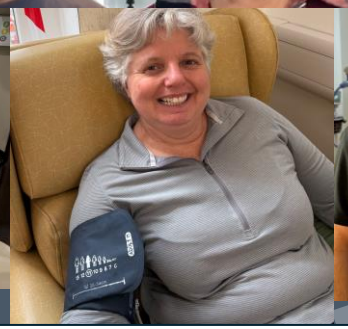













www.ukdtn.org

Thank you to our participants and partners!

Targeting α-Synuclein in Parkinson‘s Disease: Rationale and Supporting Evidence

‚From Treatment to Prevention in Parkinson‘s Disease‘ Symposium Supported by AC Immune

Werner Poewe
emeritus Professor of Neurology
Dept. of Neurology
Medical University of Innsbruck
Austria

MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

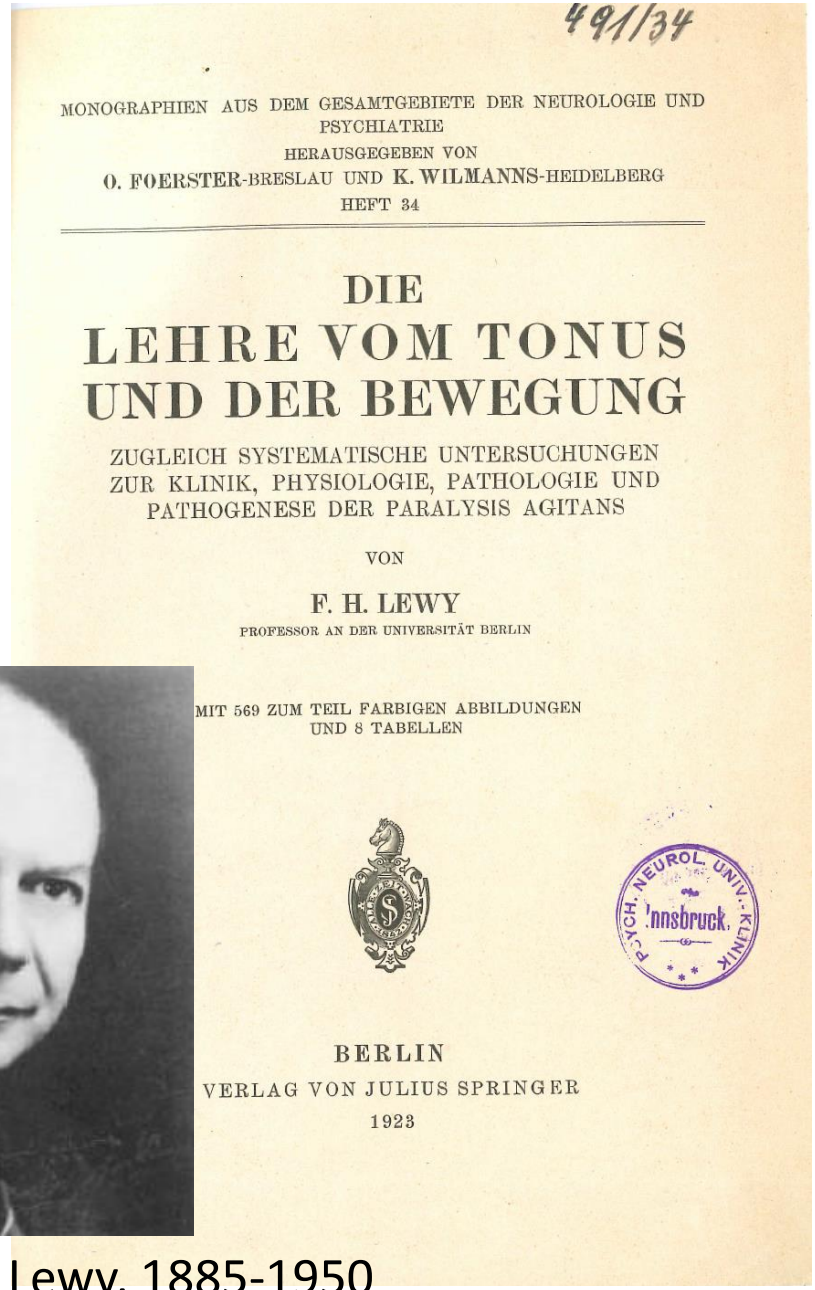
Disclosures

Consultancy	AbbVie, Affiriris, AC Immune, Alterity, BIAL, Biogen, Britannia, Lilly, Lundbeck, MSD, NeuroDerm, Neurocrine, Roche, Sanofi, Stada, Takeda, Teva, UCB
Grants	MJFF; EU FP7 & Horizon 2020
Lecture fees	AbbVie, AC Immune, BIAL, Britannia, Boehringer, Eisai, Lundbeck, Merz, Stada, Zambon

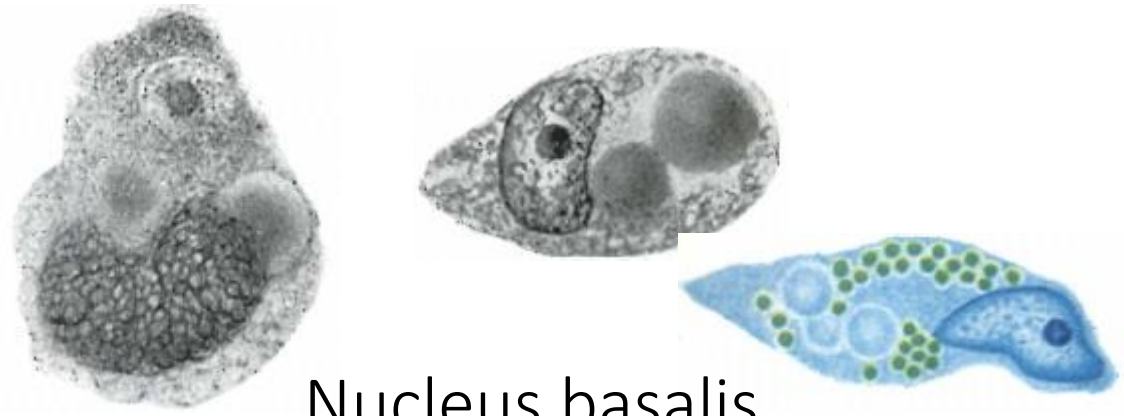
OUTLINE

- A look Back: Solving the mystery of the Lewy Body
- α-Synuclein and PD Pathogenesis
- α-Synuclein and ‘Biological‘ PD Definition:

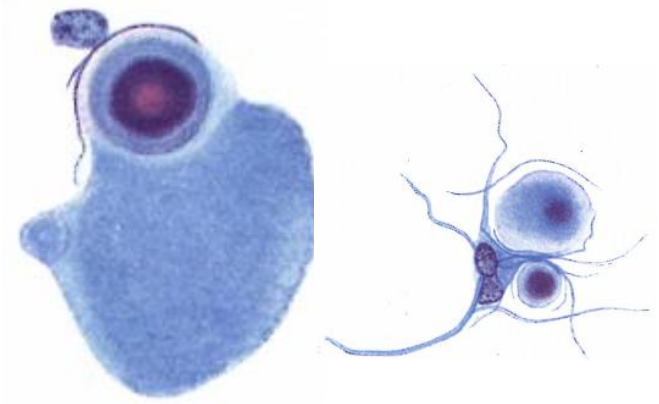
  Implications for Early Diagnosis and DM trials



Friederich H. Lewy, 1885-1950

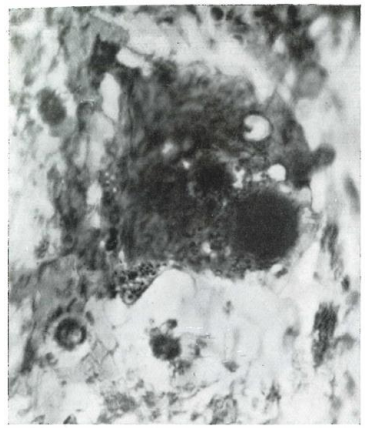


Nucleus basalis



‚vegetative nucleus of the oblongata‘

Substantia nigra



L. Golbe

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

R. Duvoisin

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

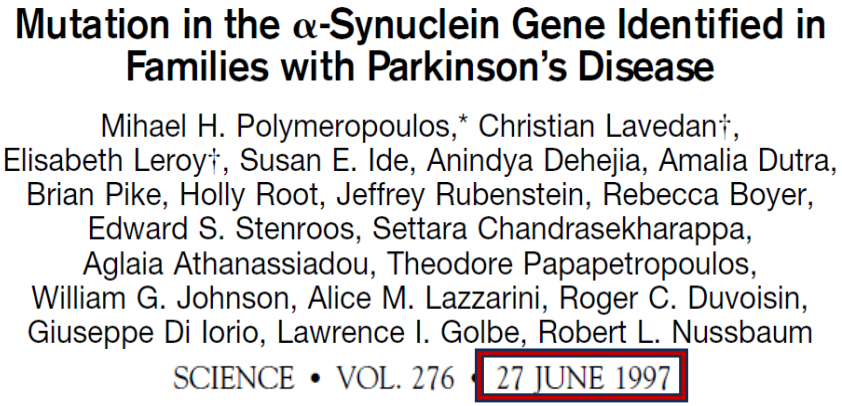
SCIENCE • VOL. 276 • 27 JUNE 1997

M. Polymeropoulos

R. Nussbaum

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]



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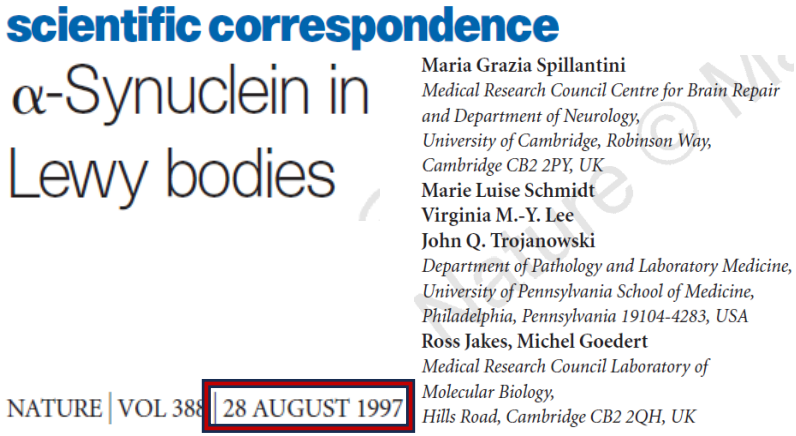

scientific correspondence

α-Synuclein in Lewy bodies

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Marie Luise Schmidt
Virginia M.-Y. Lee
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Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK

NATURE | VOL 388 | 28 AUGUST 1997

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.

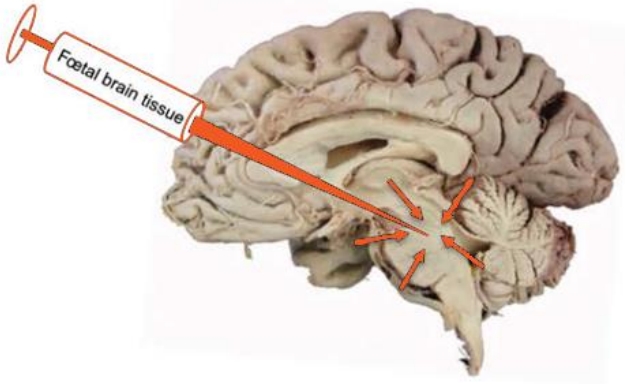
OUTLINE

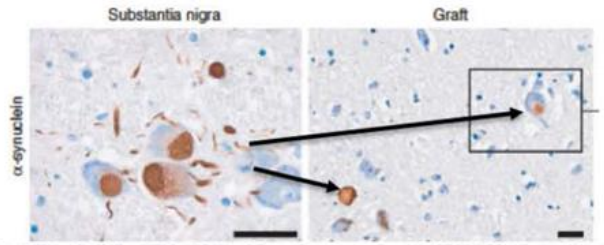
- A look Back: Solving the mystery of the Lewy Body
- **α-Synuclein and PD Pathogenesis**
- α-Synuclein and ‘Biological‘ PD Definition:

  Implications for Early Diagnosis and DM trials

α-Synuclein Propagation in PD

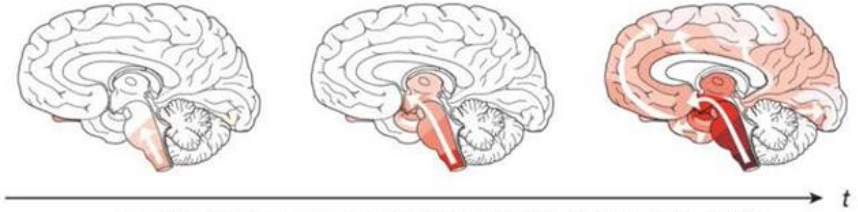
- **α-syn-rich Lewy bodies propagate from diseased parts of the brain to young healthy grafted tissue**





Li et al., (2008) Nat. Med. 14: 501-503, Kordower et al., (2008) Nat. Med. 14: 504-506

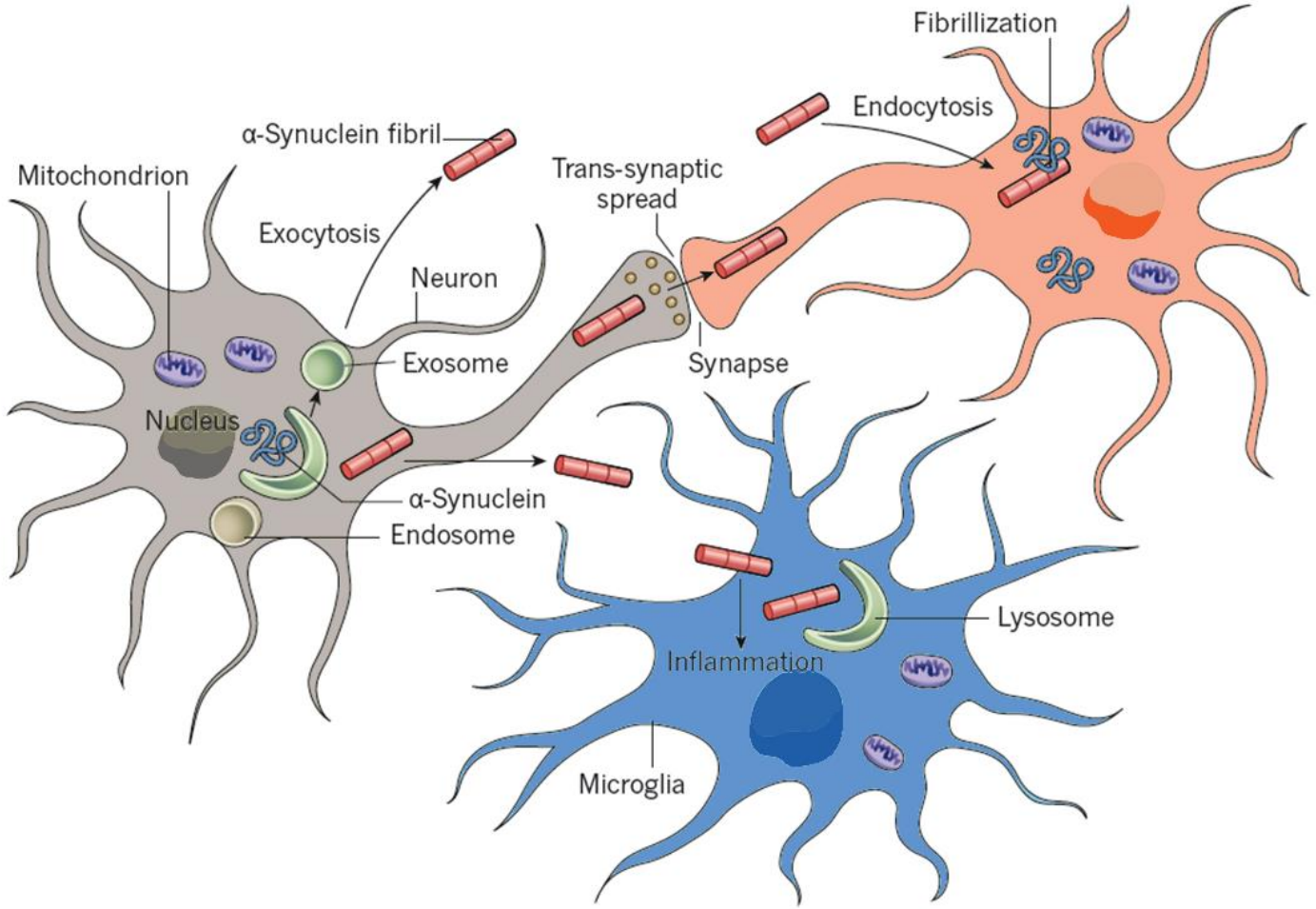
- **Relationship between Lewy bodies distribution in the brain and disease stages**



Adapted from Jucker and Walker 2013, Nature 501, 45-51

Image/slide courtesy of Professor Ronald Melki, France.
Li J-Y, et al. Nat Med. 2008.; Kordower JH, et al. Nat Med. 2008.; Jucker M, Walker LC. Nature. 2013.

Extracellular α-synuclein and the prion hypothesis

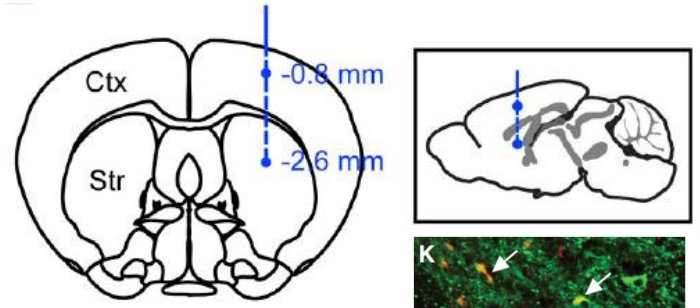


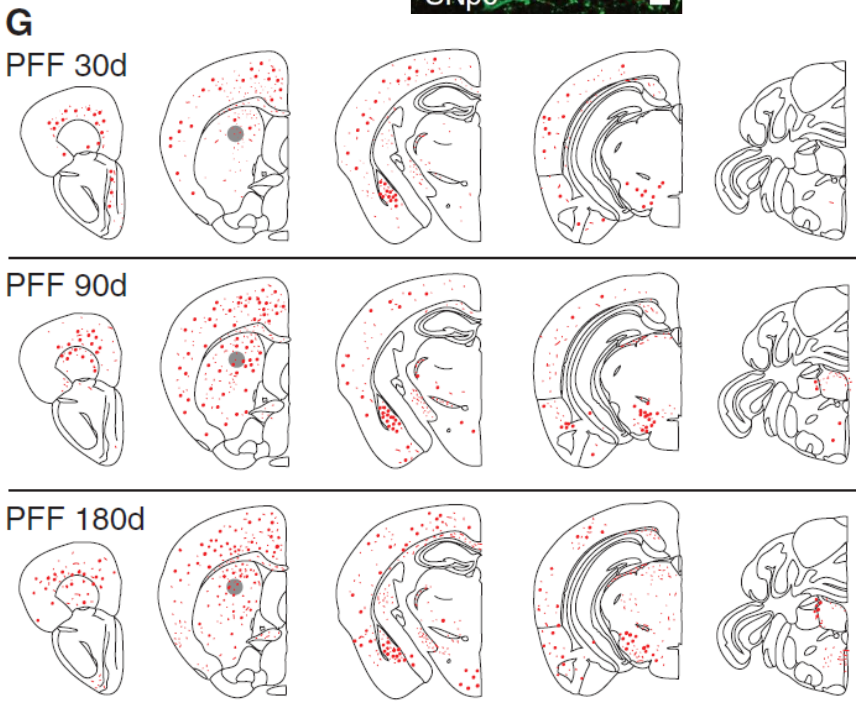
Abeliovich A, Gitler AD. Nature. 2016.

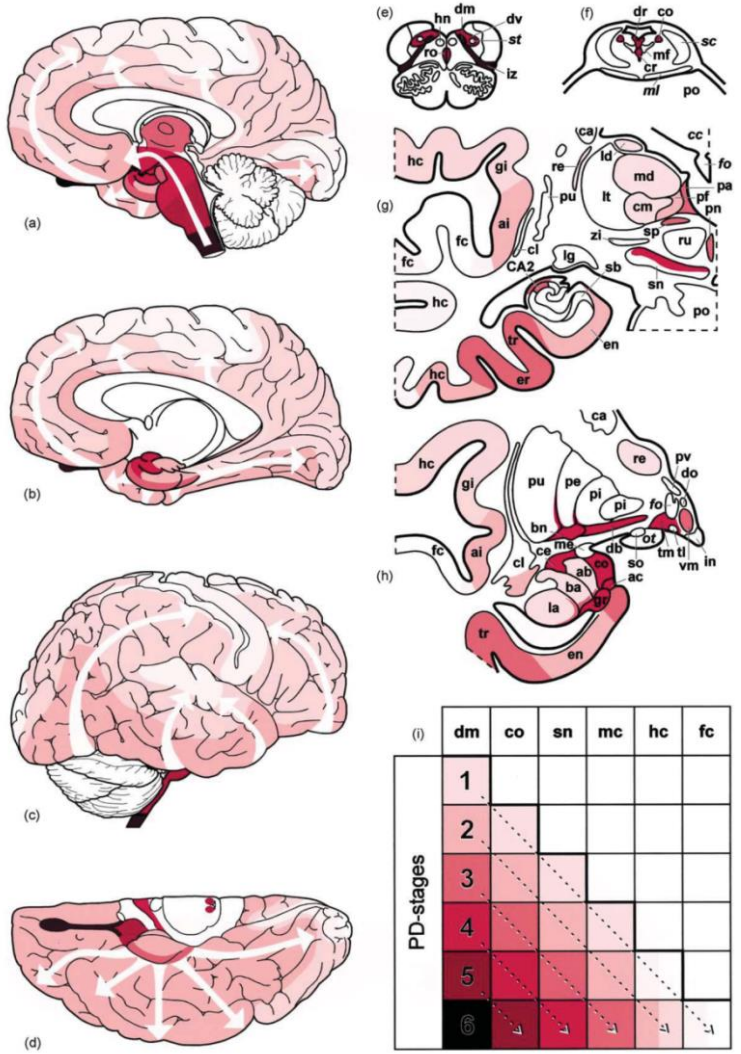
Science
AAAS

Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice
Kelvin C. Luk *et al.*
Science **338**, 949 (2012);
DOI: 10.1126/science.1227157

Braak's staging

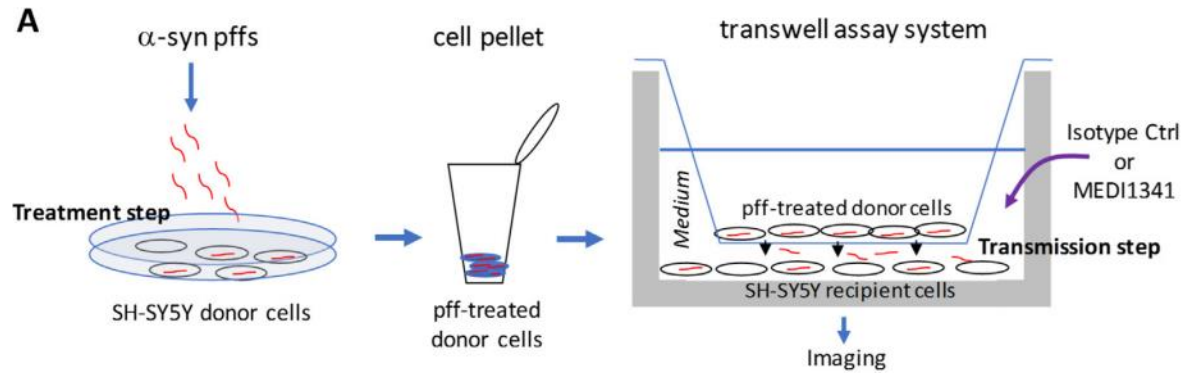


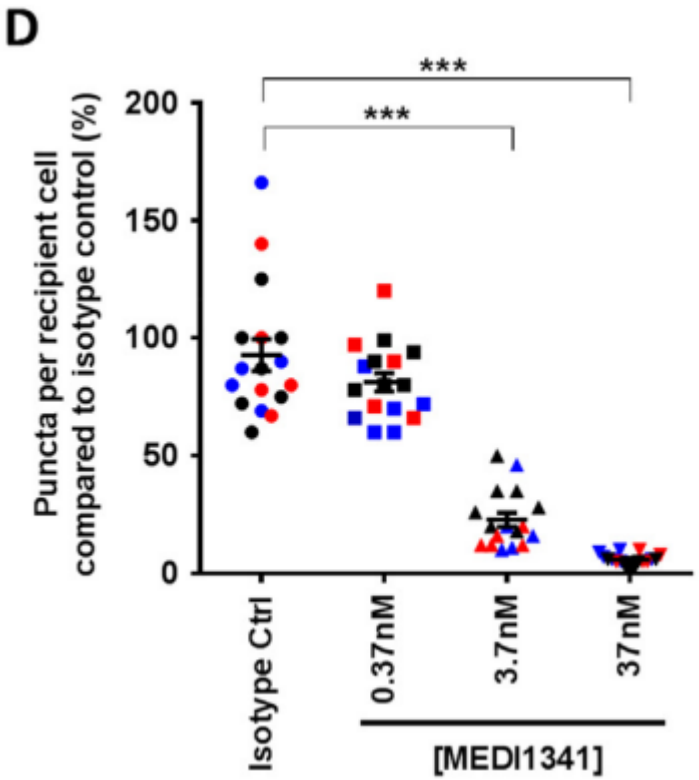


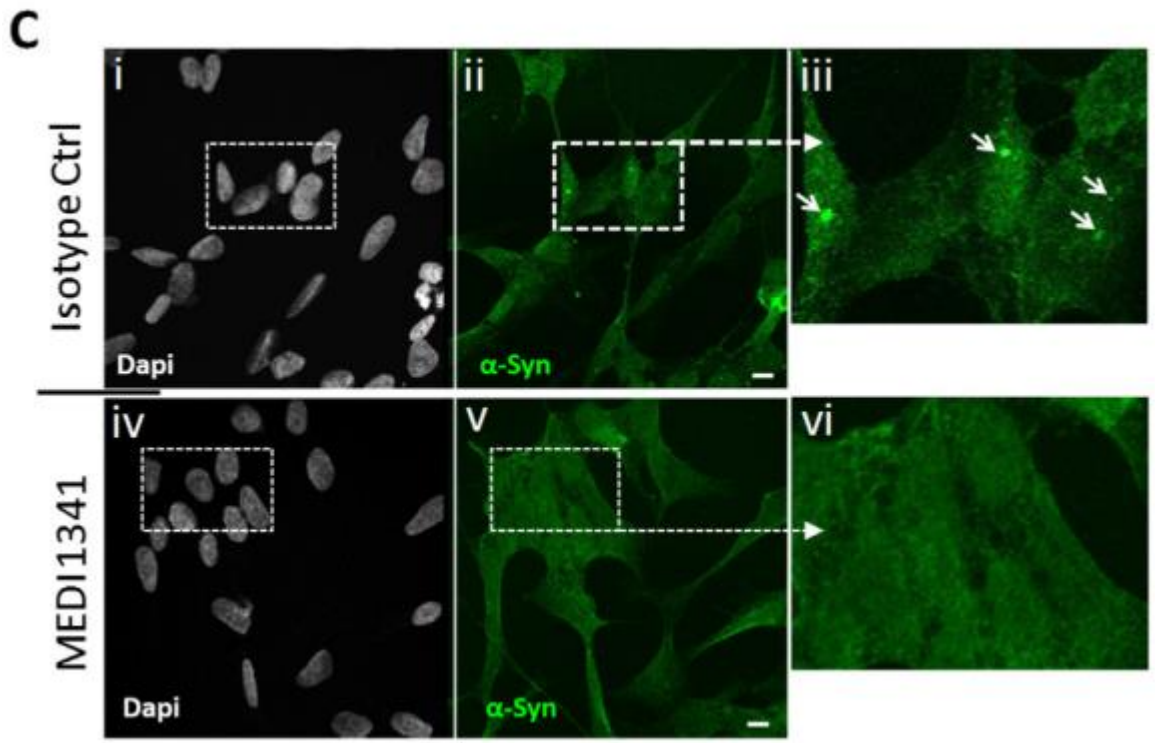


Braak et al. 2003

Inhibition of α-Synuclein Spreading by Monoclonal AB's (MEDI1341)







D.J. Schofield, et al. Neurobiology of Disease 132 (2019) 104582

PD Clinical Trial Pipeline *

- N_{tot} = 136
  - Symptomatic therapies : 76 (56%)
  - Disease-modifying ther.: 60 (44%)

- DM Trials by Phase
  - Phase 1 : 37%
  - Phase 2 : 58%
  - Phase 3 : 5%

- DM Trials by Target
  - α-synuclein : 15%
  - GBA : 12%
  - Kinase-Inhibitors (incl. LRRK2) : 11%
  - Anti-inflammatory : 10%
  - GLP-1 agonist : 8%
  - Mitochondria : 7%
  - Neurotrophic : 7%
  - Other : 15%

*based on ClinicalTrials.gov online registry

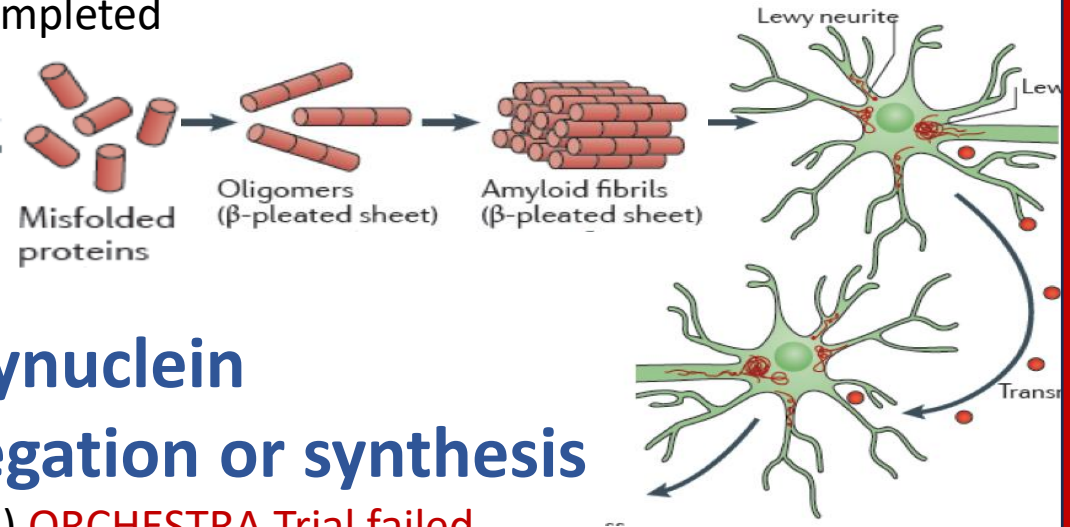
McFarthing et al. JPD 2024; 14: 899-912

α-Synuclein-targeting DM Trials in Synucleinopathies

Clearance of intracellular α-synuclein aggregates (c-ABL1 inhibition)

- **Nilotinib:** neg trials
- **Vodobatinib:** **ph.2 neg.**
- **Radotinib:** (ph2 recruiting)
- **Risvodetinib:** ph2 completed

Irwin DJ & al., Nat Rev Neuroscience 2013; 14: 626-636



Inhibition of α-synuclein misfolding, aggregation or synthesis

- **UCB0599:** (Minzasolmin) ORCHESTRA Trial failed
- **ANLE 138B: (**Emrusolmin) TOPAS Trial (MSA) ongoing
- **ATH 434:** phase 2 (MSA)+ve efficacy signals
- **ION 464**:phase 1 (MSA) ongoing

Passive Immunotherapy

- **Cinpanemab:** SPARK trial neg
- **Prazinesumab:** PASADENA&PADOVA: +ve efficacy signals
- **Amlenetug**: AMULET Trial in MSA +ve efficacy signals

Active Immunotherapy

- **PD01A/03A:** Phase 1 pos safety&immunogenicity
- **UB-312:** Phase 2a pos safety&immunogenicity
- **ACI-7104:** phase 2 ongoing

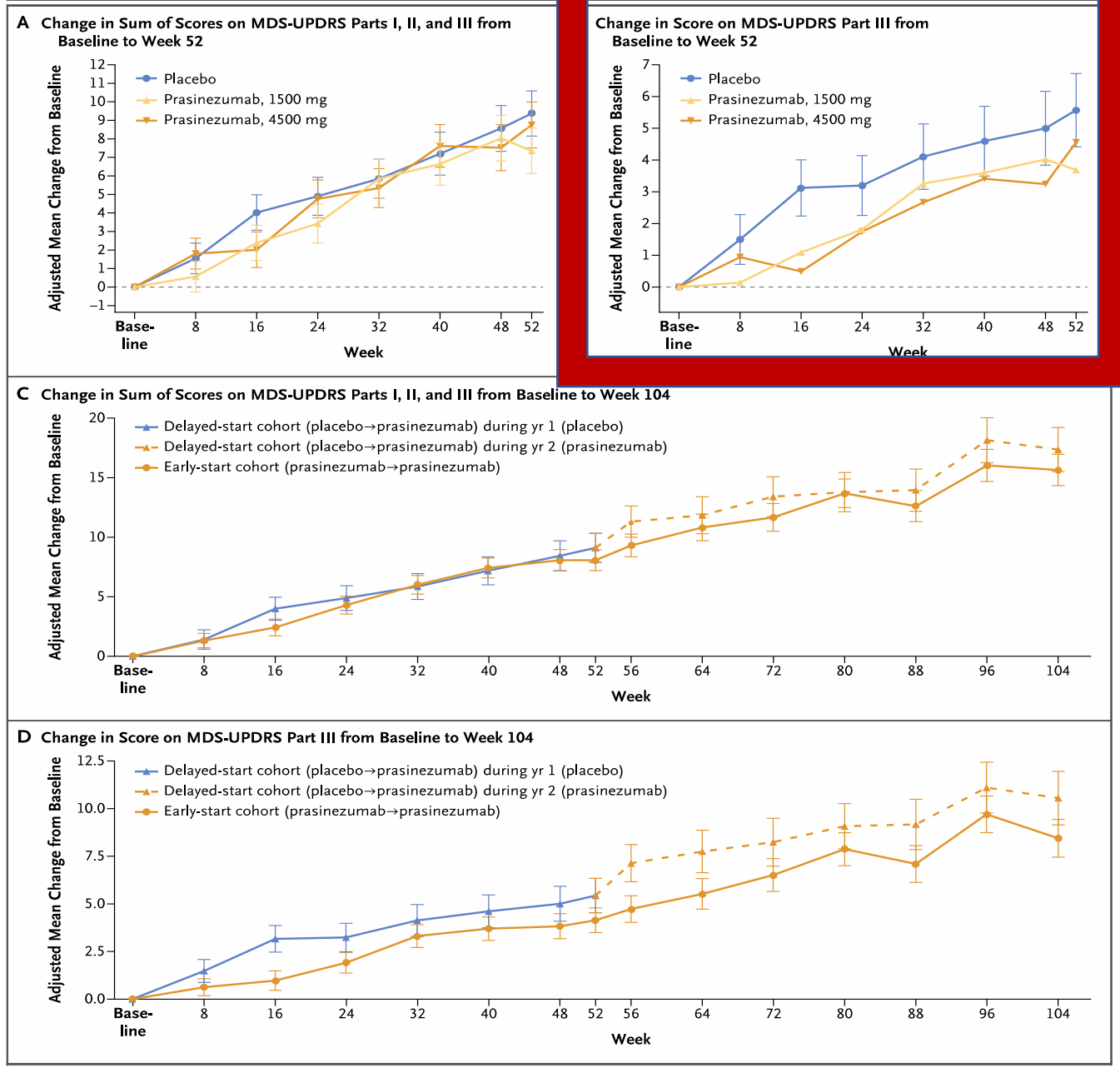
The NEW ENGLAND JOURNAL of MEDICINE

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*

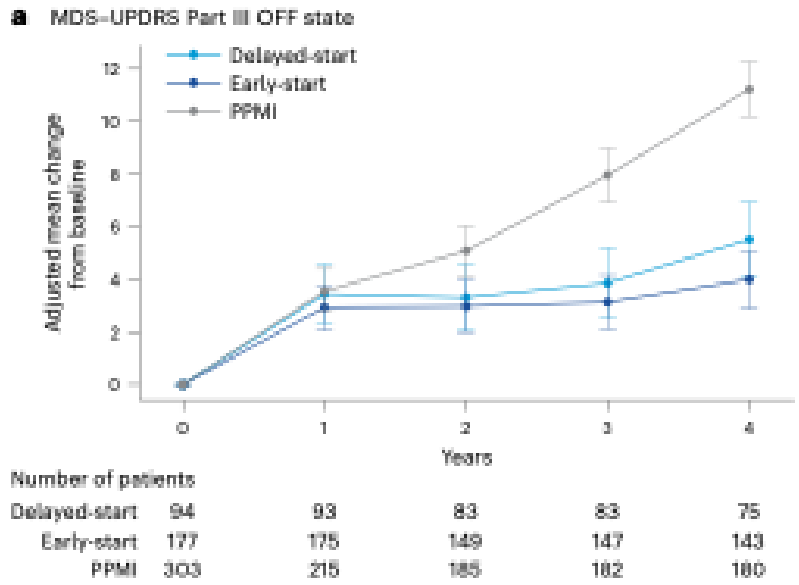
N Engl J Med 2022;387:421-32.
DOI: 10.1056/NEJMoa2202867

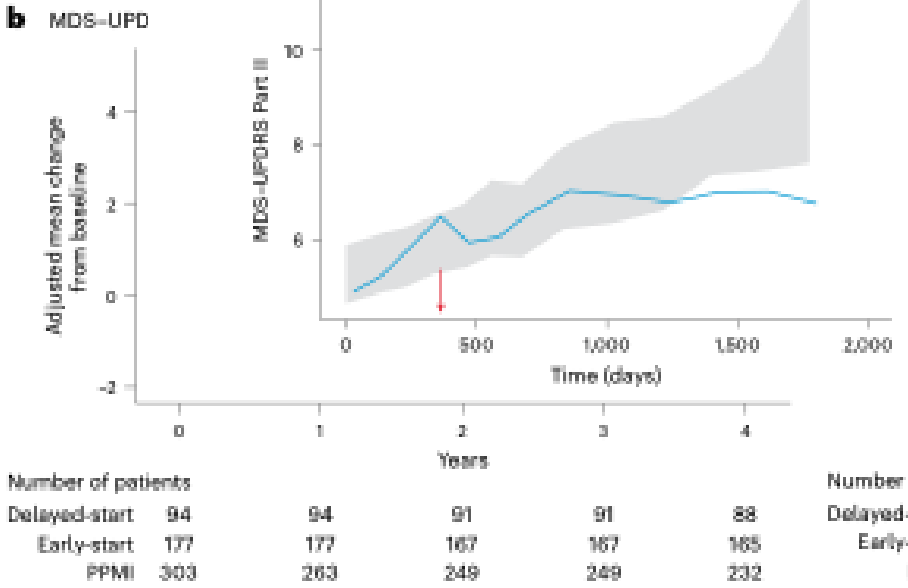


nature medicine

Article

Sustained effect of prasinezu
Parkinson's disease motor pr
open-label extension of the P

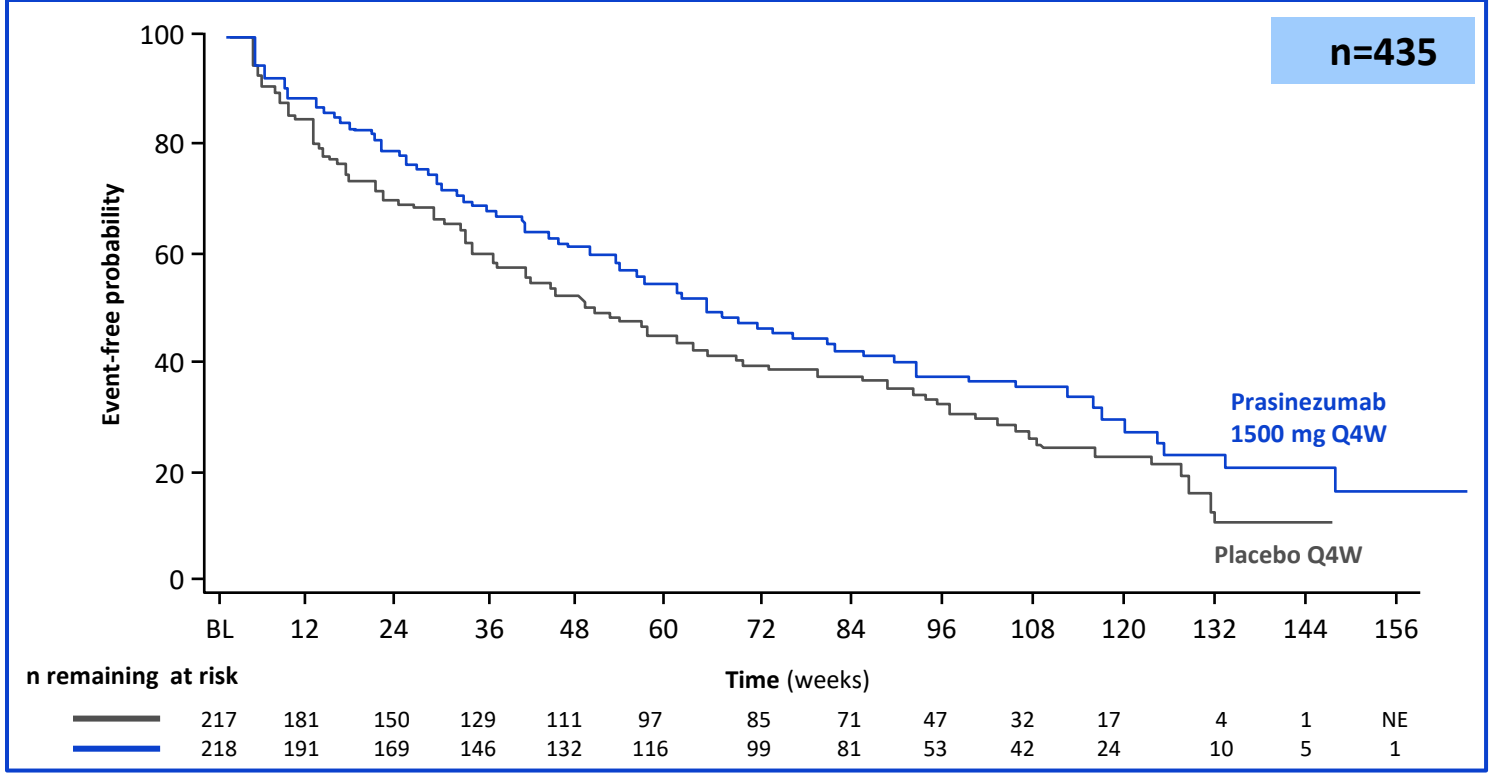




Prasinezumab delayed the time to confirmed motor progression

Signal more pronounced in prespecified L-DOPA population

Time to ≥5 points on MDS-UPDRS Part III OFF



	n	n events	Median (weeks)	95% CI
Placebo	217	160	**48.6**	40.1, 62.7
Prasinezumab	218	145	**64.4**	55.3, 81.1

Cox unadjusted (primary analysis)

HR= 0.79 [0.63, 0.99]

p-value: 0.0431#

Cox adjusted* (supplementary analysis)

HR= 0.76 [0.61, 0.95]

p-value: 0.0175#

Time saved:
15.8/48.6 weeks (32%) **difference in medians**

*Covariates used for adjustment: Medication at baseline (MAO-Bi vs L-DOPA), H&Y stage (1 vs >2), DaT-SPECT putamen ipsilateral, age (<60 vs >60), sex (male vs female), baseline dependent parameter (MDS-UPDRS Part III).

#For descriptive purposes, nominal p-values are displayed.

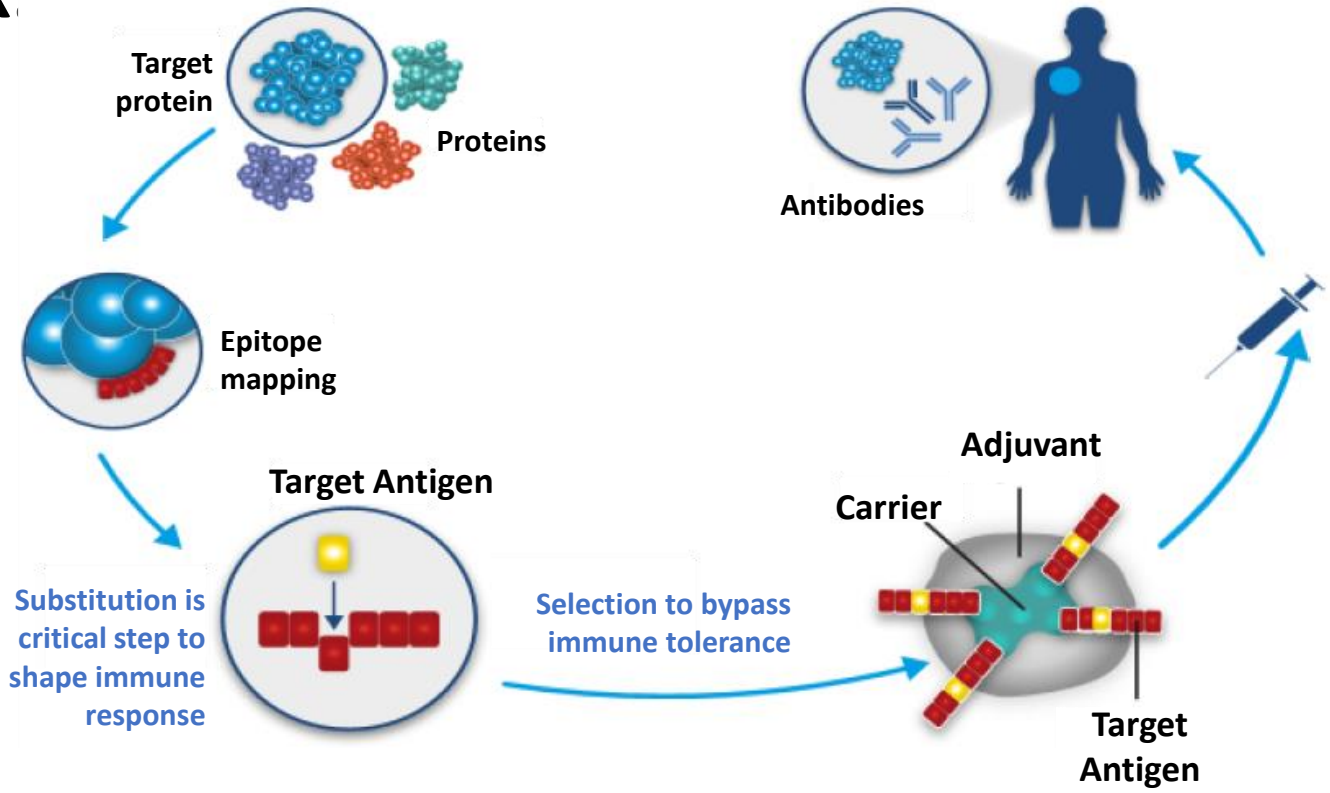
Nikolcheva&al. AD/PD 2025,Vienna April 1

BL, baseline; CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; HR, hazard ratio; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; NE, not evaluable; Q4W, every 4 weeks..

Active Immunisation: Advantages and Challenges

- **Advantages vs passive Immuno-Tx:**
  - long-lasting immune response
  - large interdose intervals
  - sc/im dosing
  - may address > one target protein

- **Challenges:**
  - Overcome immune tolerance
  - Robust immune response
  - Avoid T-cell mediated toxicity



OUTLINE

- A look Back: Solving the mystery of the Lewy Body
- α-Synuclein and PD Pathogenesis
- **α-Synuclein and 'Biological' PD Definition:**

  Implications for Early Diagnosis and DM trials

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


REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

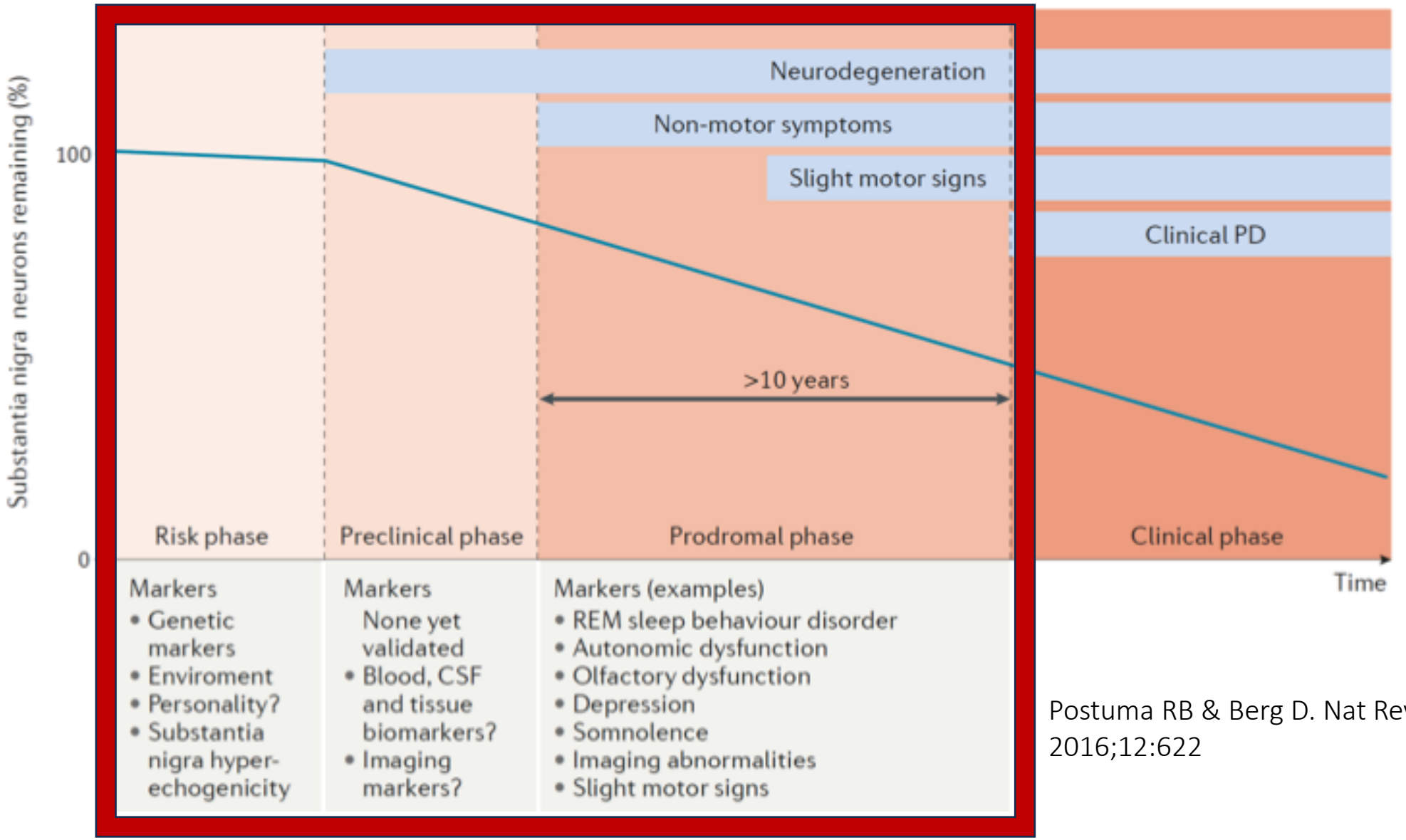
Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, 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]

2: Presence of supportive criteria for PD

3: Absence of Exclusion Criteria

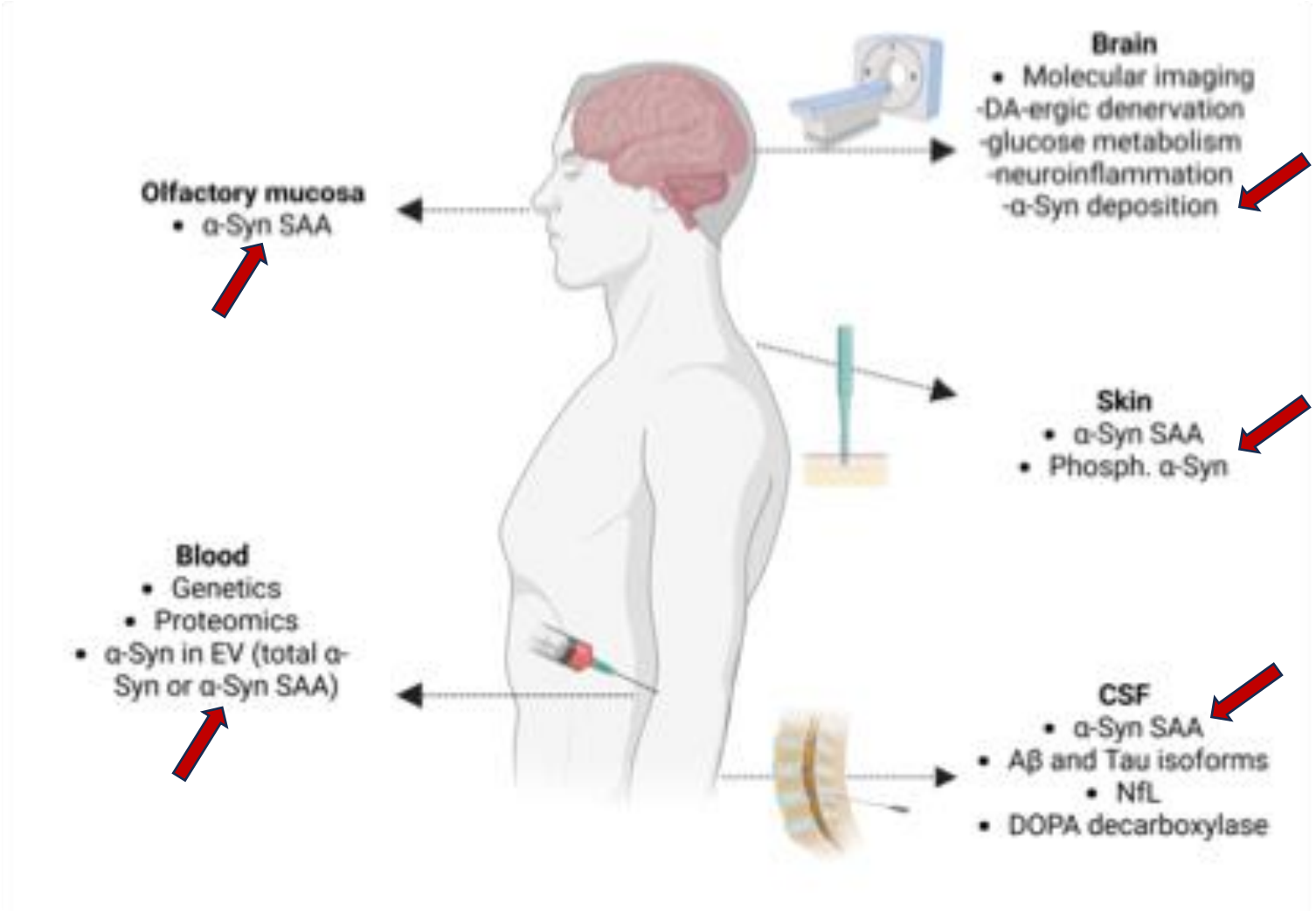
Postuma et al, Mov Disord. 2015 ;30(12):1591-601.

Evolution of Parkinson‘s Disease



Postuma RB & Berg D. Nat Rev Neurol 2016;12:622

Molecular markers and Sampling Matrices in Synucleinopathies



Tolosa, Poewe et al; Nat Rev Neurol, in press

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

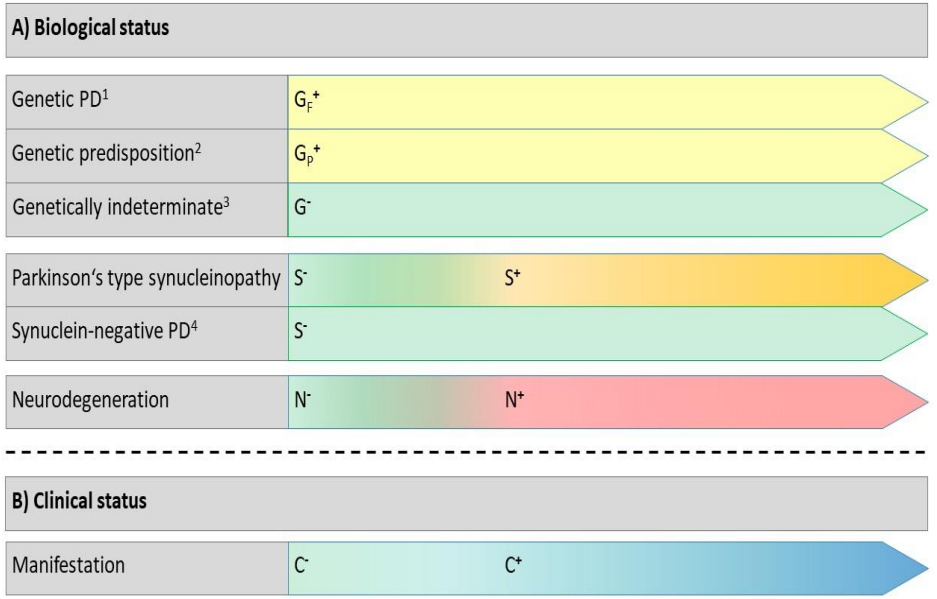
Günter U Höglinger, Charles H Adler, Daniela Berg, Christine Klein, Tiago F Outeiro, Werner Poewe, Ronald Postuma, A Jon Stoessl, Anthony E Lang

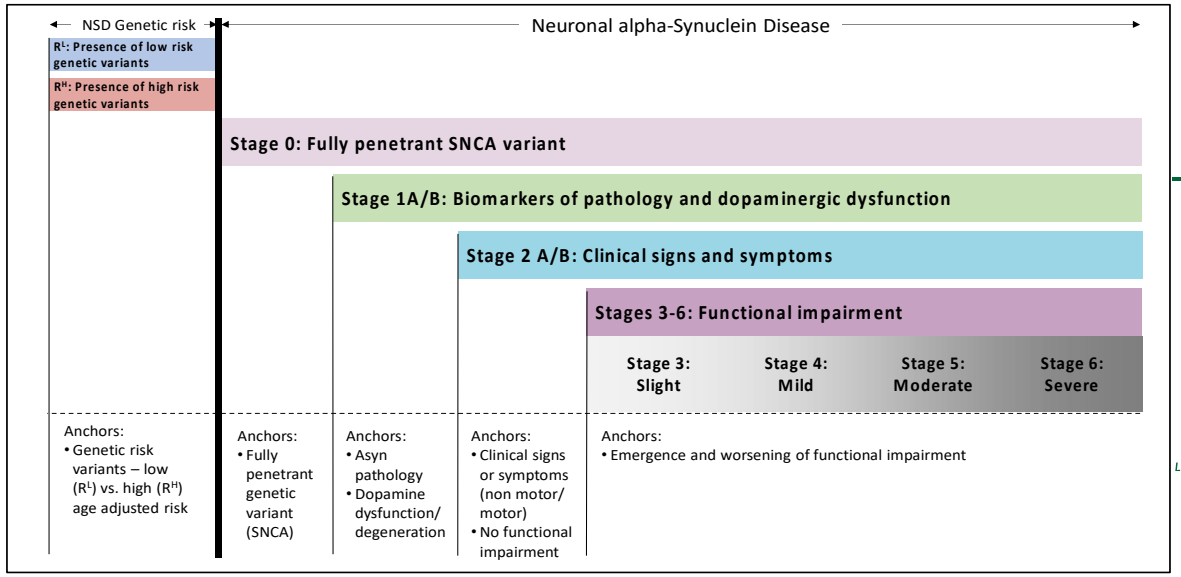
With the hope that disease-modifying treatments could target the molecular basis of Parkinson's disease, even before the onset of symptoms, we propose a biologically based classification. Our classification acknowledges the complexity and heterogeneity of the disease by use of a three-component system (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

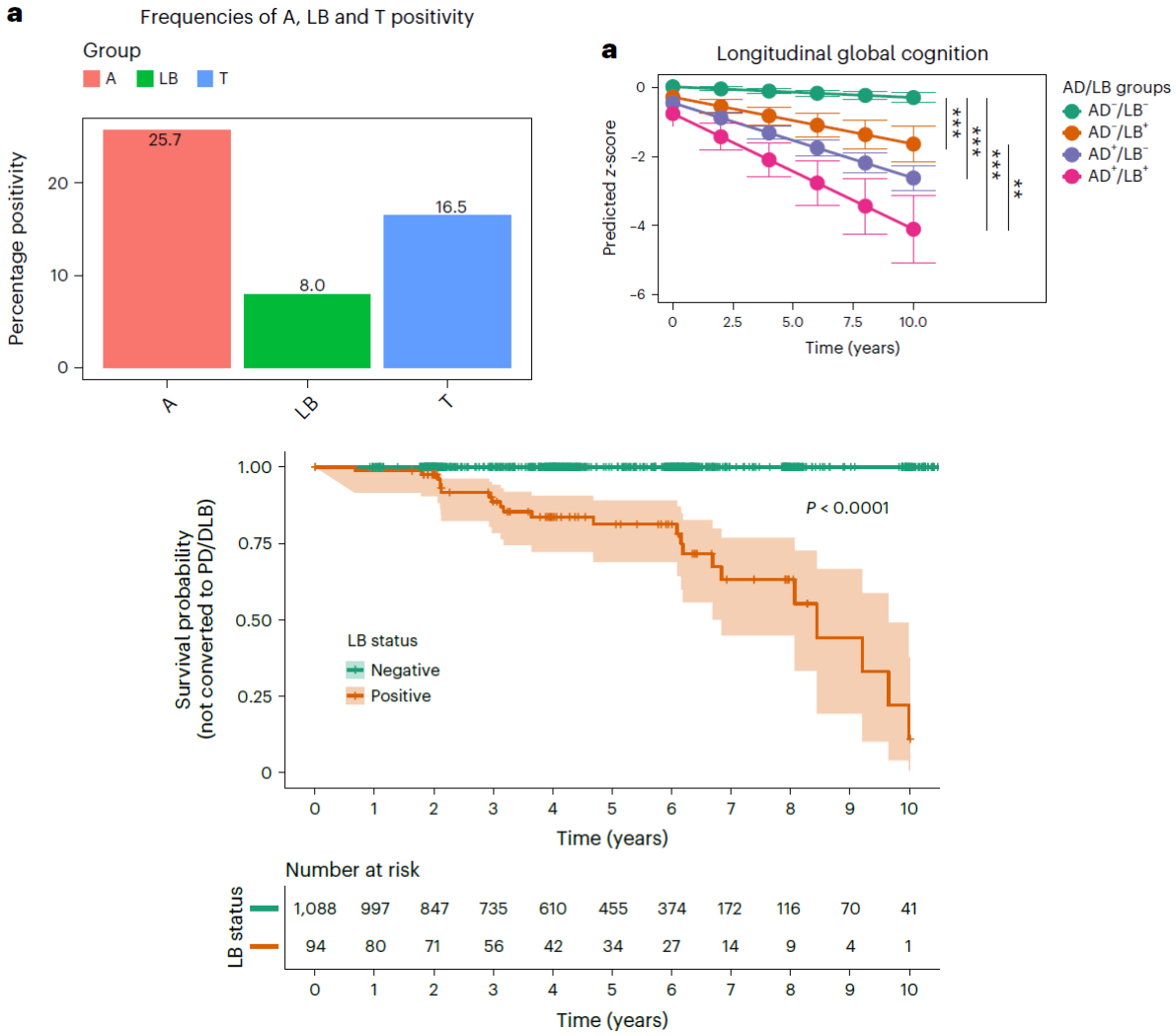
Tanya Simuni, Lana M Chahine*, Kathleen Poston, Michael Brumm, Teresa Buracchio, Michelle Campbell, Sohini Chowdhury, Christopher Coffey, Luis Concha-Marambio, Tien Dam, Peter DiBiaso, Tatiana Foroud, Mark Frasier, Caroline Gochanour, Danna Jennings, Karl Kieburtz, Catherine M Kopil, Kalpana Merchant, 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

Biological Disease Definition – what is the meaning of positive Biomarkers?

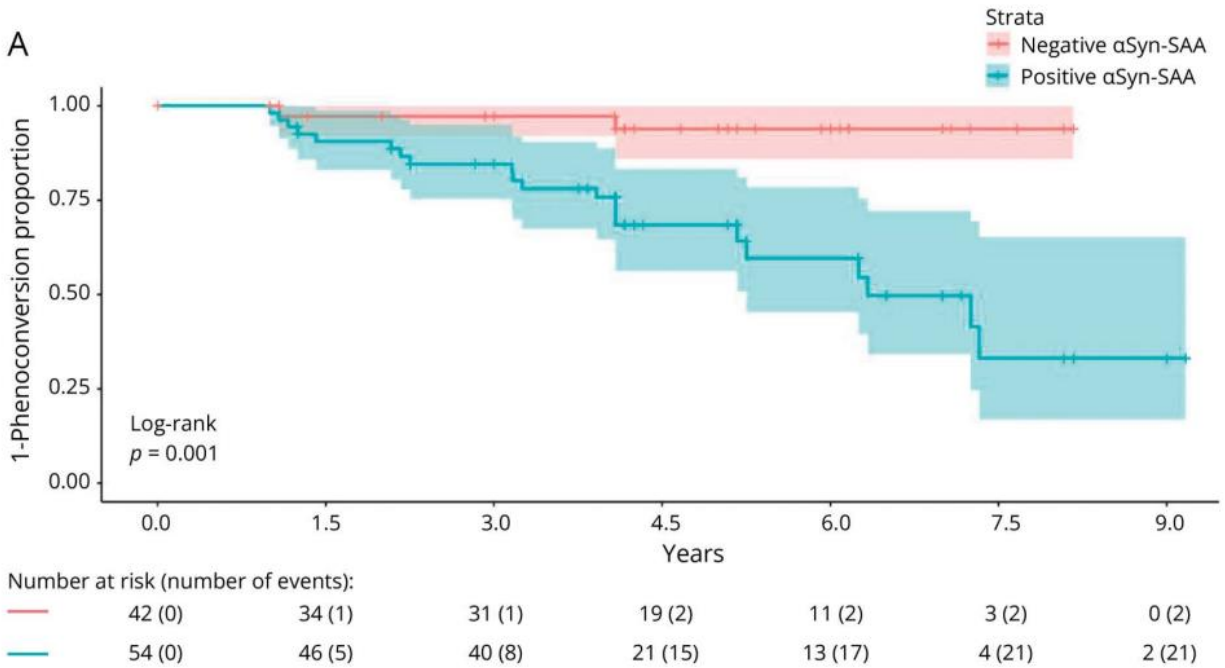
- N=1182 healthy subjects from BioFINDer Study
- Mean age 70yrs.
- CSF α-syn SAA, Aß, Tau at baseline
- Longitudinal FU (Cognition, clinical signs of LB Disorder)
- **26% Aß+, 16% T+, 8% a-syn+**
- **23% of α-syn-SAA+ participants developed PD/DLB over 4 years**



Palmqvist&al.Nat Medicine 2023;29:1971-78

Biological Definition of PD- what is the meaning of positive Biomarkers?

- n= 96 subjects from PPMI prodromal
- Hyposmia, RBD, DAT-Deficit
- n= 25 LRRK2 pos
- n=18 GBA pos
- n=2 SNCA pos
- Baseline CSF α-syn SAA : 56%
- **Phenoconversion in 39%**



Coughlin et al., *Neurology*® 2025;104:e210279. doi:10.1212/WNL.0000000000210279

Path to Prevention (P2P) Study Synopsis

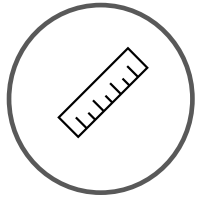
Target Population

NSD Stage 2b

Biomarker positive
- Abnormal aSyn
- DA dysfunction

Subtle symptoms with no impairment

Endpoints

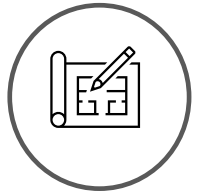


Multiple Primary

Biomarker: DaT Imaging
- Rate of Δ in mean striatum SBR (BL thru f/u)

Clinical: MDS-UPDRS Pt III
- Rate of Δ in mean striatum SBR (BL thru f/u or DA tx initiation)

Design



Platform Trial

N=125 per tx arm; N~125 shared placebo

Min 24 mo treatment duration (max 36 mo)

Therapeutics

Novel Drugs

20 industry LOI received to date

LOI reviewed by Therapeutic Evaluation Committee

<u>Proof of concept learning Phase 2A</u> randomized double blind **<u>platform study embedded in PPMI</u>** to assess impact of putative NSD therapies in participants with Early Stage NSD on DAT SPECT imaging, clinical measures of symptom worsening, feasibility, safety, and tolerability.

SUMMARY

- Disease modification remains the single most important unmet need in PD
- PD, DLB and MSA are defined as Synucleinopathies
- α-synuclein misfolding, aggregation and cell-cell transmission are key targets for DM interventions in both PD and MSA
- Immunotherapy trials targeting α-synuclein have provided signals for efficacy
- Synuclein-Biomarker-based diagnostic frameworks may pave the way towards PD ‚prevention' trials

Misfolding of α-synuclein as fluid biomarker measured with the iRS platform of betaSENSE

Prof. Dr. Klaus Gerwert

Founder & CEO of betaSENSE GmbH

AD/PD™2026
ADVANCES IN SCIENCE & THERAPY

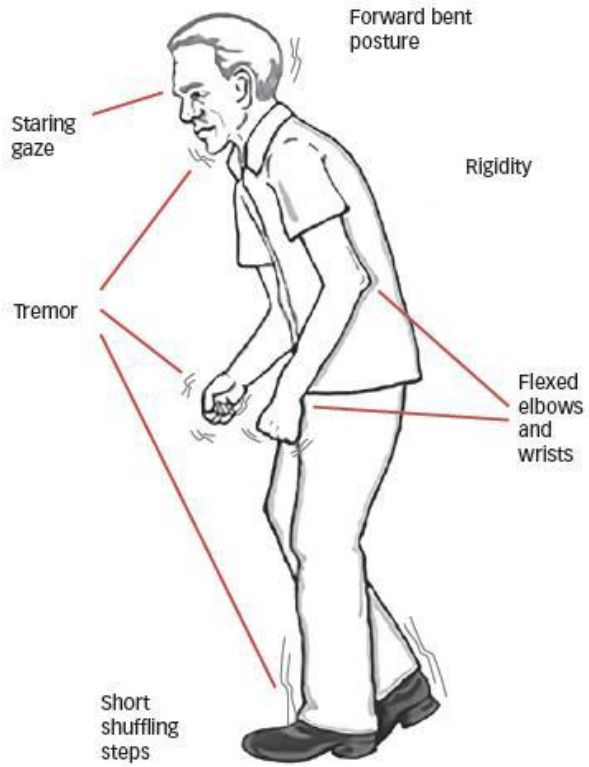
International Conference on
Alzheimer's and Parkinson's Diseases
and Related Neurological Disorders
March 17-21, 2026 | Copenhagen, Denmark Hybrid

	No, Nothing to disclose
✓	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
betaSENSE GmbH						✓		

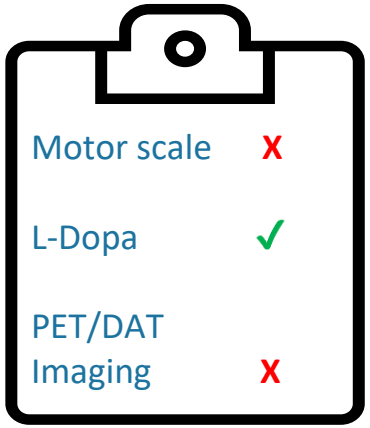
- contract research for ACI

Diagnosis of Parkinson´s disease is mostly symptome-based



Motor symptoms

Start of clinical testing



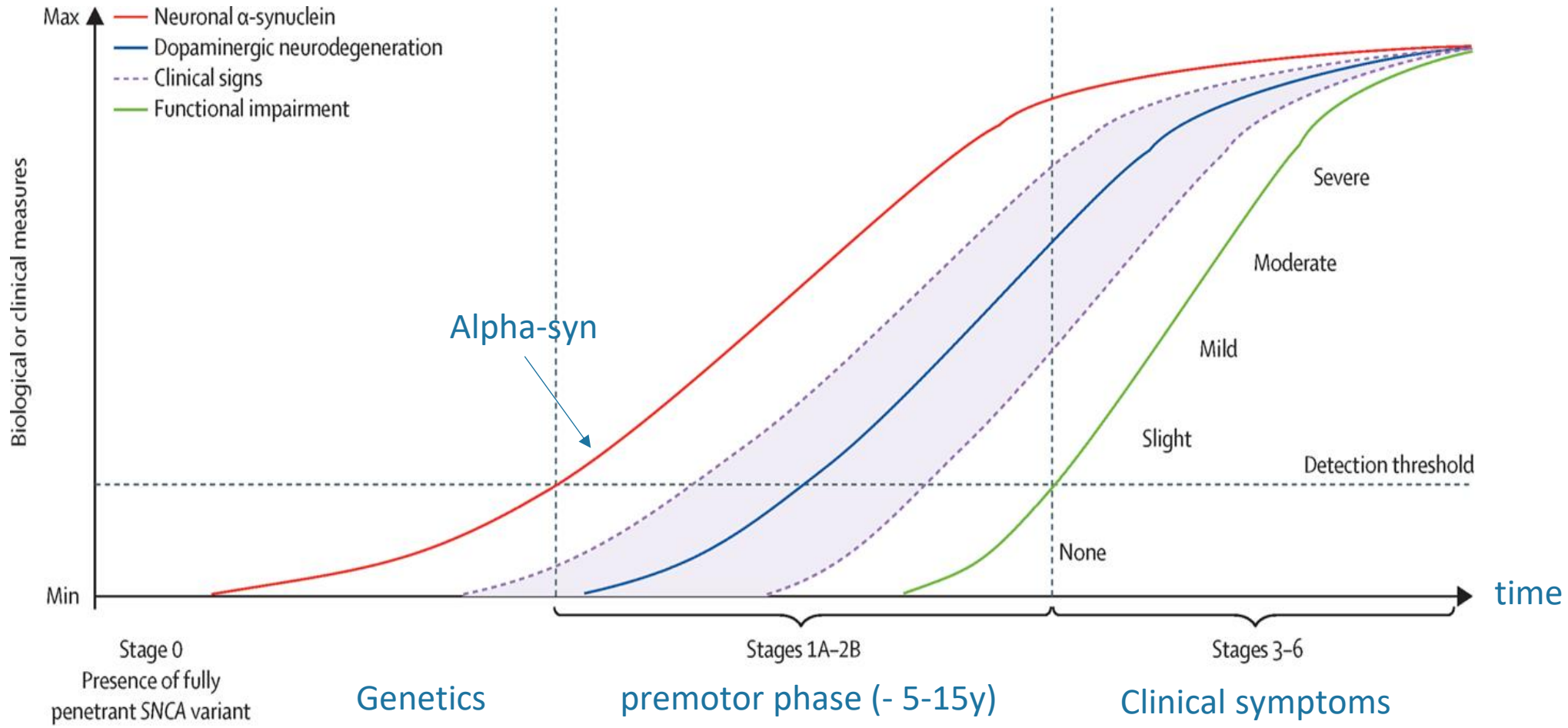
Clinical Diagnosis

unmet medical need:

biomarker for biological classification in early stages

Höglinger, G.U., Adler, C.H., Berg, D., Klein, C., Outeiro, T.F., Poewe, W.,Postuma, R., Stoessl, A.J., Lang, A.E., *A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria*, The Lancet Neurology, Volume 23, Issue 2, 2024, Pages 191-204, ISSN 1474-4422, https://doi.org/10.1016/S1474-4422(23)00404-0.

Alpha-syn indicates Parkinson`s



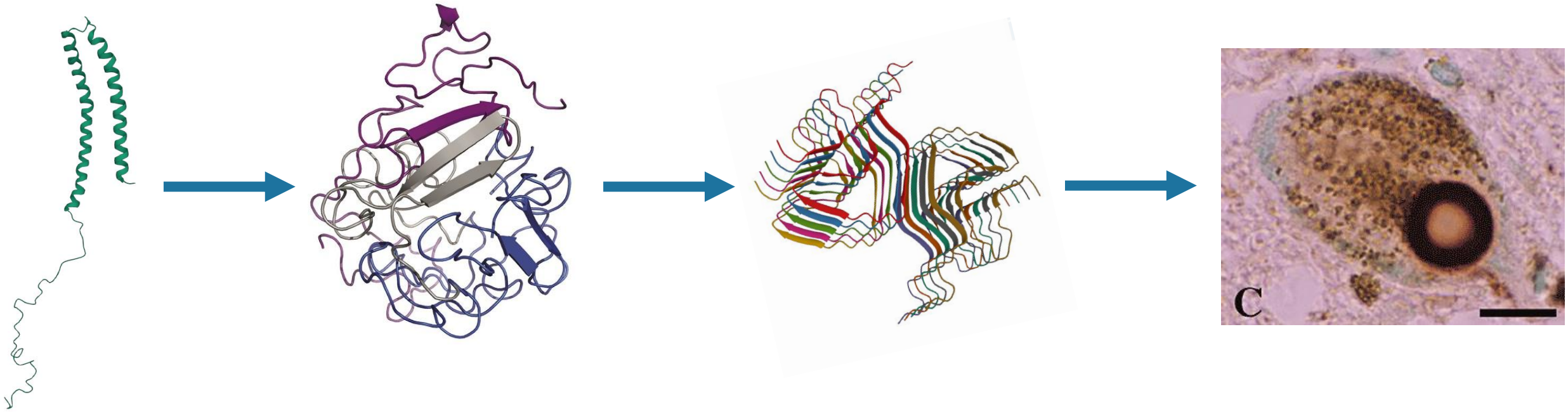
Genetics
familial PD (- 20y)

premotor phase (- 5-15y)

Clinical symptoms
Motor symptoms

Simuni, T. et al., *A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research*
The Lancet Neurology, Volume 23, Issue 2, 2024, Pages 178-190, ISSN 1474-4422, https://doi.org/10.1016/S1474-4422(23)00405-2.

Parkinson's Disease: misfolding of alpha-Synuclein



Monomers

Oligomers

Fibrils

Lewy body

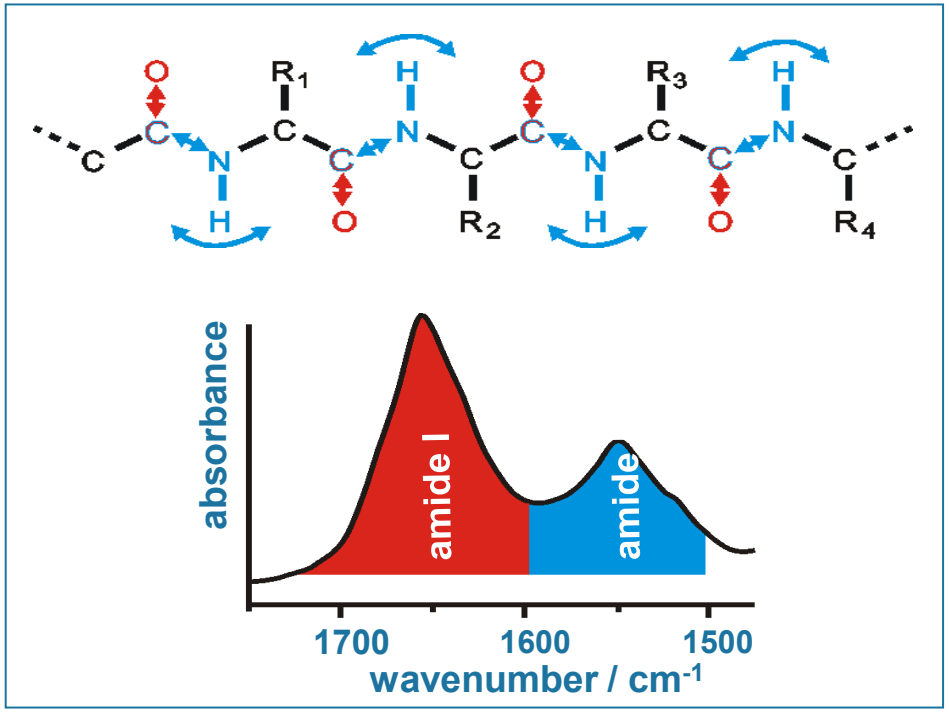
During disease progression misfolding increases

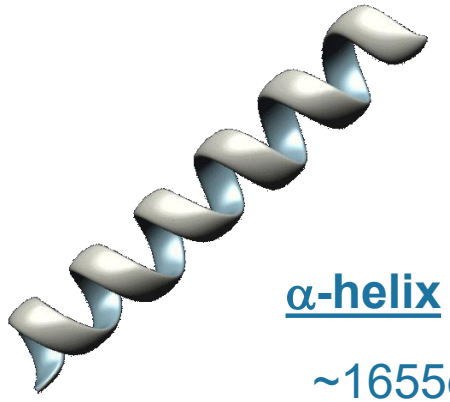
Shahmoradian, S.H., … Gerwert, K, … Van de Berg, W.D.J., Lauer, M.E. et al. *Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes*
Nat Neurosci. 2019 Jul;22(7):1099-1109.

Infrared absorbance spectrum of a protein-biomarker indicates directly and label-free misfolding

betaSENSE

- the amide I band is secondary structure sensitive
- the amide II band indicates the protein concentration





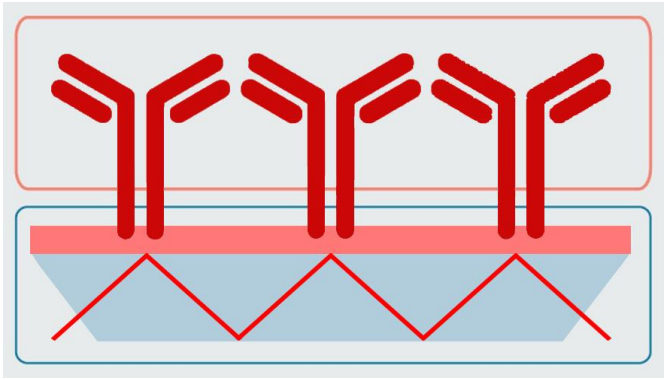
α-helix

~1655cm^{-1}

β-sheet

~1630cm^{-1}

Downshift of the Amide I band indicates increase of misfolding

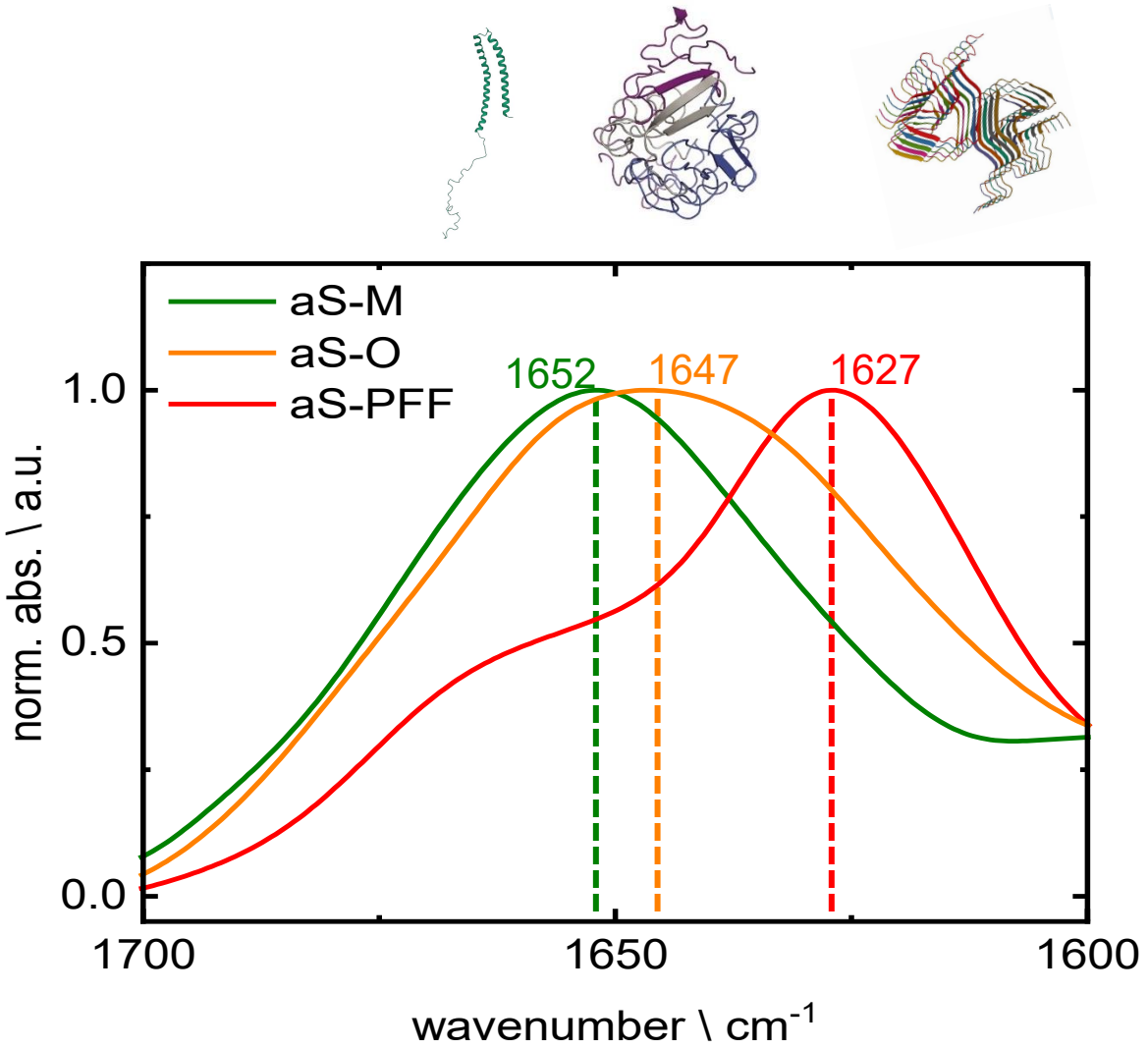


Challenges of infrared spectroscopy in fluid-analysis

- Not specific
- All molecules absorb in the IR
- Solution: catcher-antibody concentrates the biomarker on bio-chip
- Solution: the blocking layer prevents unspecific binding out of the body-fluid

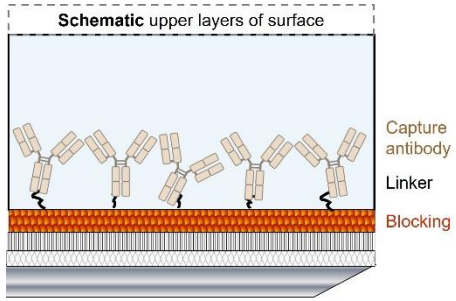
Only a-syn specific binding on the biochip

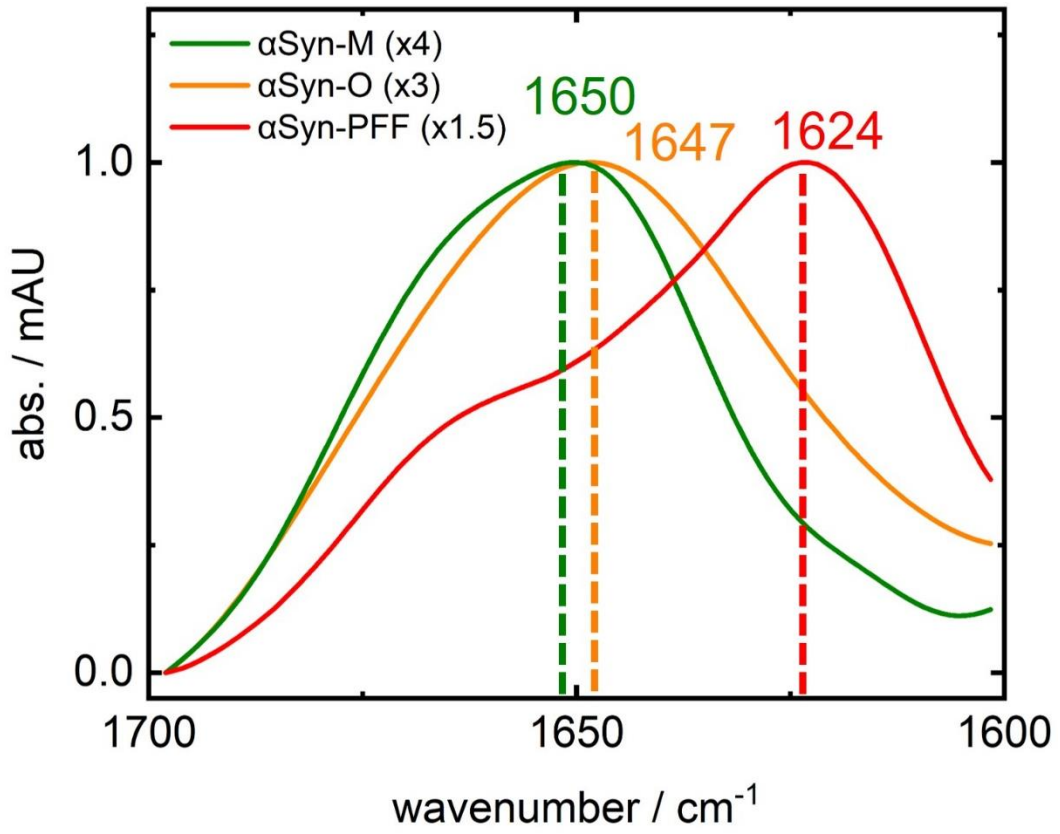
Pan-ACI-Antibody binds all alpha-syn conformers of a-Syn-antigens



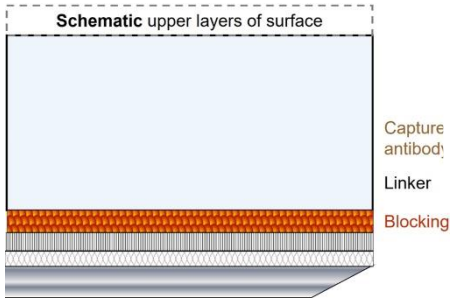
Increase of misfolding can be followed by a downshift of the amide I band

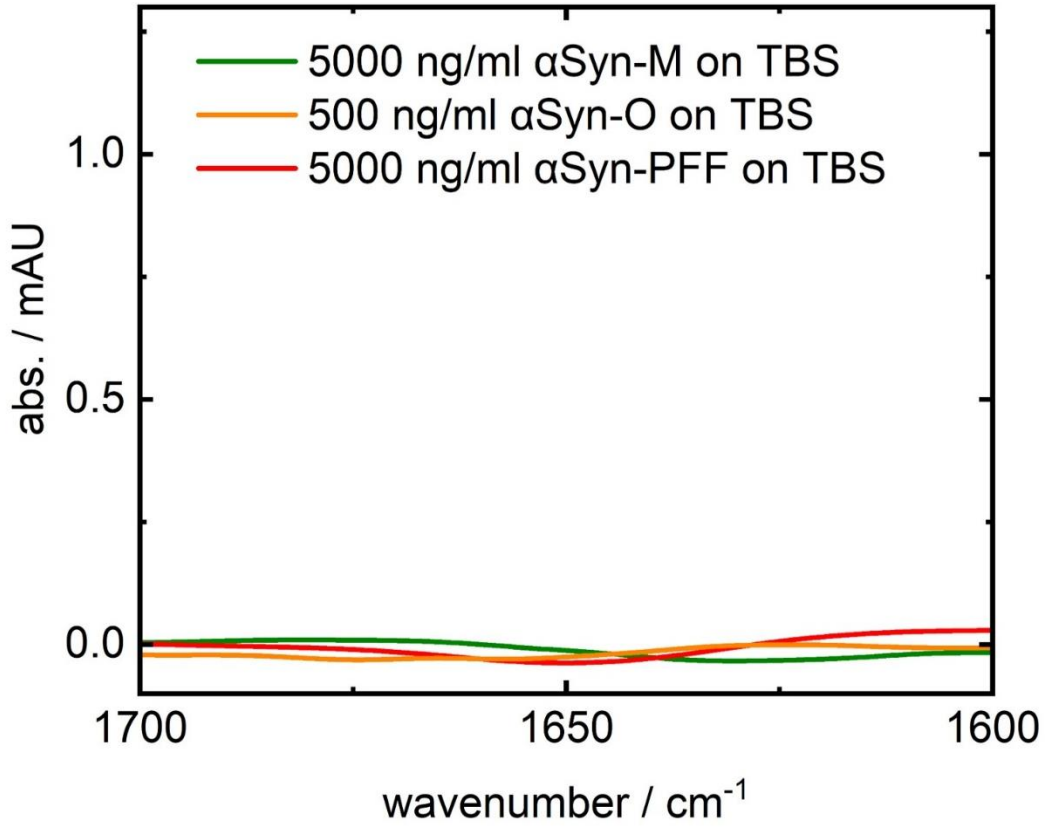
Specific binding of alpha-syn to antibody





Blocking layer prevents unspecific binding

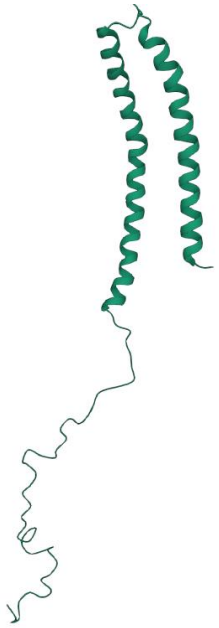




Misfolding of alpha-Synuclein indicates Parkinson's Disease

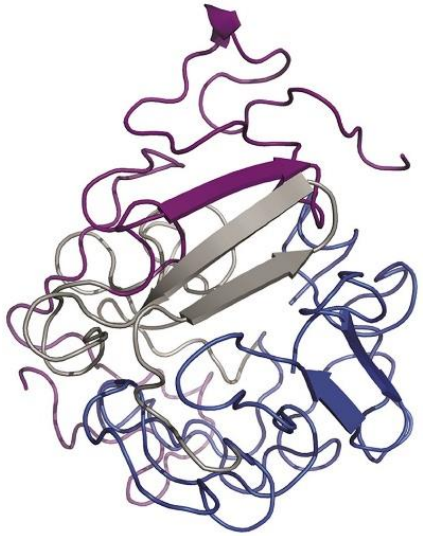
betaSENSE

Monomers



years

Oligomers

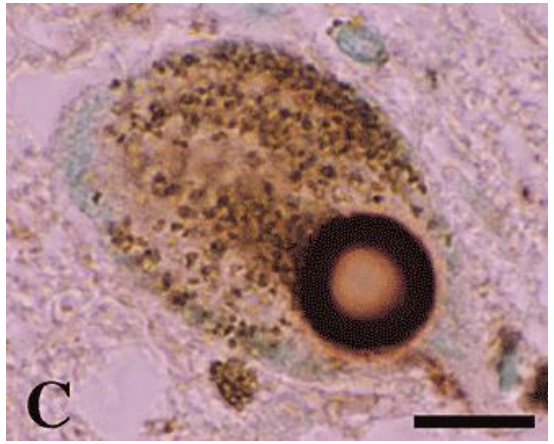


years

Fibrils

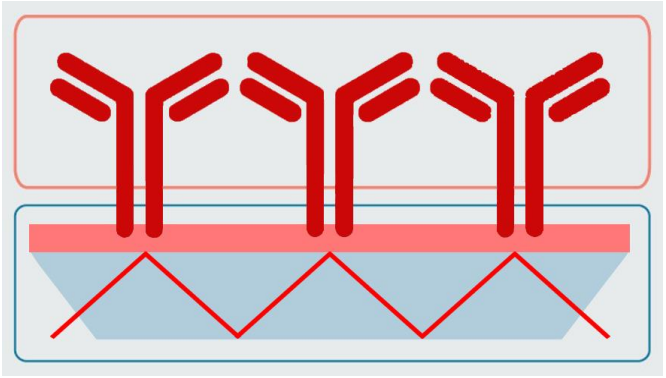
years

Lewy body



IR-Readout tracks progression of disease by down-shift of the absorbance maximum

1652 cm^{-1} → 1647 cm^{-1} → 1627 cm^{-1}



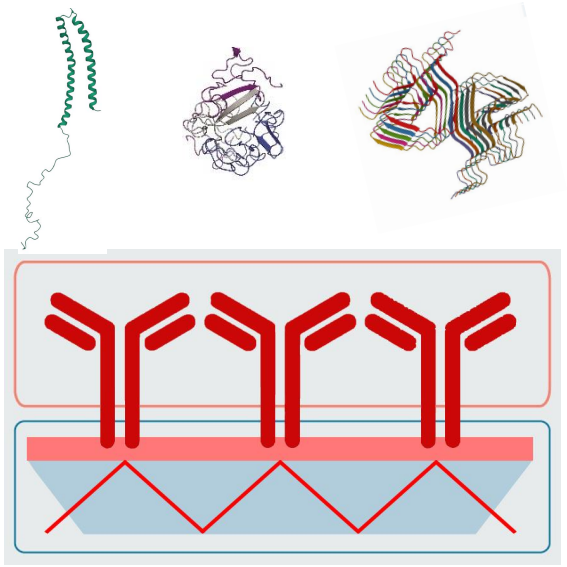
Challenges of infrared spectroscopy in fluid-analysis

- **Fluids**
  - Strong water background absorbance prevents fluid analysis in thick films
  - Solution: thin films in ATR technology
  - Solution: background subtraction by difference spectroscopy

Difference spectroscopy isolates the a-syn spectra from the background

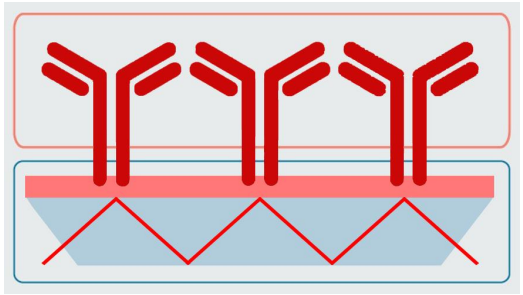
Measurement of disease continuum

Body fluids



minus

Background absorbance as reference



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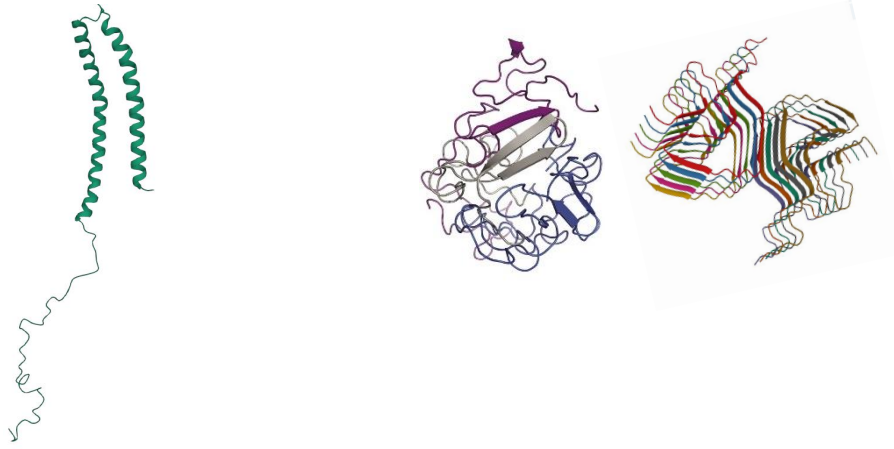
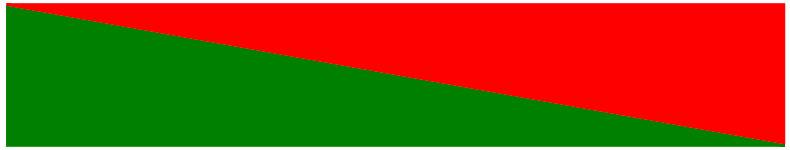


healthy diseased

Downshift of the absorbance maximum indicates progression of the misfolding

1652 cm^{-1} progression to 1627cm^{-1}



EMBO Molecular Medicine

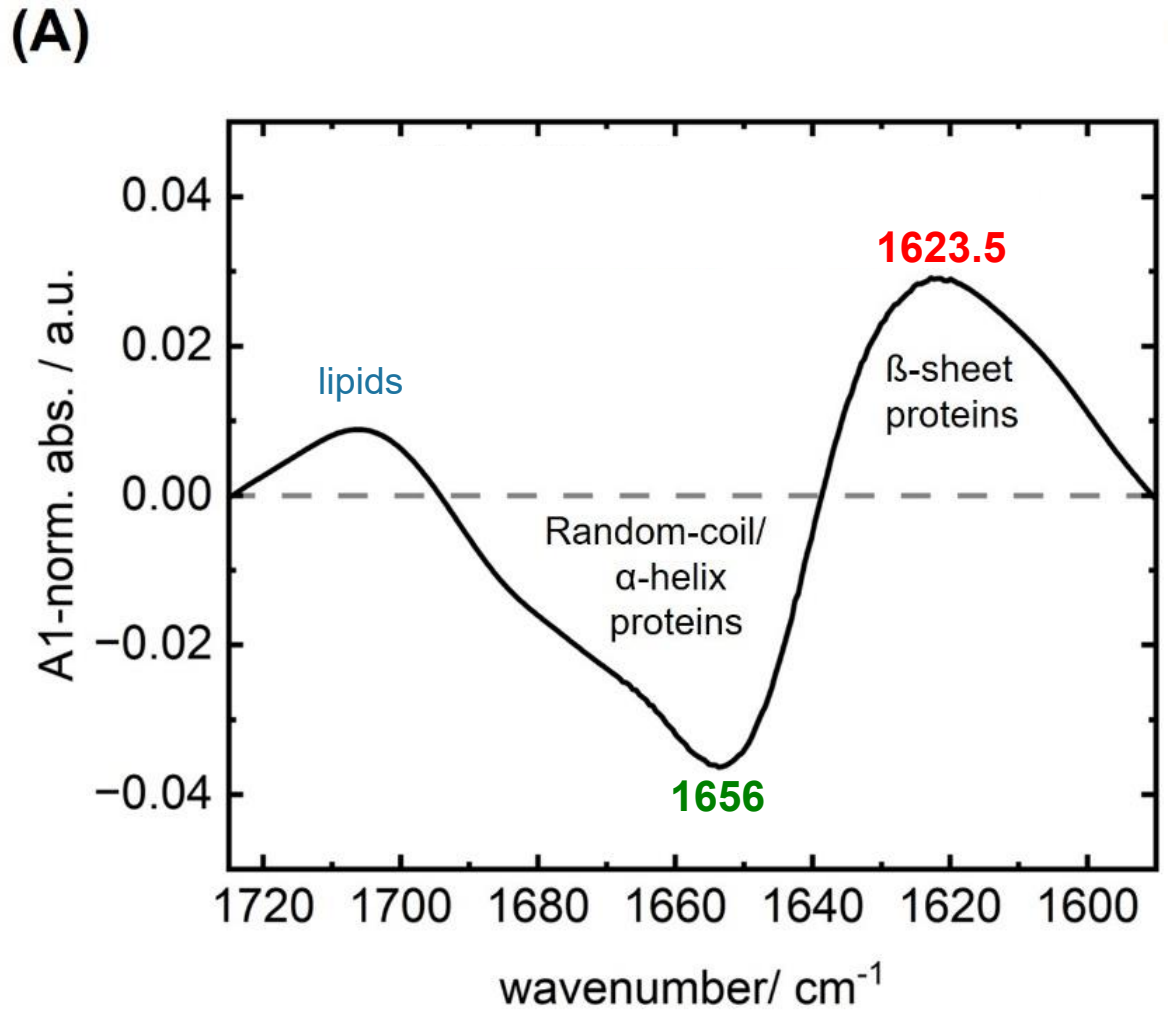
Schuler, M., Gerwert, G., Mann, M., Woitzik, N., Langenhoff, L., Hubert, D., Duman, D., Höveler, A., Galkowski, S., Simon, J., Denz, R., Weber, S., Kwon, E. H., Wanka, R., Kötting, C., Güldenhaupt, J., Beyer, L., Tönges, L., Mollenhauer, B., Gerwert, K.

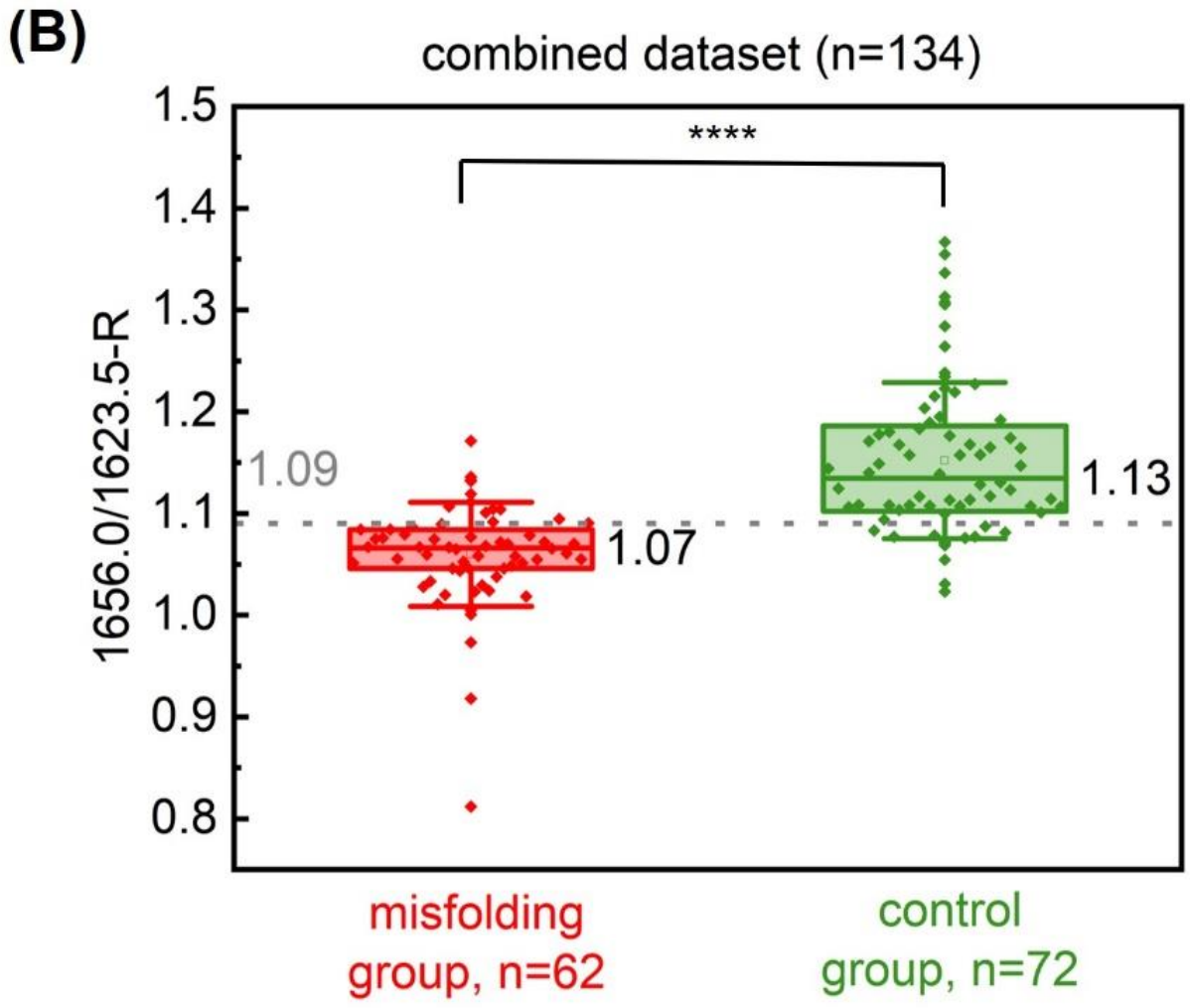
Alpha-synuclein misfolding as fluid biomarker for Parkinson's disease measured with the iRS platform

EMBO Molecular Medicine / European Molecular Biology Organization, 2025, Article 10

- **CSF**
- **Discovery cohort, Kassel**
- **Validation cohort, Goettingen**

Difference spectrum between all control and all diseased spectra indicates misfolding of a-syn in synucleinopathies

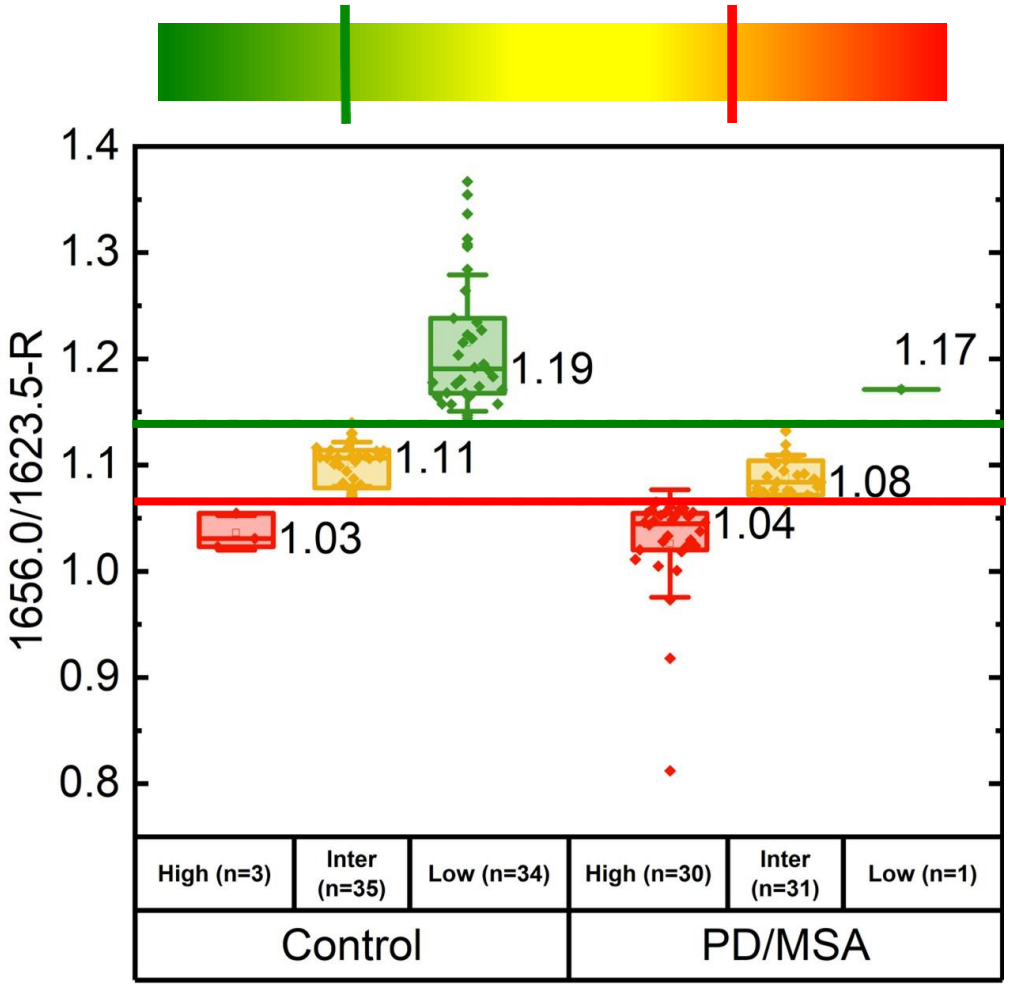




Misfolding of a-syn in CSF directly monitored

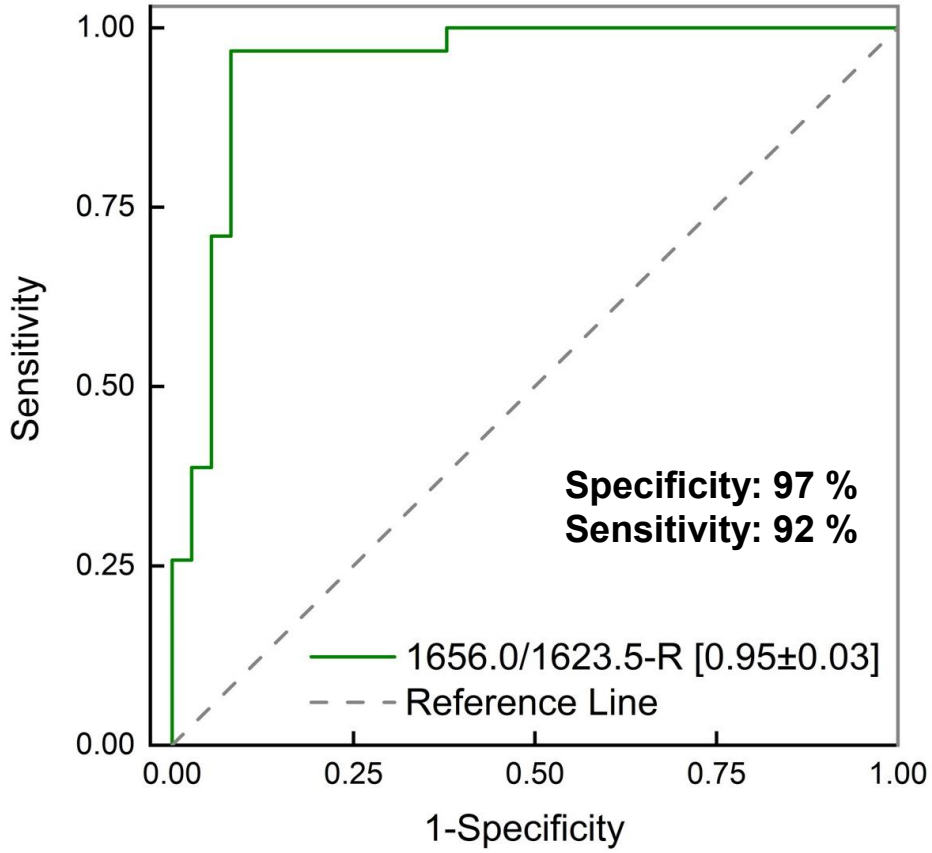
Schuler M, et al. EMBO Mol Med. 2025 Jun;17(6):1203-1221. doi: 10.1038/s44321-025-00229-z. Epub 2025 Apr 25.

Two thresholds to regard the continuum in the disease progression



high

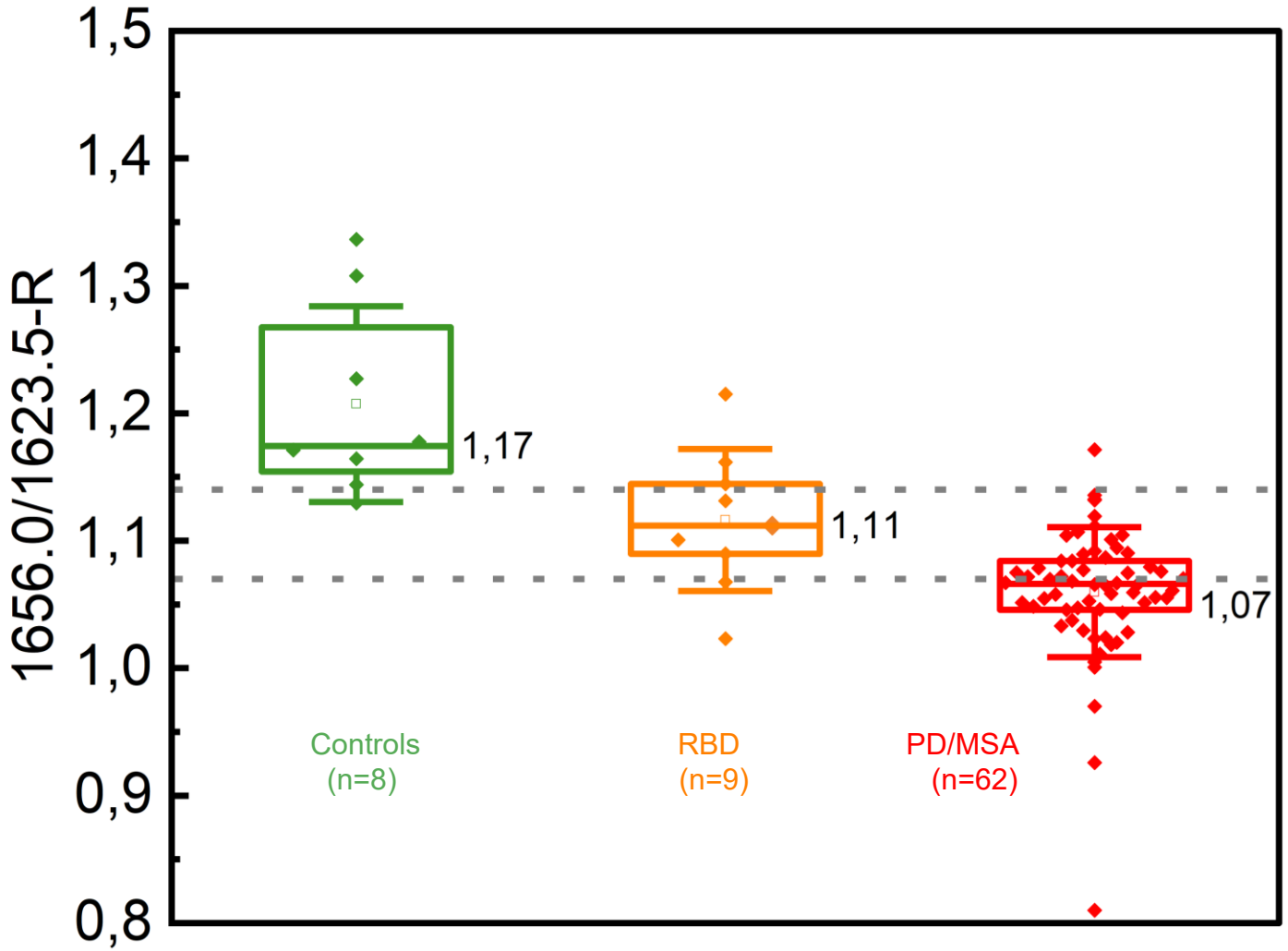
low



Parkinson's can be classified with a high accuracy in CSF

Schuler M, et al. EMBO Mol Med. 2025 Jun;17(6):1203-1221. doi: 10.1038/s44321-025-00229-z. Epub 2025 Apr 25

RBD appear in the yellow intermediate misfolding range



Schuler M, et al. EMBO Mol Med. 2025 Jun;17(6):1203-1221. doi: 10.1038/s44321-025-00229-z. Epub 2025 Apr 25.

Blood-based biomarker, under peer review

betaSENSE

MISFOLDING OF ALPHA-SYNUCLEIN AS BLOOD-BASED BIOMARKER FOR PARKINSON'S DISEASE

Lennart Langenhoff, Jonas Simon, Sandrina Weber, Diana Hubert, Martin Schuler, Marvin Mann, Vuk Puzovic, Grischa Gerwert, Adrian Höveler, Léon Beyer, Lars Tönges, Carsten Kötting, Jörn Güldenhaupt, Brit Mollenhauer, Klaus Gerwert

doi: https://doi.org/10.64898/2025.12.19.25342662

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

Abstract | Full Text | Info/History | **Metrics** | Preview PDF

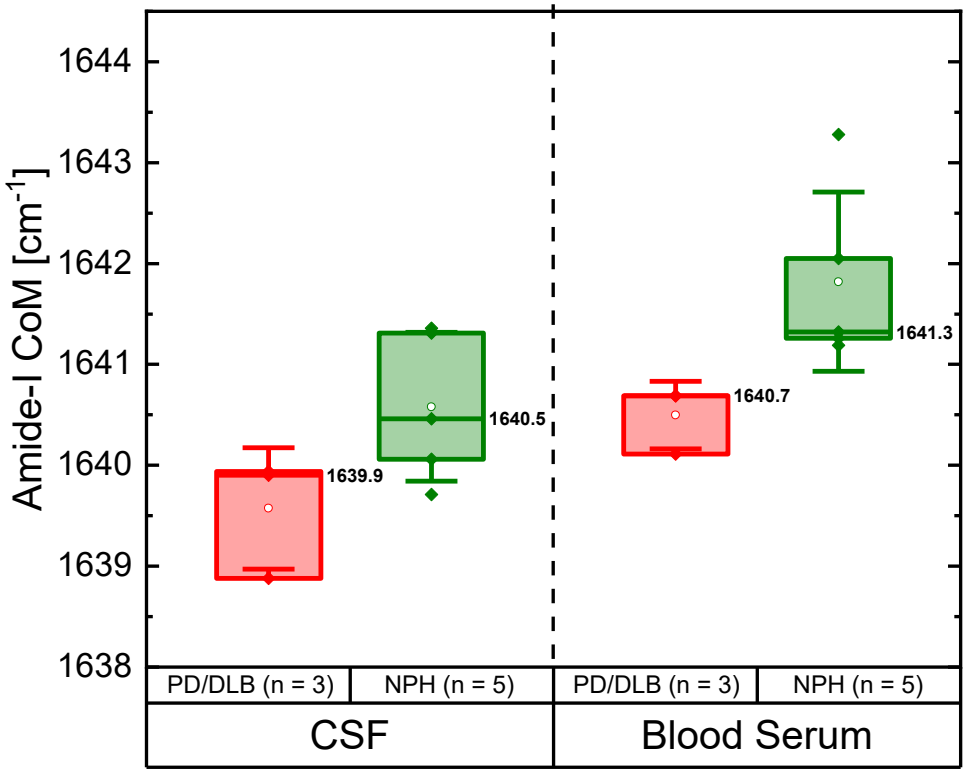
ARTICLE USAGE

Article lifetime | Last 6 months | This month

Article usage: October 2025 to March 2026 (published December 21, 2025)

Show by month	Abstract	Full-text HTML	PDF
Total	1,199	459	264

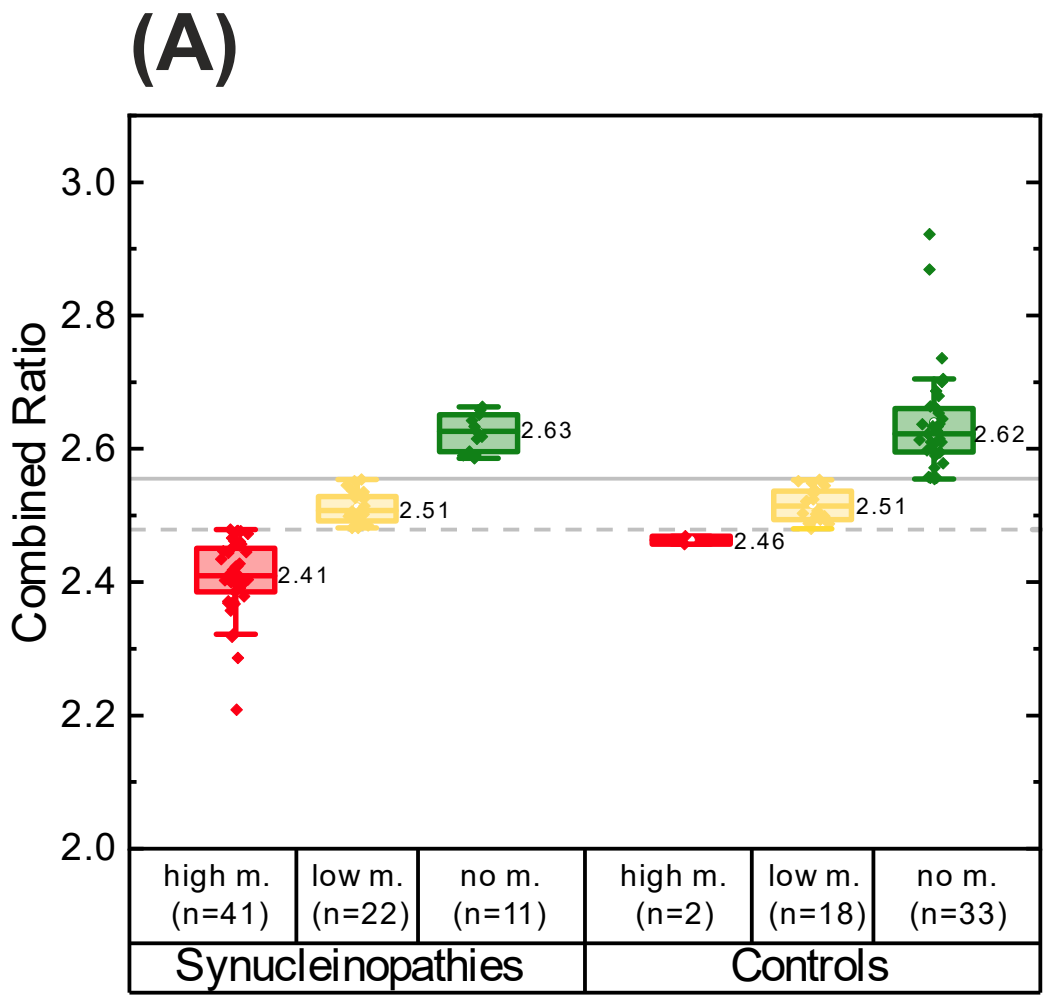
CSF and blood from same patients in a pilot study



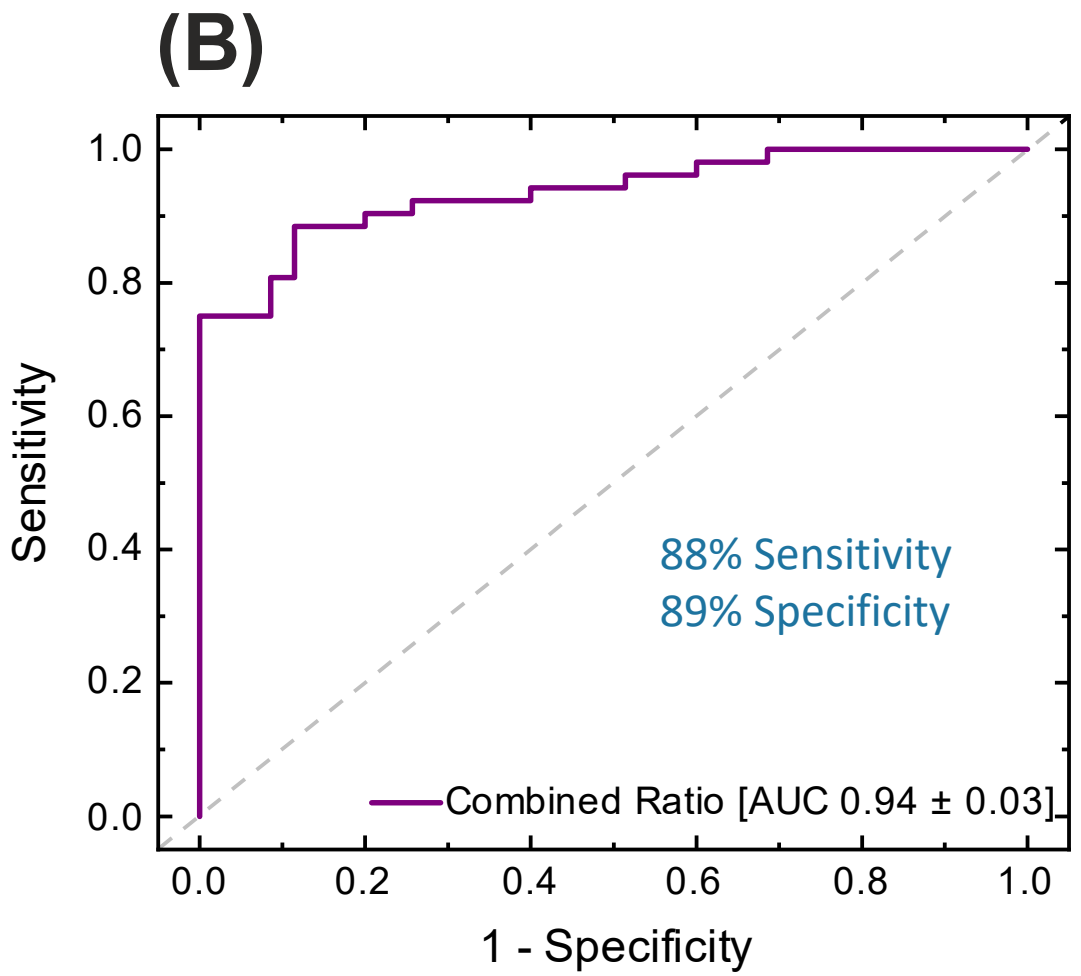
Both in CSF and in blood, healthy controls and Parkinson's patients can be distinguished

Langenhoff, J.,Simon,J. Weber, S. et al. medRxiv, doi: 10.64898/2025.12.19.25342662. Posted 2025 Dec. 21.

Serum results: two thresholds



high vs. no misfolding



Synucleinopathies can be classified in blood with a high degree of accuracy

Langenhoff, J.,Simon,J. Weber, S. et al. medRxiv, doi: 10.64898/2025.12.19.25342662. Posted 2025 Dec. 21

Summing up: the iRS platform

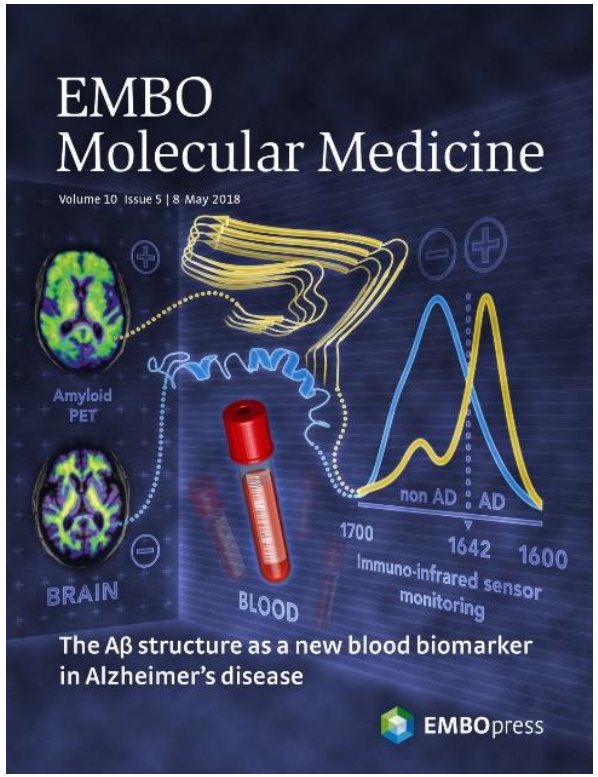
betaSENSE

- classifies PD in CSF and blood
- classifies MSA in CSF and blood
- differentiates both from atypical PD
- very early stages can be identified (RBD)

Status betaSENSE:

- 10 CE-certified QCL-based fully automated iRS systems
- QC-Laser will allow to scale up by parallel measurements
- Contract research under GCLP conditions for ACI
- results will be presented by Günther Staffler

The story continues…



2018
MCI & Symptom-free

Further Talks:

Wednesday: 15:30-15:45 Hall A3
Klaus Gerwert "MISFOLDING OF ALPHA-SYNUCLEIN AS **BLOOD-BASED-BIOMARKER** FOR PARKINSON'S DISEASE"

Saturday: 09:25-09:40 Auditorium 15
Lennart Langenhoff, Jonas Simon
"DETECTION OF ALPHA-SYNUCLEIN MISFOLDING **IN BLOOD SE**RUM USING A CHARGE-OPTIMIZED IRS SENSOR"

Posters (slot 1):

- **Dr. Grischa Gerwert**
- **Dr. Frederik Großerüschkamp**
- **M. Sc. Adrian Höveler**
- **M. Sc. Deniz Duman**
- **M. Sc. Melina Helfrich**

Meet us at

booth #24

offer
Clinical studies,
contract research

Sustain Longevity

betaSENSE

Targeting alpha-synuclein in early Parkinson's Disease: Interim results of the Phase 2 VacSYn trial of ACI-7104

Günther Staffler, PhD | ADPD 2026 | March 2026

AC Immune

Disclaimer

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Disclosures

Günther Staffler is employed by AC Immune and is entitled to stock options.

Parkinson’s disease

Pathological deposition of alpha-synuclein

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

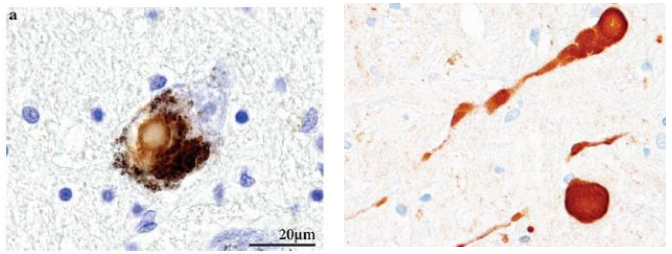
Etiology
5-10% genetic, 90-95% idiopathic, unknown cause

Cardinal motor symptoms
Tremor, rigidity, bradykinesia

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

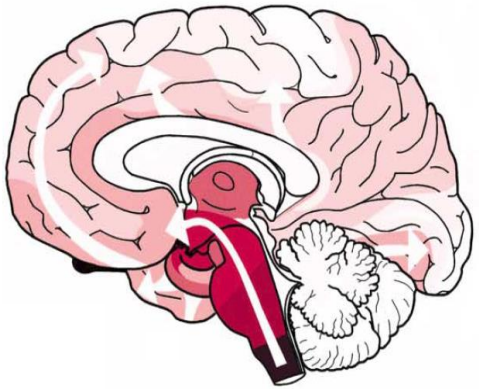
Pathological hallmarks
Neuron loss, alpha-synuclein aggregates – Lewy bodies

Main component of Lewy bodies: Alpha-synuclein



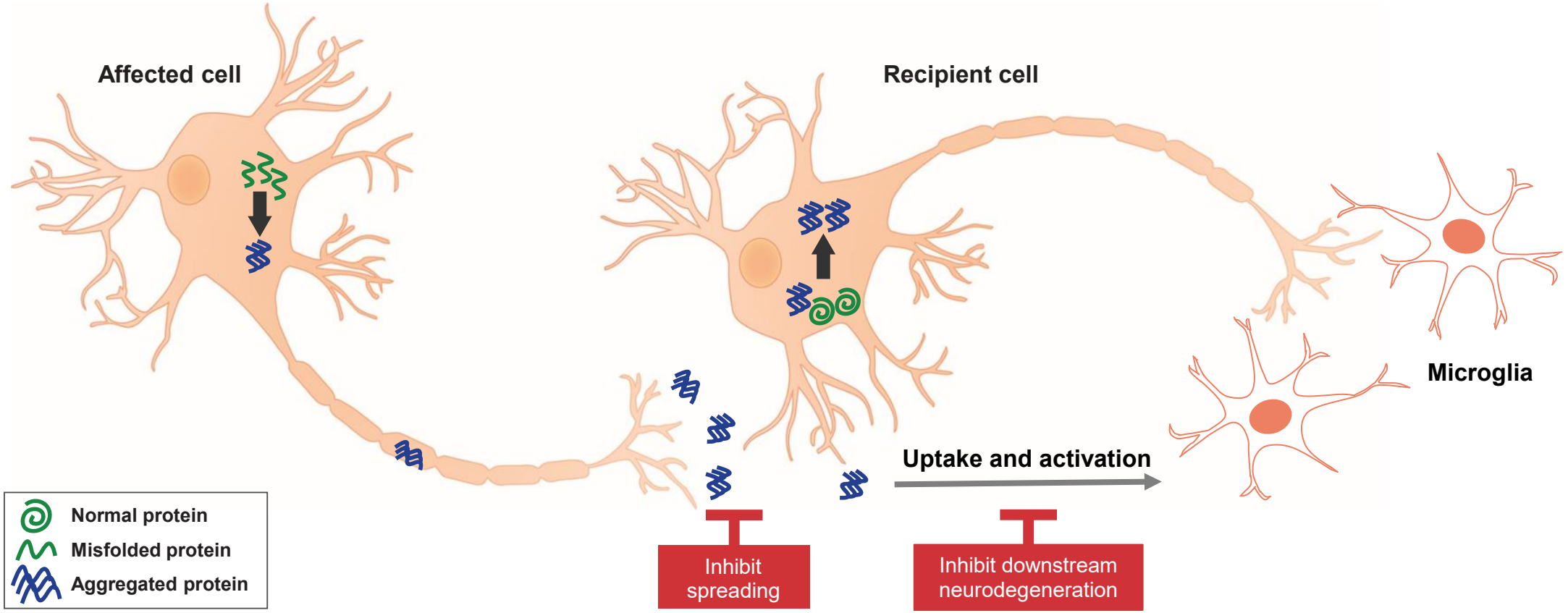
Halliday *et al.* 2011

Progression of pathology



Braak *et al.* 2003

Pathological oligomeric a-syn[1] is causally linked to PD[2] and other NDD[3]



- A-syn misfolding and aggregation are the molecular basis for a-synucleinopathies, e.g. PD, DLB[4] and MSA[5]
- Seeding and spreading of a-syn are potential drivers of disease progression

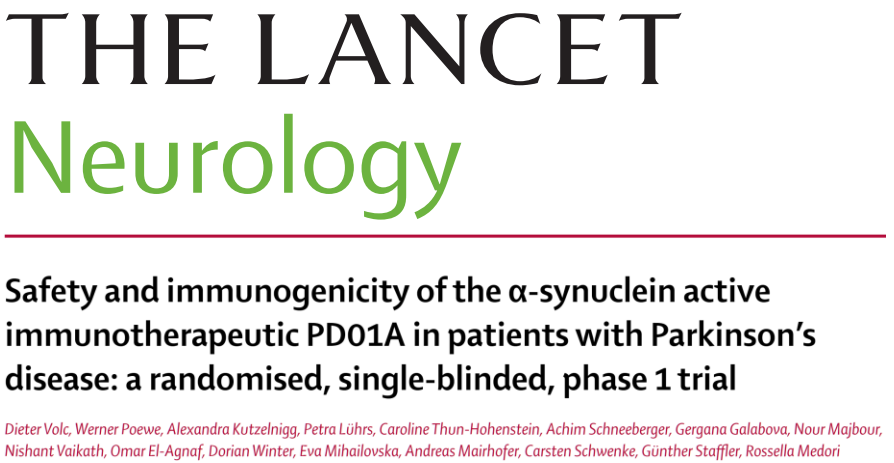
(1) Alpha-synuclein; (2) Parkinson's disease; (3) Neurodegenerative diseases; (4) Dementia with Lewy bodies; (5) Multiple system atrophy

Clinically validated anti-a-syn

ACTIVE Immune Therapy

Phase 1 results published in *The Lancet Neurology*[1] support best-in-class profile

1. Safe and well tolerated with no safety concerns noted in PD[2] 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[3] in the CSF[4]
4. UPDRS III[5] scores correlated with reductions in oligomeric α-syn


THE LANCET
Neurology

Safety and immunogenicity of the α-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial

Dieter Volc, Werner Poewe, Alexandra Kutzelnigg, Petra Lührs, Caroline Thun-Hohenstein, Achim Schneeberger, Gergana Galabova, Nour Majbour, Nishant Vaikath, Omar El-Agnaf, Dorian Winter, Eva Mihailovska, Andreas Mairhofer, Carsten Schwenke, Günther Staffler, Rossella Medori

(1) Volc *et al.*, Lancet Neurol. 2020; (2) Parkinson's disease; (3) alpha-synuclein; (4) Cerebrospinal fluid; (5) Unified Parkinson's Disease Rating Scale

VacSYn: Adaptive biomarker-based Phase 2 study of ACI-7104 in early PD

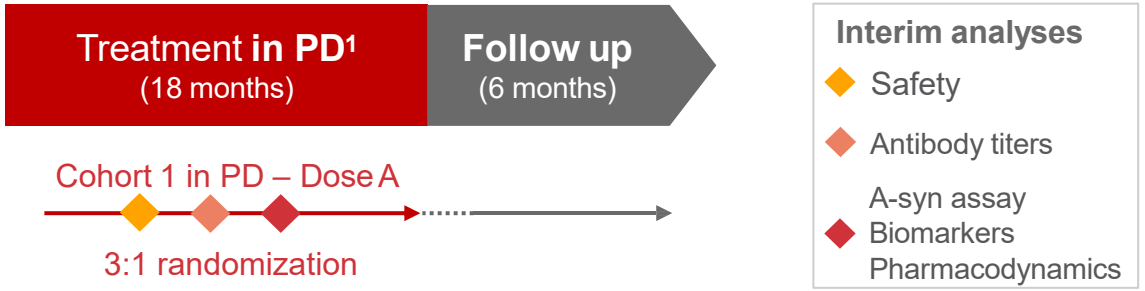
Placebo-controlled Phase 2 Study Overview (clinicaltrials.gov identifier: NCT06015841)

All participants from Part 1 will contribute to final analysis

Biomarker based interim analyses
- Early immunogenicity to tailor dose and/or dose regimen
- Apply disease-relevant biomarkers for early transition to filing

Part 1: Safety & PK/PD

- Key immunogenicity measures
- Measures of pathological a-syn (a-syn oligomers and aggregates)



Part 2: Proof of Concept in Early PD

- Motor and Non-Motor Functioning (UPDRS[2] based)
- Degeneration of dopaminergic terminals (DaT SPECT[3] imaging)
- Advanced MRI (including ASL[4] and DTI[5])
- Digital biomarkers of motor and non-motor function
- Functional and patient reported outcomes

(1) 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; (2) Unified Parkinson's disease rating scale; (3) Dopamine Transporter Single Photon Emission Computed Tomography; (4) Arterial spin labeling; (5) Diffusion tensor imaging

VacSYn an adaptive biomarker-based Phase 2 study of ACI-7104 in early PD[1]

Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Aged ≥40 to ≤75 years
- Diagnosis of clinically established early PD[1] (confirmed by DaT-SPECT[2])
- ≤ 2 years from time of onset motor symptoms
- H&Y[3] Stage I to II
- Monotherapy treatment with L-Dopa[4] at 300 mg per day or treatment naïve

Key Exclusion Criteria

- Carriers of certain familial PD[1] gene mutations
- Parkinsonian syndrome other than idiopathic PD[1]
- Significant CNS[5] disease[6]

- Total enrolment: 34 patients
- In future analyses, the number of subjects beyond week 50 are expected to increase as participants reach later timepoints

(1) Parkinson's disease; (2) Dopamine Transporter Single Photon Emission Computed Tomography; (3) Hoehn & Yahr scale; (4) Levodopa; (5) Central Nervous System; (6) Parkinsonian syndrome other than idiopathic PD, including but not limited to, progressive supranuclear palsy, multiple system atrophy, drug induced parkinsonism, essential tremor, vascular parkinsonism, primary dystonia.

VacSYn: Patient baseline characteristics and interim safety/tolerability findings

Placebo-controlled Ph 2 Study: No safety concerns raised by DSMB[1,5]

Baseline profile	Unit	Total
Total number of patients	n	34
Age	Years mean (std)	62.1 (6.7)
Sex		
Male	n (%)	22 (65%)
Female	n (%)	12 (35%)
Hoehn and Yahr stage		
Stage I	n (%)	16 (47%)
Stage II	n (%)	18 (53%)
MDS-UPDRS scores		
Part 1: Non-motor experiences of daily living	mean (std)	4.09 (3.1)
Part 2: Non-motor experiences of daily living	mean (std)	4.09 (3.2)
Part 3: Motor examination	mean (std)	21.09 (9.8)
Time since initial PD Diagnosis	Months mean (std)	10.3 (7.5)
PD Treatment		
treatment-naïve	n (%)	11 (32%)
L-Dopa 300mg/day	n (%)	23 (68%)

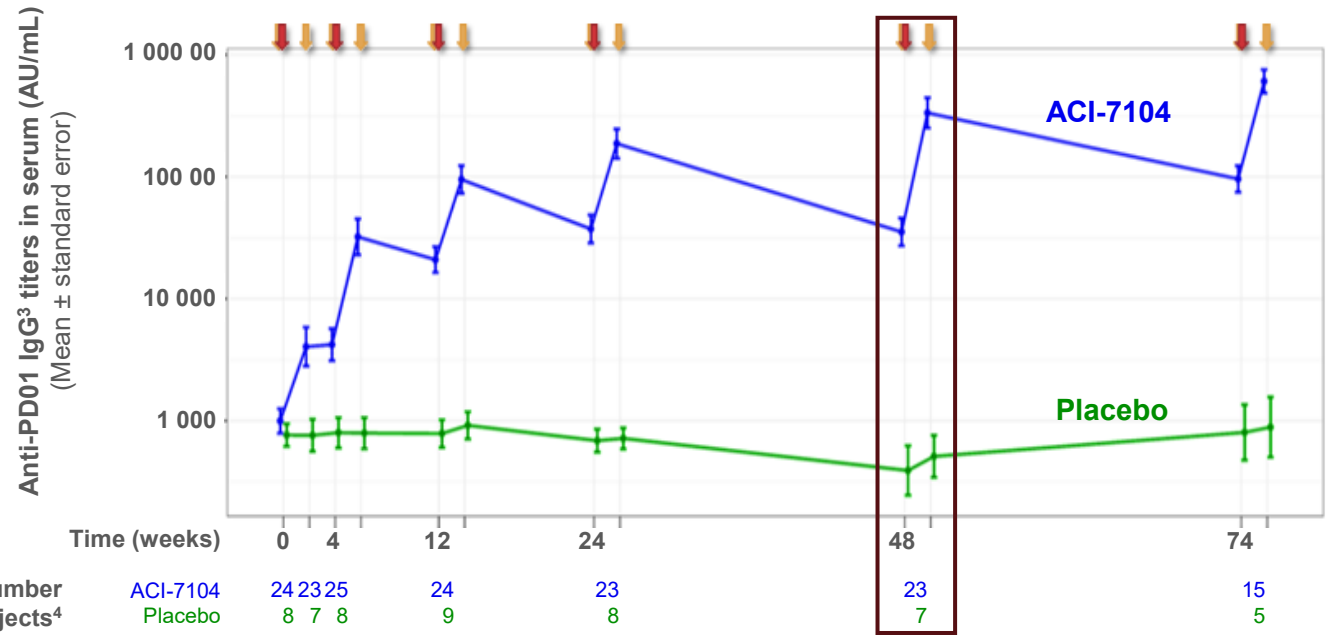
1. **Overall good safety/tolerability to date[5]**
2. **No SAE[2] considered related to the study drug, incl. 1 subject who died during participation in the study (unlikely related to the study drug)**
3. **Two discontinuations from the study[3] due to AEs, unrelated or unlikely related to study drug**
4. **Most common AEs are transient and generally of mild severity: Injection Site Reactions (55.9%) and headaches (14.7%) and fatigue (11.8%) [4]**
5. **No significant MRI[6], lab, ECG[7] abnormalities reported to date**

(1) Data Safety Monitoring Board; (2) Serious Adverse Events: Upper limb fracture, osteoarthritis, perforated appendicitis and intraabdominal sepsis (in the same subject), radical prostatectomy are considered unrelated to study drug, death of unknown cause is considered unlikely related to study drug; (3) One worsening of preexisting generalized anxiety disorder unrelated to study drug and one SAE of death of unknow cause; (4) incidence in the pooled active and placebo subjects; (5) Extraction date December 4, 2025; (6) Magnetic Resonance Imaging; (7) Electrocardiogram

Repeated ACI-7104 immunizations boost anti-a-syn[1] antibody responses

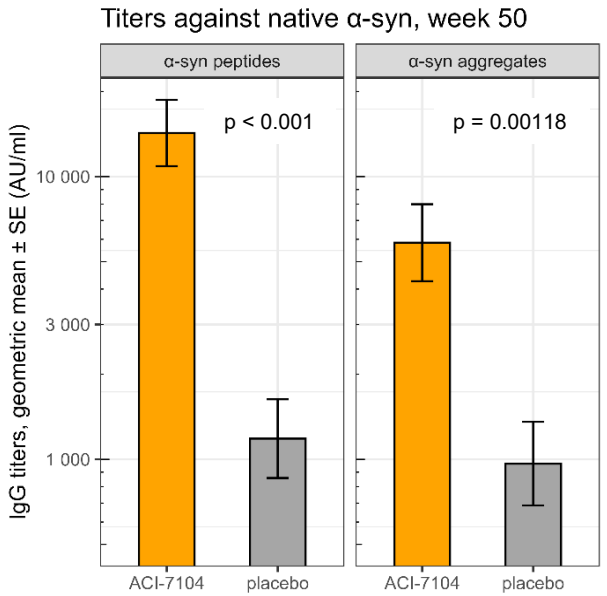
100% responder rate observed for modified a-syn antigen antibody titers in serum

Mean antibody titers in serum



Immunizations at:
0, 4, 12, 24, 48, and 74 weeks

CSF sampling at:
0, 24 and 76 weeks

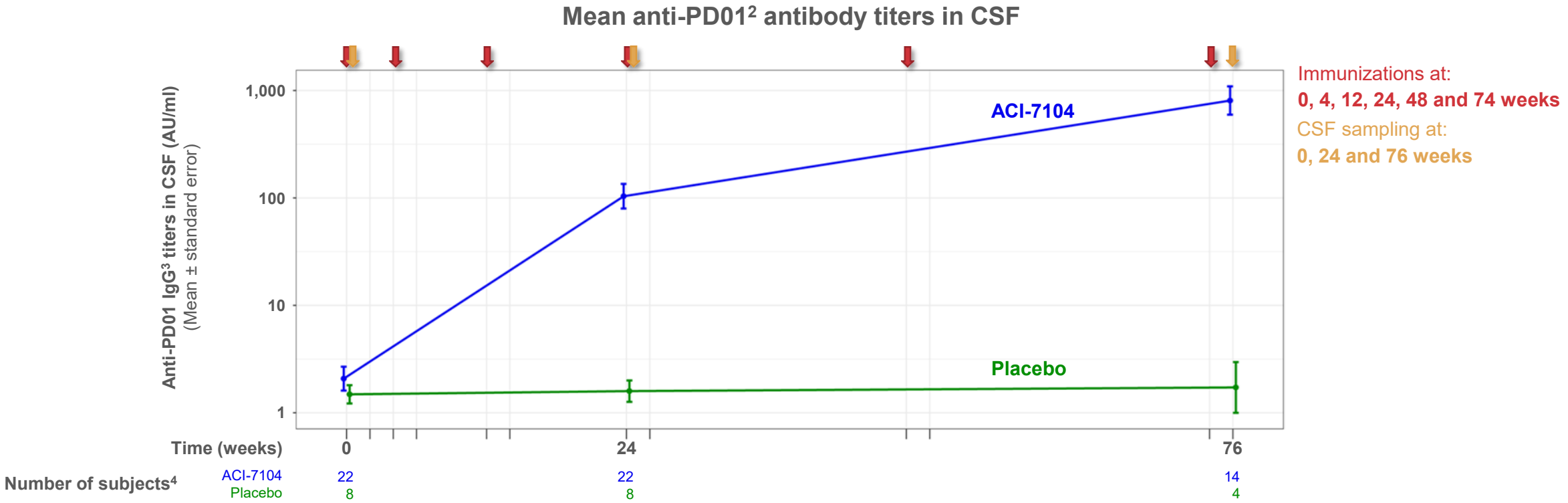


- Antibody responses were boosted after each dose
- ACI-7104-induced antibodies show high reactivity against a-syn peptide and a-syn-aggregates
- The placebo group did not show any detectable change from baseline

(1) Alpha-synuclein; (2) Modified a-syn peptide antigen; (3) Immunoglobulin; (4) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Antibody titers in CSF[1] increase with successive immunizations

ACI-7104 generates antibodies against modified a-syn that cross the blood-brain barrier

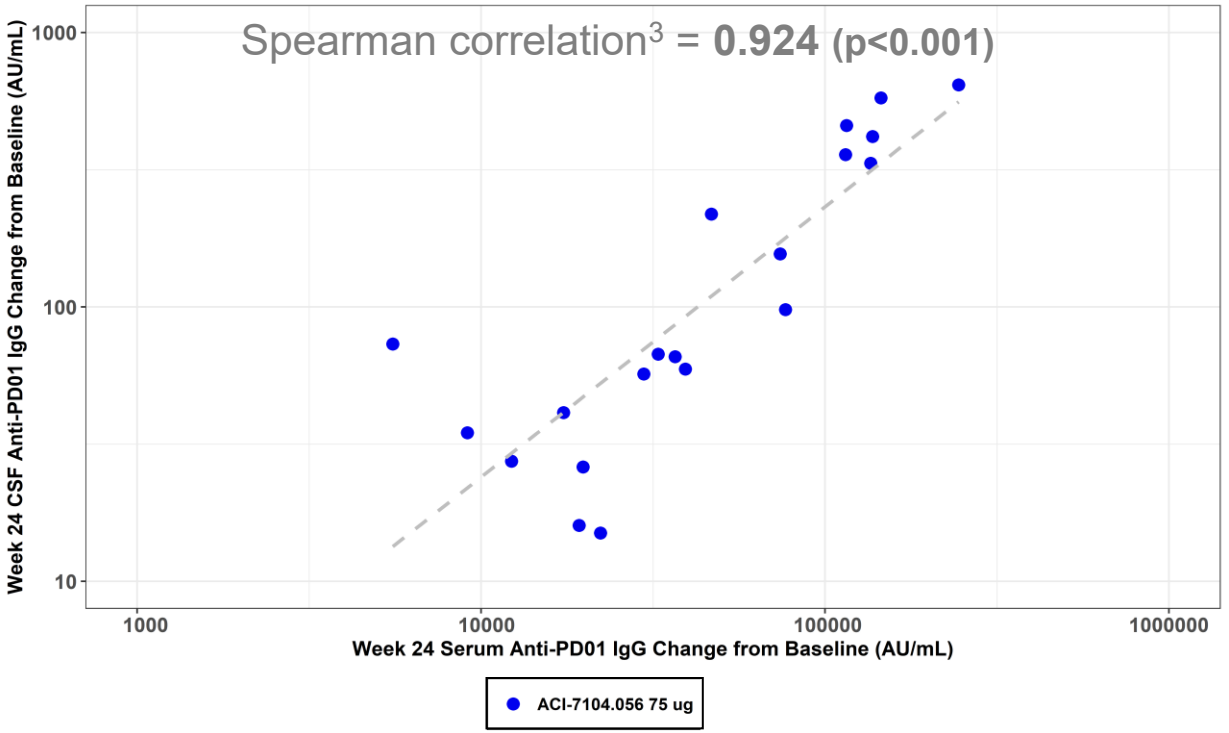


- Antibody exposure in the CNS is enhanced with increasing number of doses
- IgG antibody levels in CSF were an order of magnitude higher after the 6th (week 76) compared to the 3rd immunization (week 24)

(1) Cerebrospinal fluid; (2) Modified a-syn peptide antigen; (3) Immunoglobulin; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Correlation between antibody titers in serum and CSF[1]

Scatterplots[2] showing changes from baseline at weeks 24

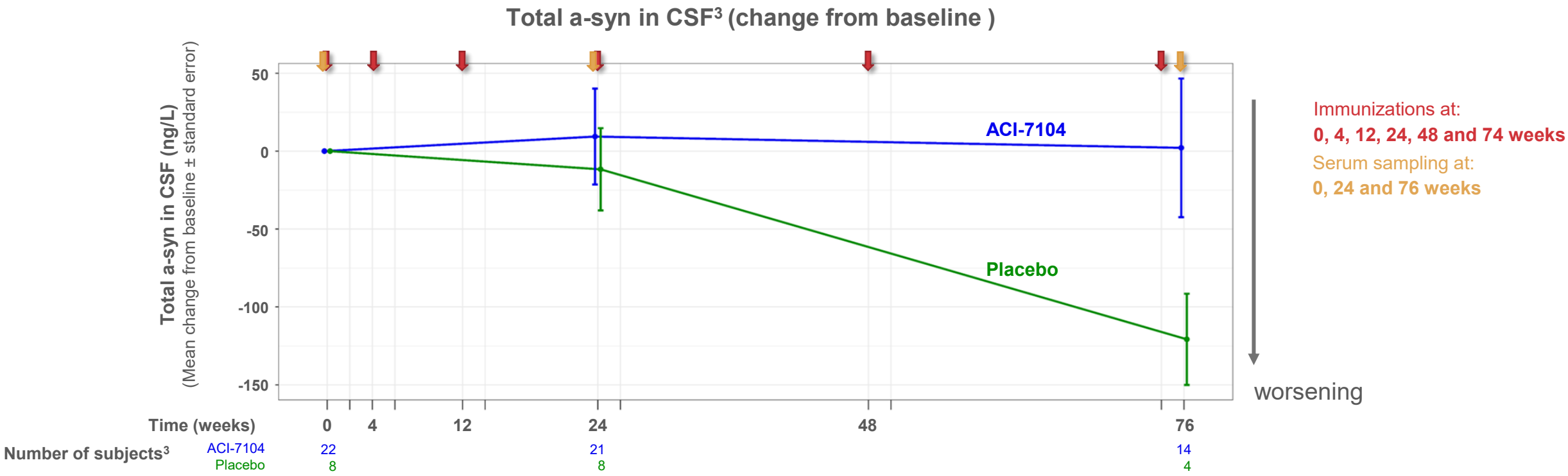


- Strong correlation observed between serum and CSF anti-PD01 IgG titers
- CSF-to-plasma concentration ratio of 0.1–0.3%
- Treatment-induced antibodies detected in CSF of all subject

(1) Cerebrospinal fluid; (2) Scatterplots generated internally and do not comprise official CRO Figures; (3) Correlation coefficients generated internally match correlations extracted from official CRO TFLs.

Immunization with ACI-7104 stabilizes total a-syn[1] levels in CSF[2]

A-syn levels in CSF[2] remain stable after treatment with ACI-7104



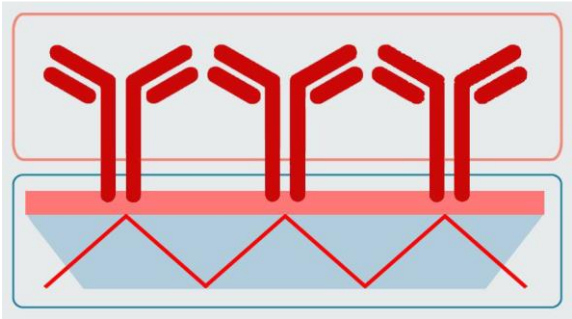
Post-hoc analysis showed a statistically significant difference (p = 0.018, one-sided Welch t-test) at week 76 between active and placebo groups.

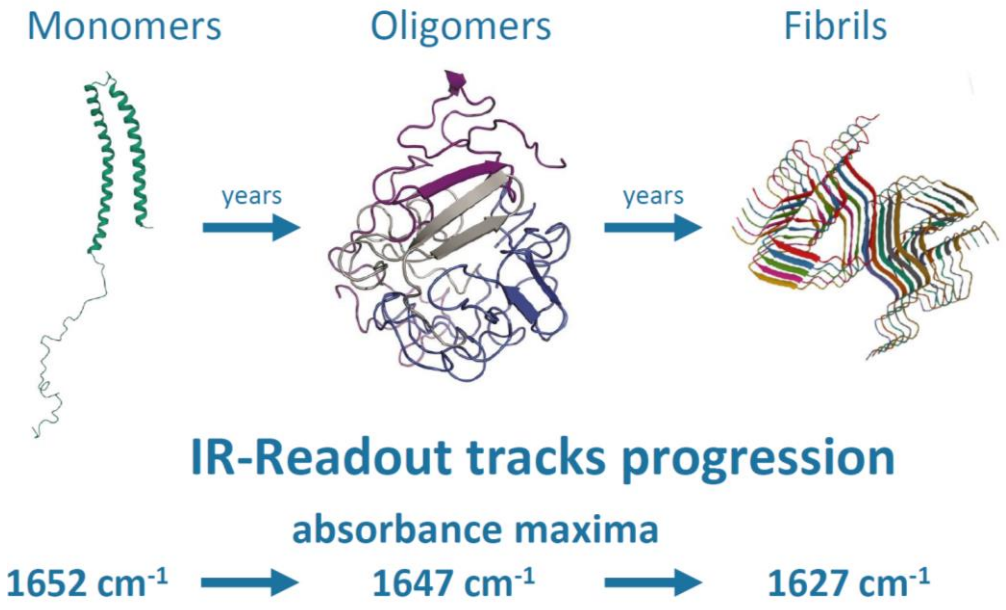
- Stabilization of total CSF a-syn levels in treatment arm suggest target engagement
- In the placebo group, a decrease in total CSF a-syn was observed over time

(1) Alpha-synuclein; (2) Cerebrospinal fluid; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints. One patient with very high a-syn levels at only week 24, likely an outlier value, needs further technical investigation and was removed here.

Alpha synuclein-specific Immuno-InfraRed Biosensor (iRS)

Secondary structure analysis of a-syn in CSF

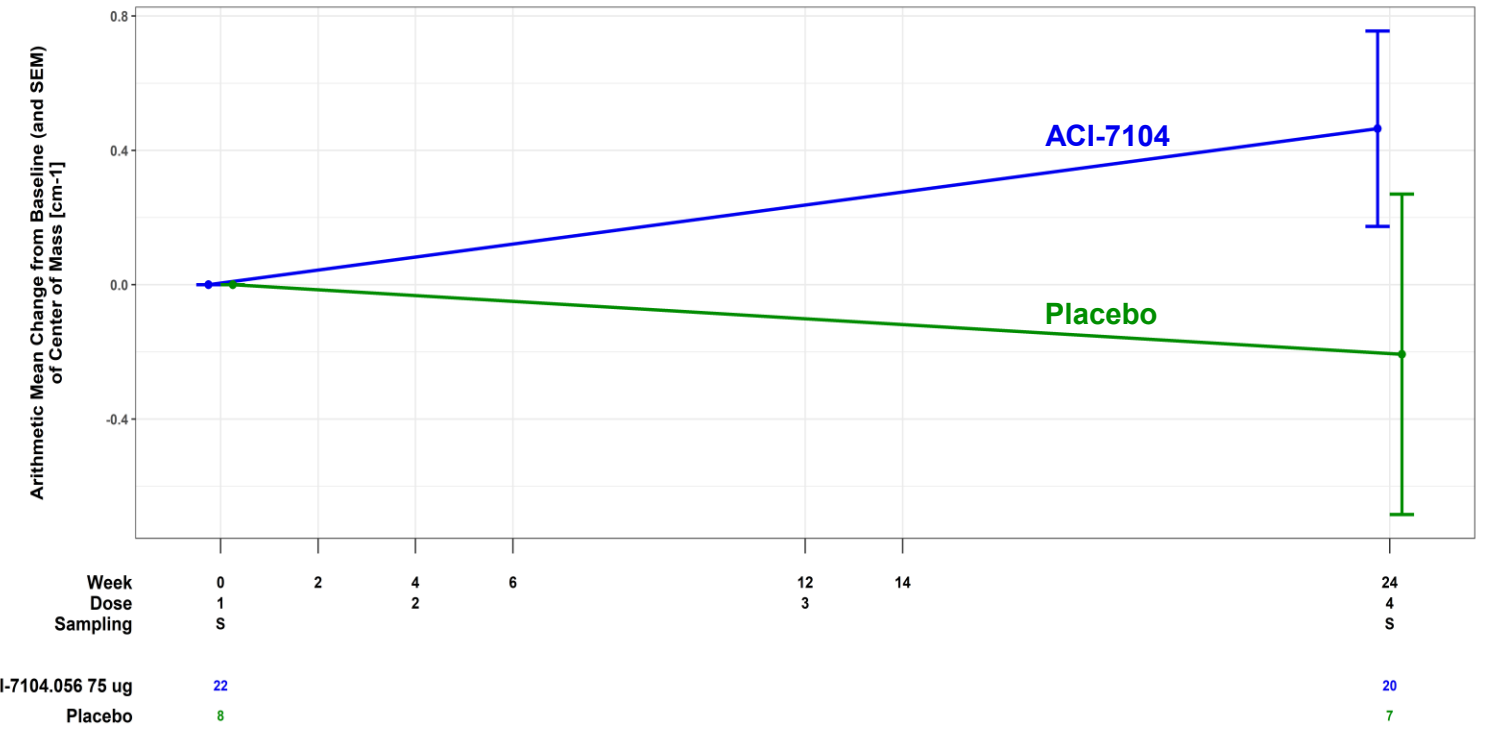




- AC Immune antibody against pan-a-syn is used to functionalize the biosensor
- Immuno-InfraRed sensor binds a-syn species of different secondary structures
- The assay measures the ratio of bound β-sheet to α-helical a-syn structures

IRS analysis suggests lower levels of beta-sheet a-syn species in CSF[1] at week 24

ACI-7104-induced antibodies potentially demonstrate a target-specific pharmacodynamic effect



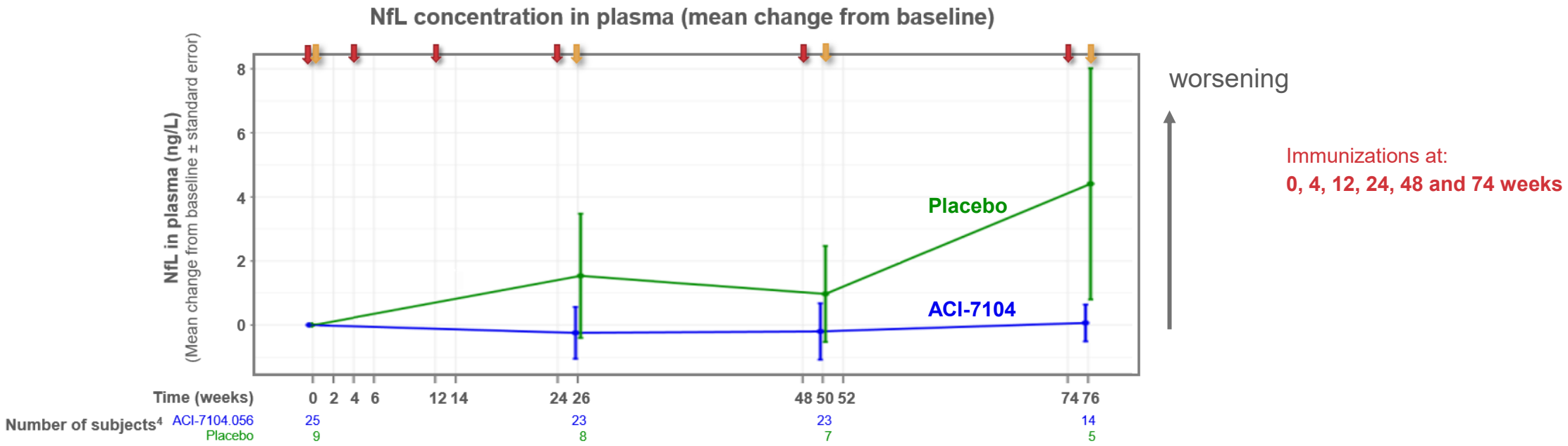
Increase in pathological a-syn

- In the ACI-7104 75 µg group at week 24, average increase in CoM[2] of ~0.45 cm^{-1}
- High variability in the Placebo group at week 24 with decrease of ~0.2 cm^{-1}

(1) Cerebrospinal fluid; (2) Center of Mass (expressed in cm^{-1}) (wavenumbers)

Stabilization of NfL[1] levels suggests potential slowing of neurodegeneration

NfL[1] in plasma (and CSF[2]) remains stable during treatment with ACI-7104



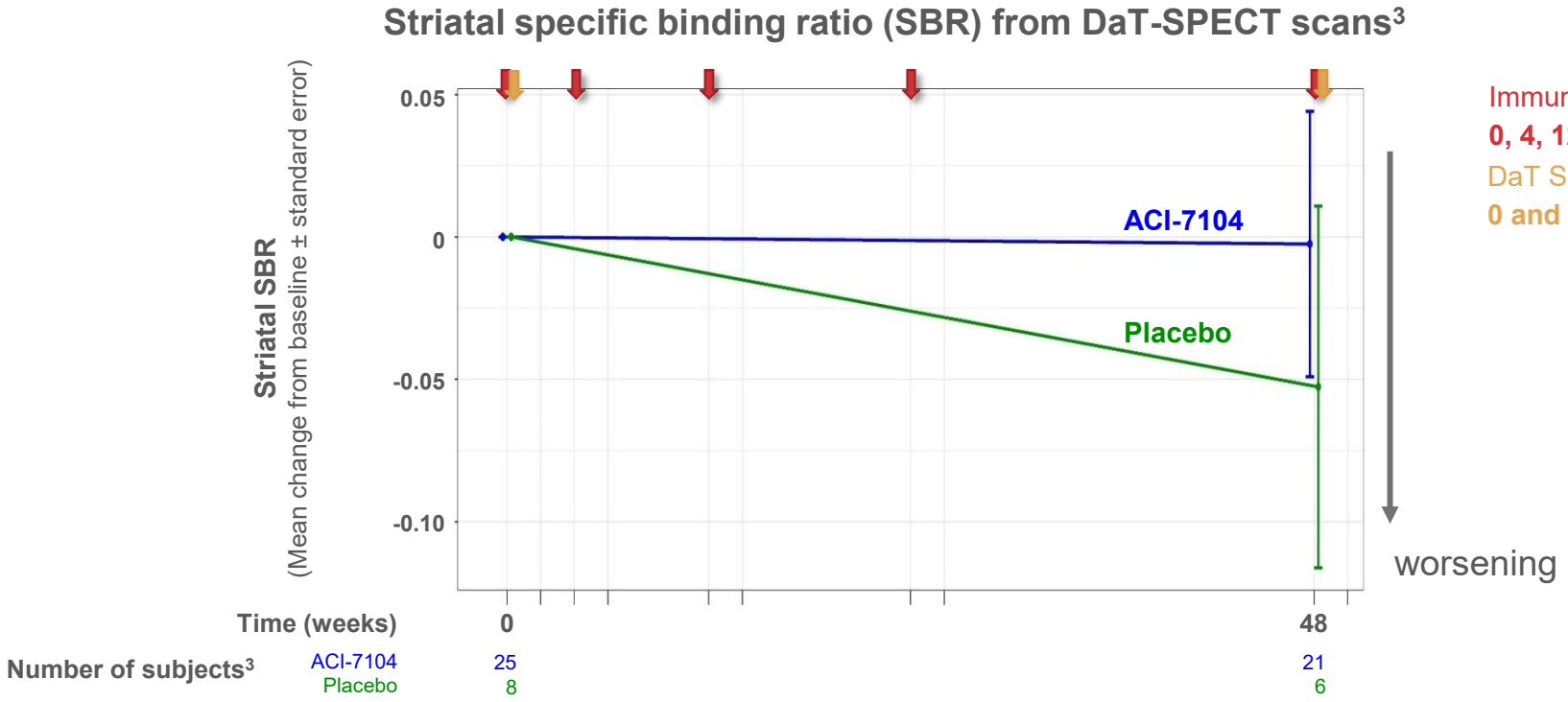
Immunizations at:
0, 4, 12, 24, 48 and 74 weeks

- NfL in plasma and CSF remained stable in the ACI-7104 group, consistent with slowing of disease
- In the placebo group, NfL levels in plasma and CSF increase over time, as previously reported in PD[3]

(1) Neurofilament light chain; (2) Cerebrospinal fluid; (3) Parkinson's disease; Mollenhauer *et al.*, Movement Disorders, 2021; (4) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Dopamine transporter imaging suggests stabilization of PD[1] pathology

DaT-SPECT[2] scans show trends of slowing degeneration of midbrain dopaminergic neurons



Immunizations at:
0, 4, 12, 24, 48 and 74 weeks
DaT SPECT scans at:
0 and 48 weeks

- Lower SBR values in striatum indicate reduced dopaminergic input from the midbrain to the striatum, and are linked to disease progression and motor symptoms
- In the ACI-7104 arm, minimal progression after 48 weeks suggests stabilized pathology

(1) Parkinson's disease; (2) Dopamine transporter single-photon emission computed tomography; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints. One outlier was removed from the placebo group.

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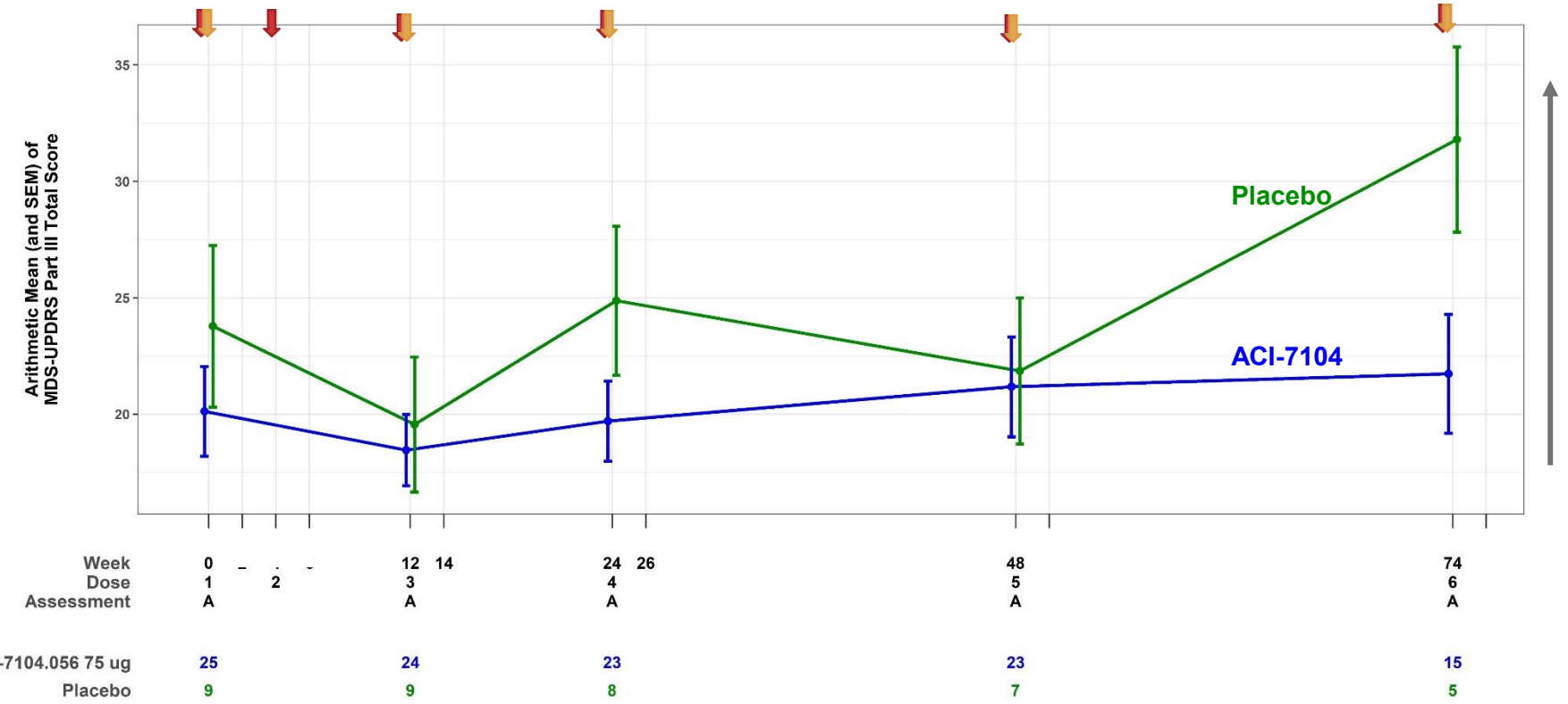
Treatment with ACI-7104 limits progression of motor symptoms

MDS-UPDRS[1] Part III examination of motor symptoms suggests faster decline in the placebo group



Immunizations at:
0, 4, 12, 24, 48 and 74 weeks
Assessment at:
0, 12, 24, 48 and 74 weeks

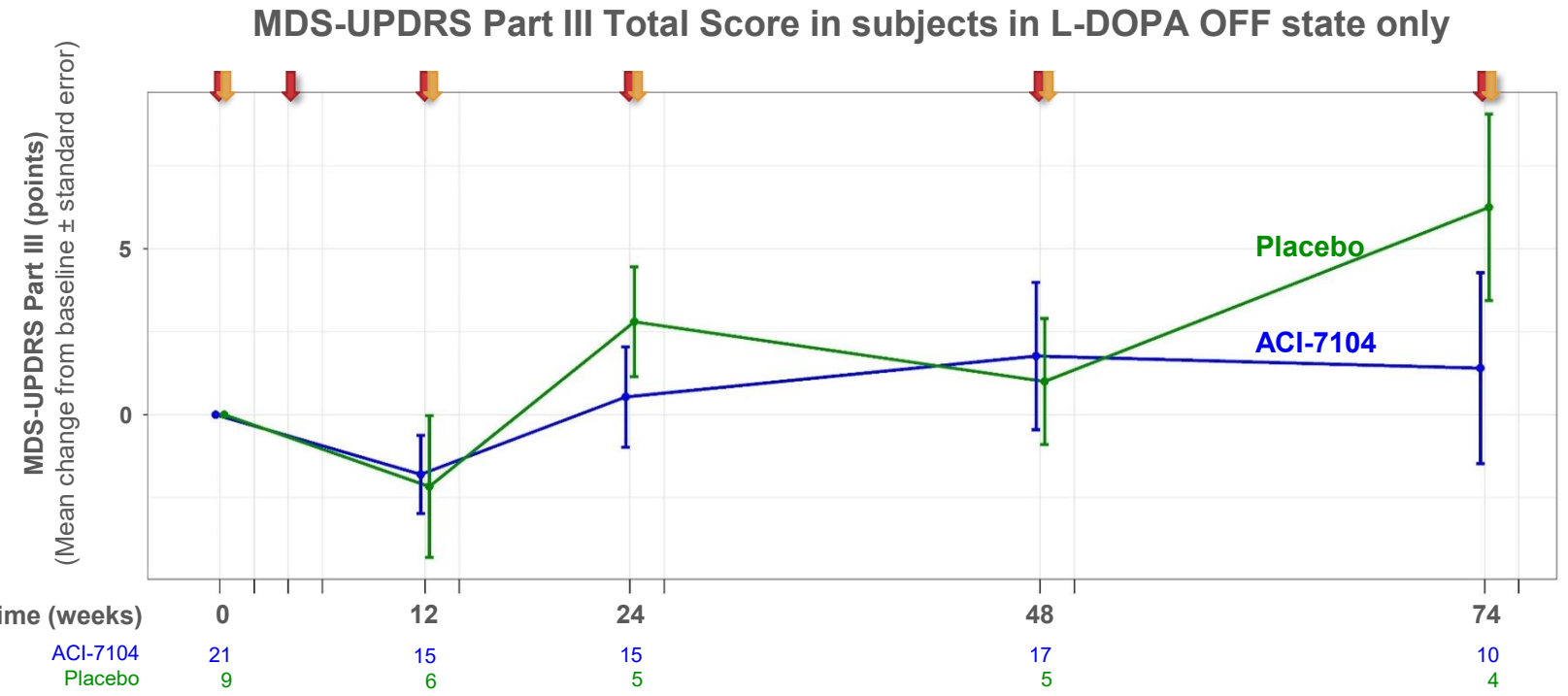
- The MDS-UPDRS Part III score is expected to increase by 2–3 points per year in early PD[2]
- At week 74, the ACI-7104 group did not show signs of meaningful progression, while the placebo arm trends towards an increase in mean MDS-UPDRS Part III total score

(1) Movement Disorder Society - Unified Parkinson's Disease Rating Scale; (2) Parkinson's disease; Holden *et al.*, Movement Disorders, 2018

AC Immune
Figure 14.2.4.1.1

MDS-UPDRS[1] Part III suggests slowing of disease after stratifying by L-DOPA[2] state

In the L-DOPA OFF state, Part III total score also points toward slowed decline in the treatment arm



Immunizations at:
0, 4, 12, 24, 48 and 74 weeks

Assessment at:
0, 12, 24, 48 and 74 weeks

- The MDS-UPDRS Part III score is expected to increase by 2–3 points per year in early PD[2]
- At week 74, the ACI-7104 group did not show signs of meaningful progression, while the placebo arm trends towards an increase in mean MDS-UPDRS Part III total score

(1) Movement Disorder Society - Unified Parkinson's Disease Rating Scale; (2) Levodopa; (3) Number of subjects beyond week 50 is expected to increase as subjects reach later timepoints.

Conclusion – VacSYn Phase 2 Part 1 interim results

Safety and tolerability

- ACI-7104 has demonstrated a favorable benefit/risk ratio
- No serious adverse events related to the study drug
- Most common AEs[1] are transient and generally of mild severity

Immunogenicity

- 100% responder rate observed for the a-syn[2] target antigen
- Anti-a-syn antibody levels were boostable
- Antibody levels in CSF[3] correlated strongly with levels in serum

(1) Adverse event; (2) Alpha-synuclein; (3) Cerebrospinal fluid

Conclusion – VacSYn Phase 2 Part 1 interim results

Biomarkers

- Effects on total and aggregated a-syn[1] in CSF[2] aligned with target engagement
- NfL[3] in plasma and CSF suggest slowing of Parkinson's disease pathology
- Dat-SPECT[4] imaging show trends of disease stabilization

Clinical measures

- ACI-7104-treated subjects showed trend to slowing of disease progression
- MDS-UPDRS[5] Part III total score is suggestive of a trend for stabilization

(1) Alpha-synuclein; (2) Cerebrospinal fluid; (3) Neurofilament light chain; (4) Dopamine transporter single-photon emission computed tomography; (5) Movement Disorder Society - Unified Parkinson's Disease Rating Scale

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Dr Qamar and Prof. Chaudhuri (London, UK, King's College Hospital NHS Foundation Trust)

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

AC Immune

Morphomer® a-synuclein: Targeting intracellular a-synuclein pathology

Francesca Capotosti, PhD | ADPD 2026 | March 2026

AC Immune

Disclaimer

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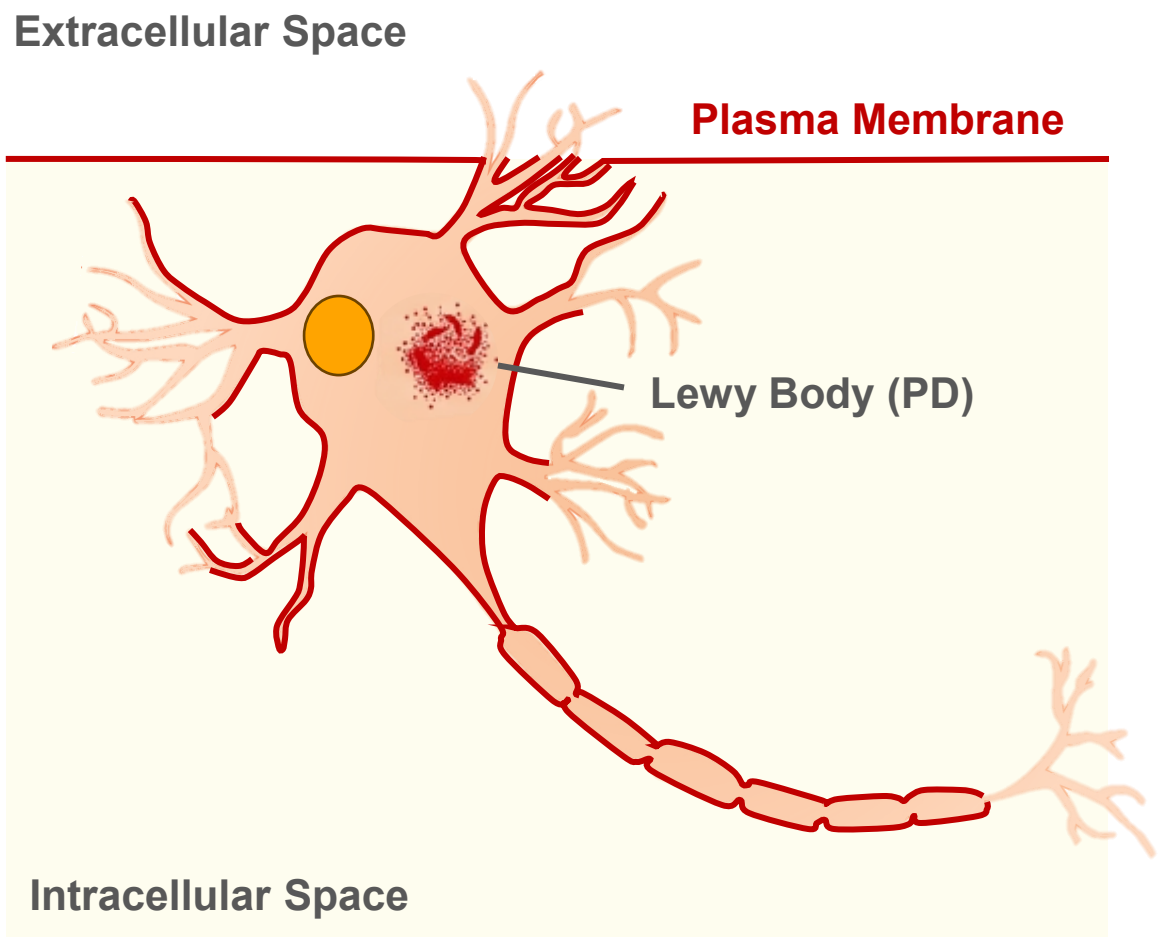
SupraAntigen® is a registered trademark of AC Immune SA in the following territories: AU, CH, EU, GB, JP, RU, SG and USA. Morphomer® is a registered trademark of AC Immune SA in CH, CN, GB, JP, KR, NO and RU.

Conflict of interest disclosure

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

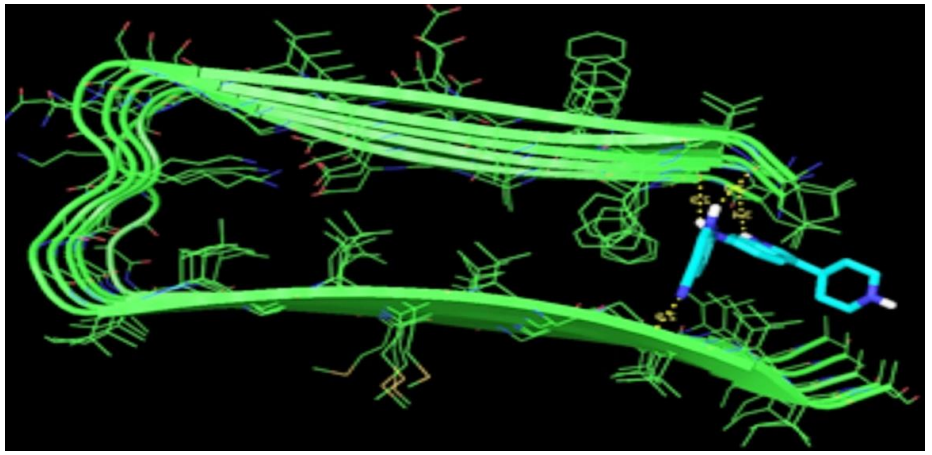
To halt disease progression Intracellular targeting matters



Morphomers® Intracellular Targeting: Acting where it matters

- Pathological alpha-synuclein (a-syn) aggregates accumulate intracellularly
- **In Parkinson's Disease (PD):** Aggregates form Lewy bodies within neurons
- **In Multiple System Atrophy (MSA):** Aggregates form in Glial cytoplasmic inclusions (GCIs)
- **Unmet Need:** Therapies must cross the blood brain barrier and plasma membrane to prevent aggregation at the source

Targeting intracellular a-syn aggregation with Morphomers®



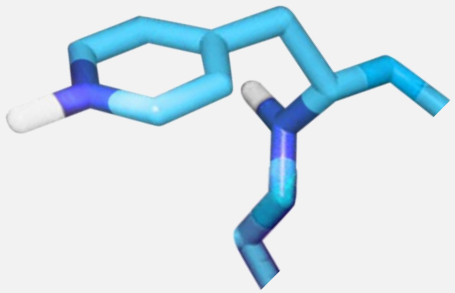
The Morphomer® library

- Large library of conformation-specific small molecules with CNS[1] properties continuously expanded via rational design
- Used with comprehensive screening assays of high translational value to rapidly generate highly specific hits
- Clinically validated platform with two diagnostic PET tracers showing excellent target engagement

(1) Central nervous system

Morphomers® for optimal CNS[1] delivery and intracellular access

Morphomer® Small Molecules



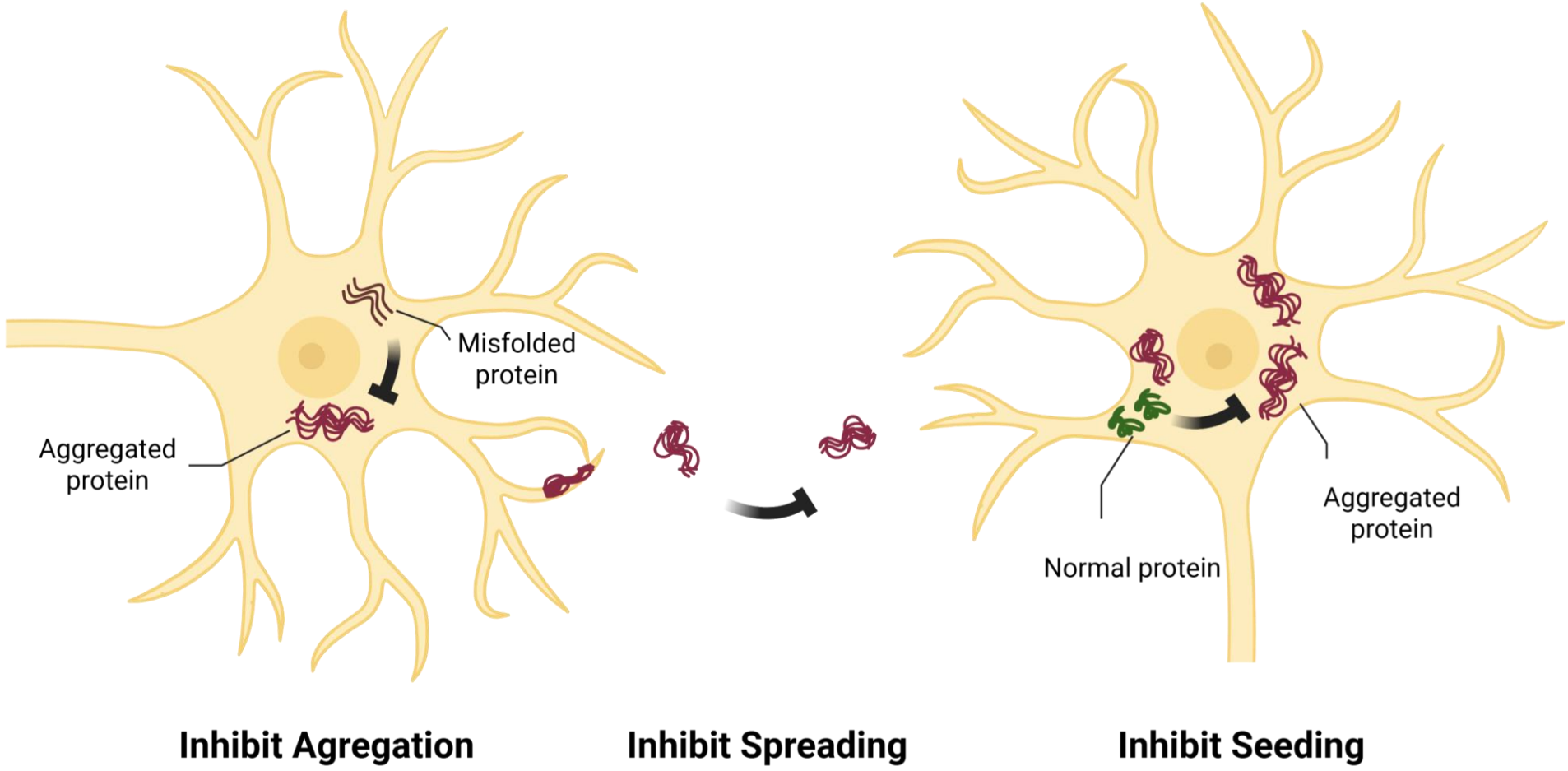
- ✓ Orally available
- ✓ Highly CNS penetrant
- ✓ Cell plasma membrane permeable
- ✓ Targets intracellular and extracellular pathology

Immunotherapy approaches

- Invasive administration (injection/infusion)
- Limited CNS penetration
- Complementary to Morphomers® for extracellular targeting

(1) Central Nervous System; image created with Biorender

A-syn[1]-targeting Morphomers® to halt pathology at multiple points

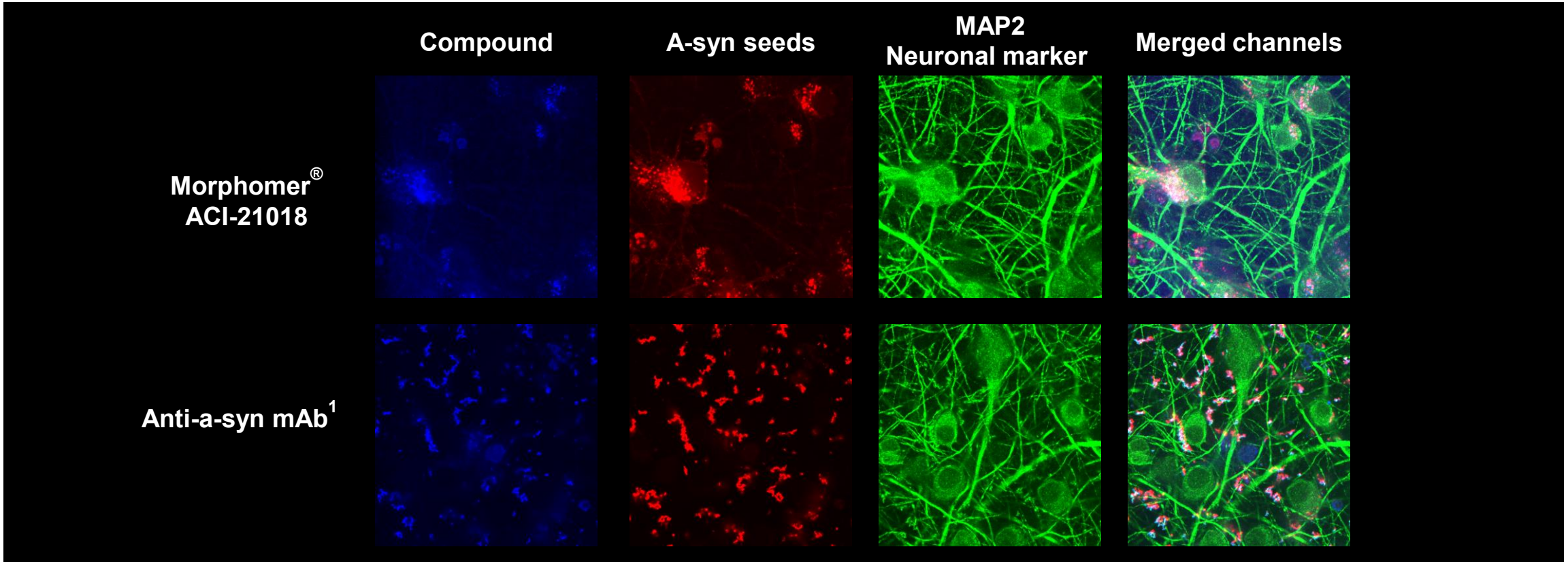


- The unique combination of inhibition of intracellular aggregation and extracellular spreading is expected to result in a strong disease modification

(1) alpha-synuclein; image created with Biorender

Intracellular localization of Morphomer®

Co-localization of a-syn aggregates and Morphomer® inside neurons



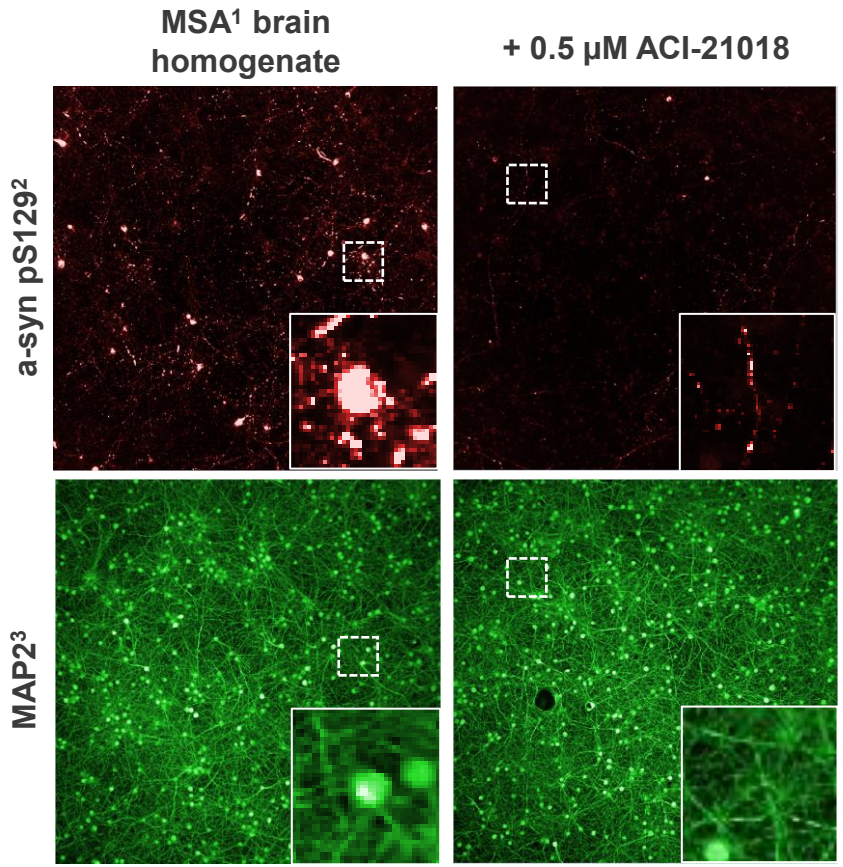
- Morphomers® co-localize with a-syn seeds inside neurons in contrast to an a-syn monoclonal antibody[1] which binds a-syn seeds only in the extracellular space[2]
- This should potentially result in both the inhibition of a-syn spreading and prevention of intracellular aggregation

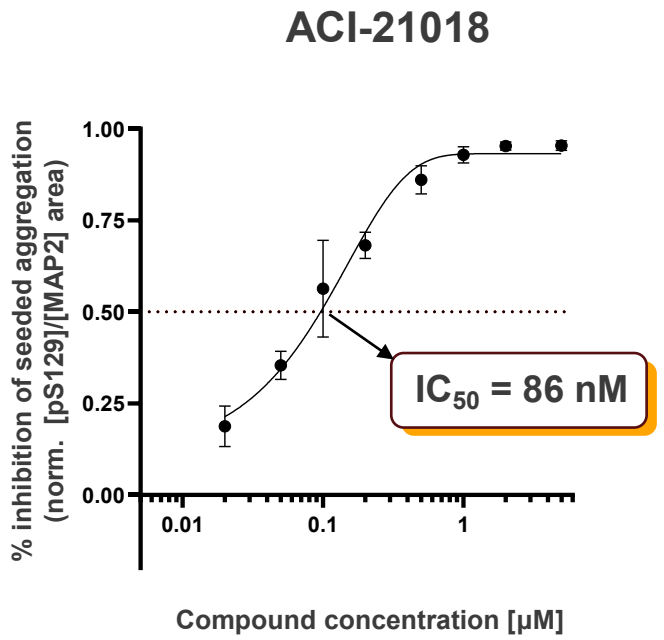
(1) antibody based on the Prasinezumab's sequence as per patent; (2) Representative images of neurons stained 9 days after seeds / compound treatment

AC Immune, unpublished data

Morphomers® halt a-syn aggregation

Potent inhibition using disease brain[1]-derived a-syn aggregates as seeds





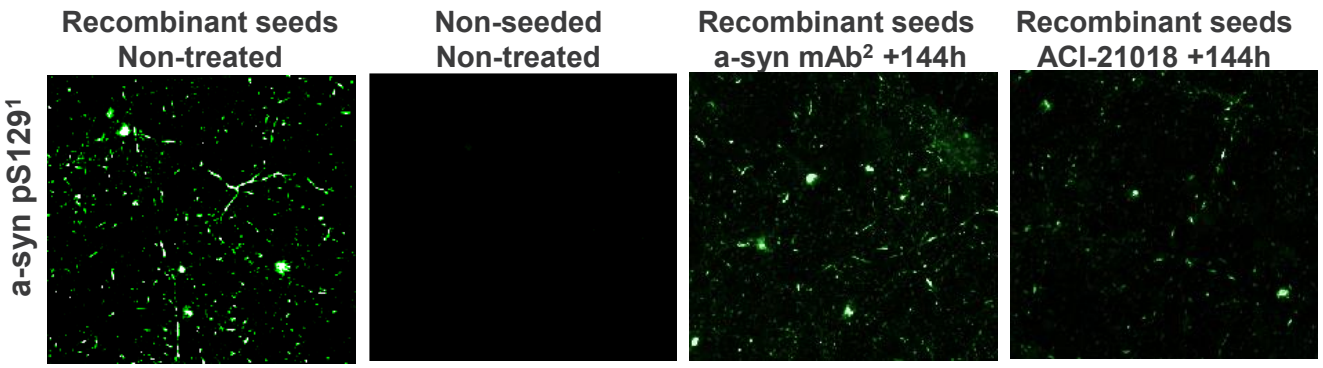
Tsika et al., ADPD™ 2024

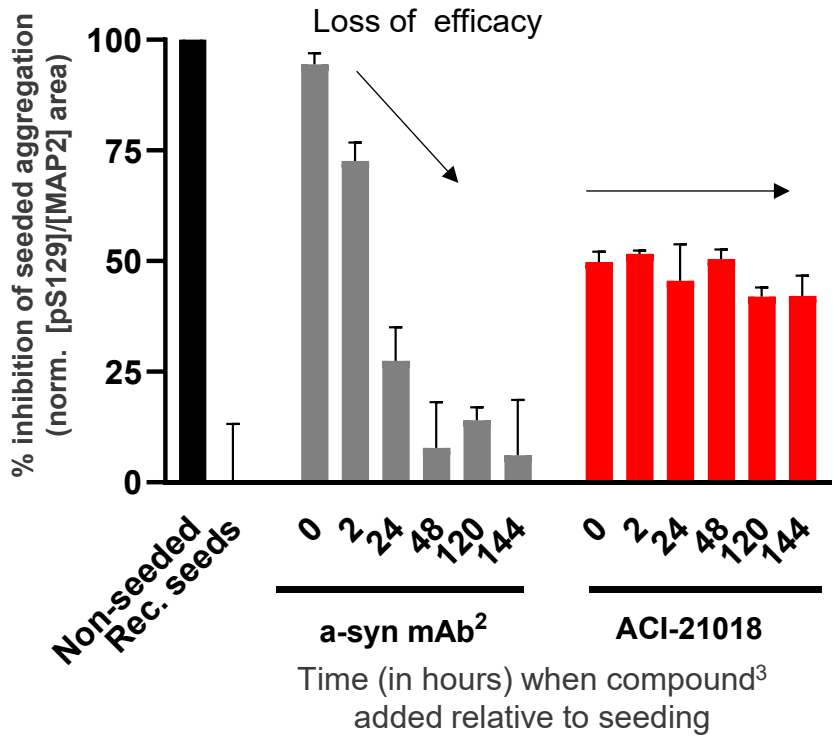
- Morphomers® reduce intracellular a-syn[2] inclusions, indicating a potent effect at blocking seeding and therefore spreading of the a-syn pathology

(1) Multiple system atrophy; (2) Phospho-Serine 129; (3) Microtubule associated protein 2

Morphomers® halt intracellular a-syn aggregation

Treatment of primary neurons with monoclonal antibody or Morphomer® post-seeding initiation





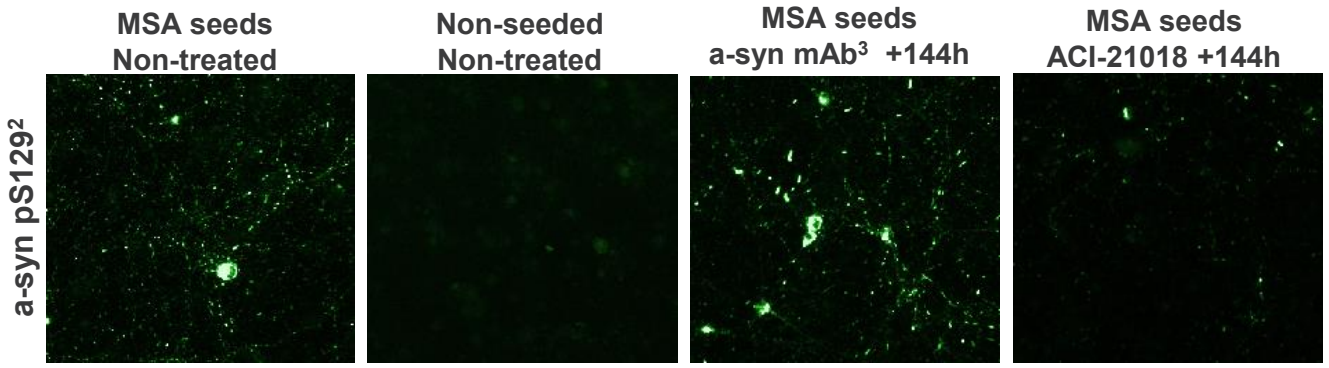
AC Immune, unpublished data

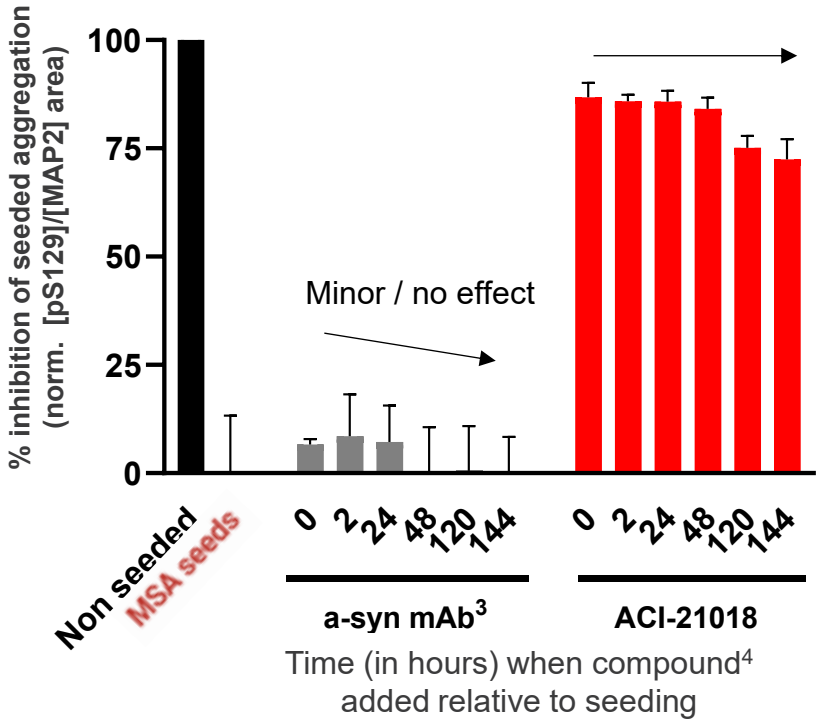
- Morphomers® sustained efficacy suggest disruption of a-syn intracellular seeding and aggregation
- In contrast, an a-syn monoclonal antibody[2] can only inhibit seeds uptake

(1) phosphoserine 129; (2) antibody based on the Prasinezumab's sequence as per patent (3) anti-a-syn mAb: 100nM; ACI-21018: 1000nM

Morphomers® halt intracellular aggregation induced with MSA[1]-seeds

Treatment of primary neurons with monoclonal antibody or Morphomer® post-seeding initiation





AC Immune, unpublished data

- Morphomers® show sustained efficacy on different a-syn pathological conformations
- In contrast, an anti a-syn monoclonal antibody[5] has only a weak inhibitory activity on MSA seeds
- Broad potential to treat a-syn-associated disease including MSA

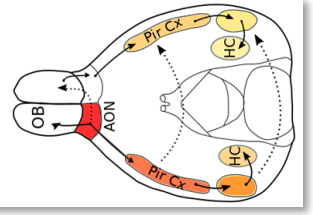
(1) Multiple system atrophy; (2) phosphoserine 129 (3) antibody based on the Prasinezumab's sequence as per patent; (4) anti-a-syn mAb: 100nM; ACI-21018: 1000nM

ACI-21018 reduces a-syn pathology and prevents neuron loss *in vivo*

Efficacy study in the a-syn M83$^{+/-}$ hPFF^{1} model of PD

Study Design:

- ✓ Transgenic heterozygous mice expressing a-syn A53T injected in the olfactory nucleus with human a-syn preformed fibrils
- ✓ Therapeutic paradigm: treatment initiated 48h post-inoculation of pathological a-syn
- ✓ Once daily oral administration for 15 weeks at doses covering IC_{50} of the *in vitro* assay as free brain concentration for the dosing interval



- Significant reduction of a-syn seeding species, even with a therapeutic regimen
- Complete rescue of neuronal loss demonstrated in regions proximal and distal to disease initiation

(1) Transgenic line M83 injected in the olfactory nucleus with human a-syn preformed fibrils; (2) One-Way ANOVA; Post-hoc Tukey's test; ns: non-significant, *p<0.05; **p<0.01; **** p<0.0001

Tsika *et al.*, ADPD™ 2025

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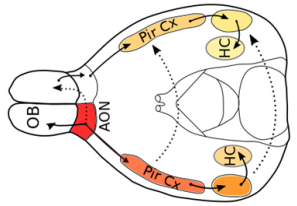
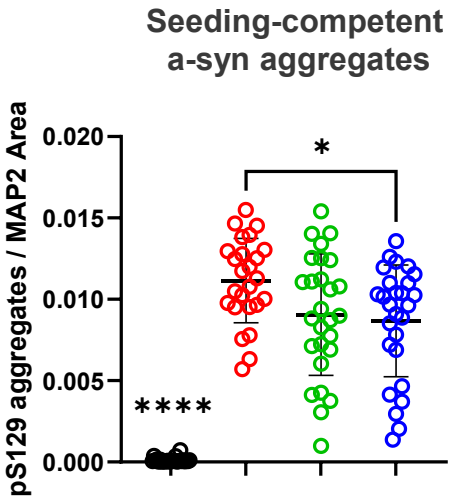
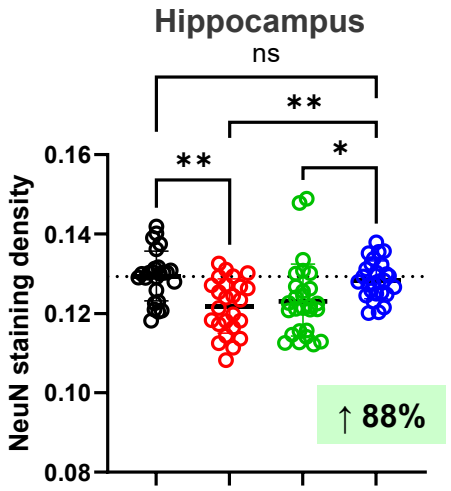
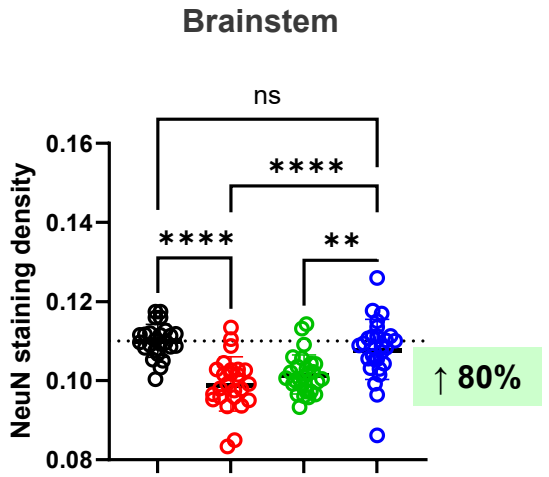
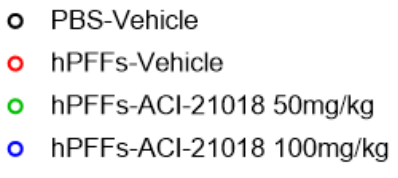


Neuronal Survival - NeuN staining









Mean ± SD[2]

Geometric means ± geometric SD[2] % change from hPFF-vehicle (relative to PBS-vehicle), group mean values

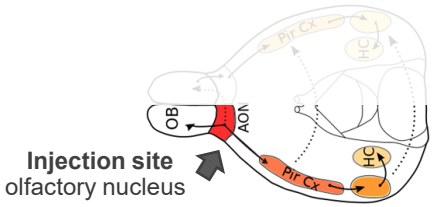
- Significant reduction of a-syn seeding species, even with a therapeutic regimen
- Complete rescue of neuronal loss demonstrated in regions proximal and distal to disease initiation

(1) Transgenic line M83 injected in the olfactory nucleus with human a-syn preformed fibrils; (2) One-Way ANOVA; Post-hoc Tukey's test; ns: non-significant, *p<0.05; **p<0.01; **** p<0.0001

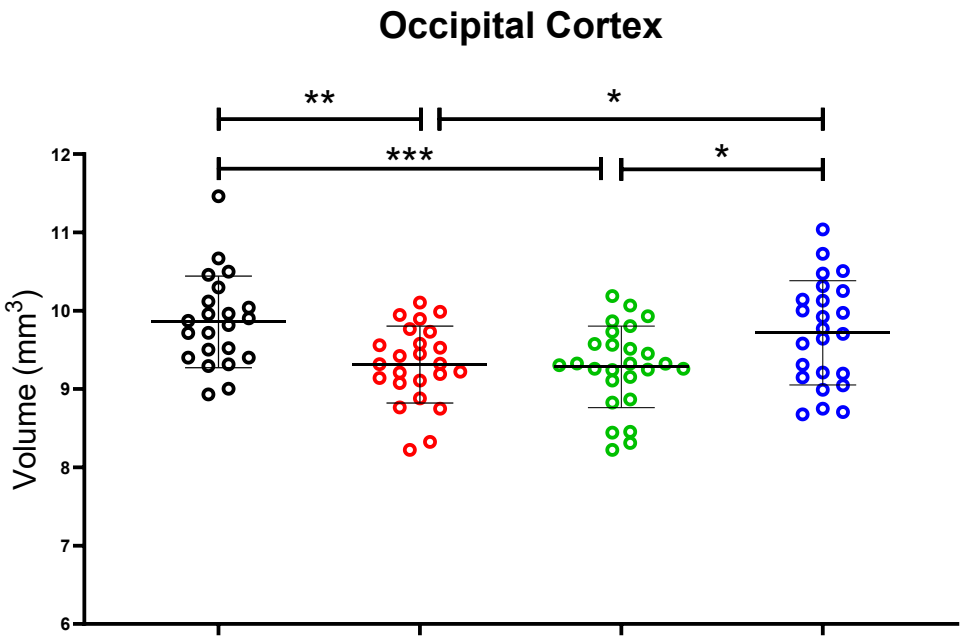
Tsika *et al.*, ADPD™ 2025

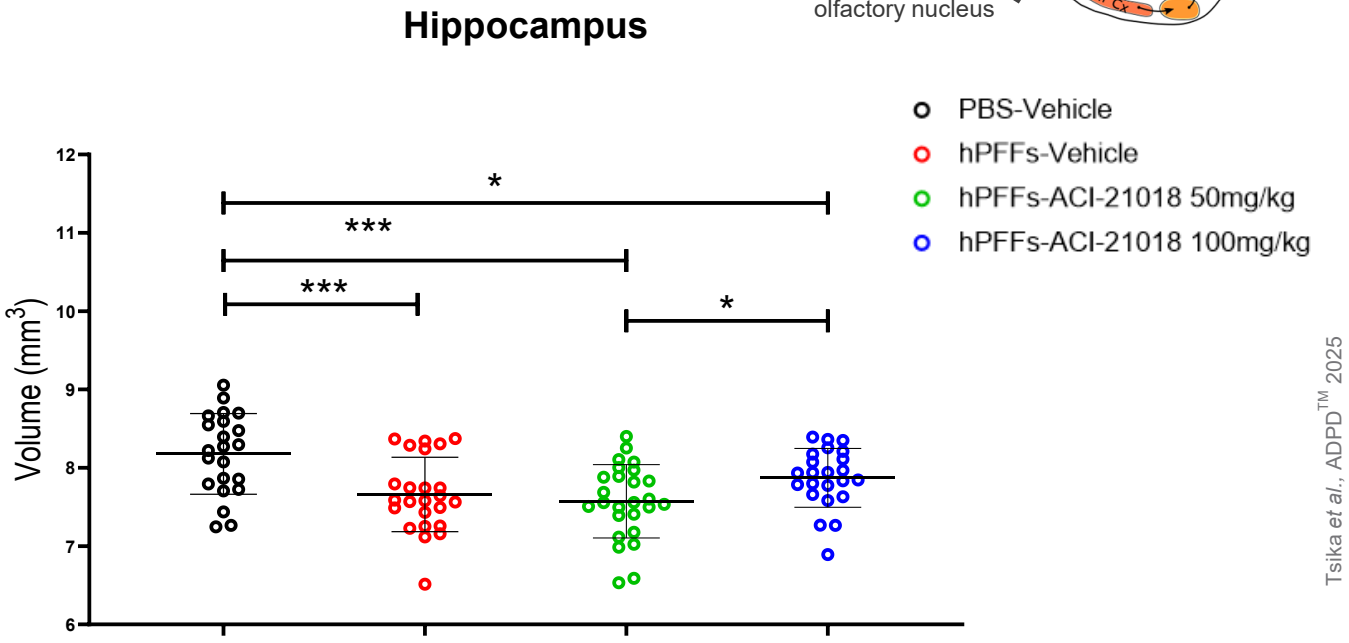
ACI-21018 prevents regional brain atrophy

MRI[1] analysis of regional brain volumes ipsilateral to the injection site[2]



Injection site
olfactory nucleus





Mean +/- SD; t-test *p<0.05; **p<0.01; ***p<0.001

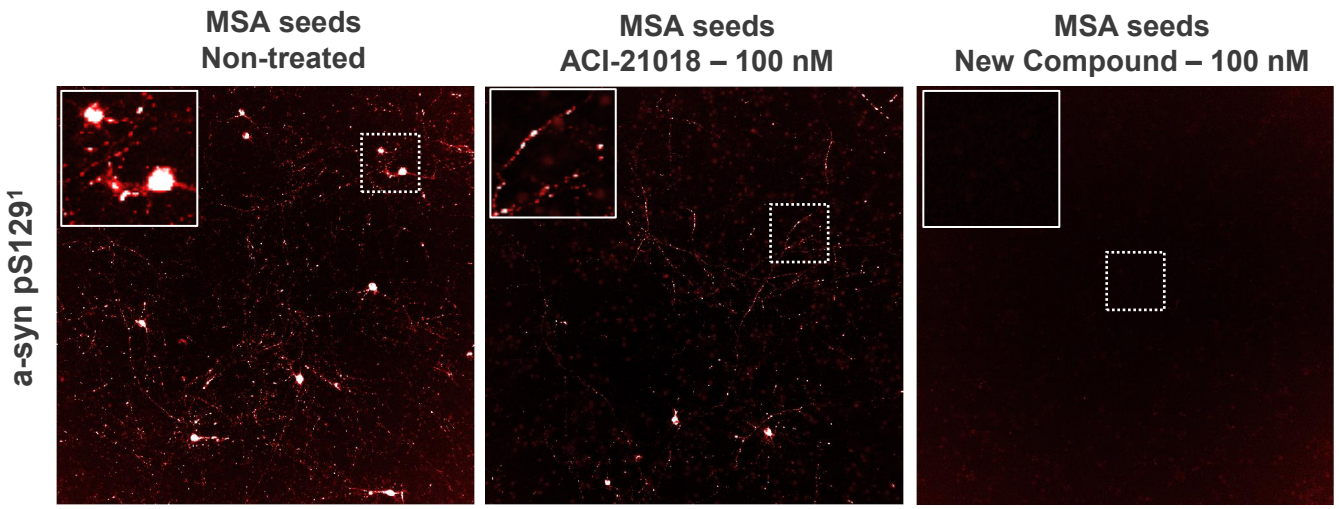
Tsika *et al.*, ADPD™ 2025

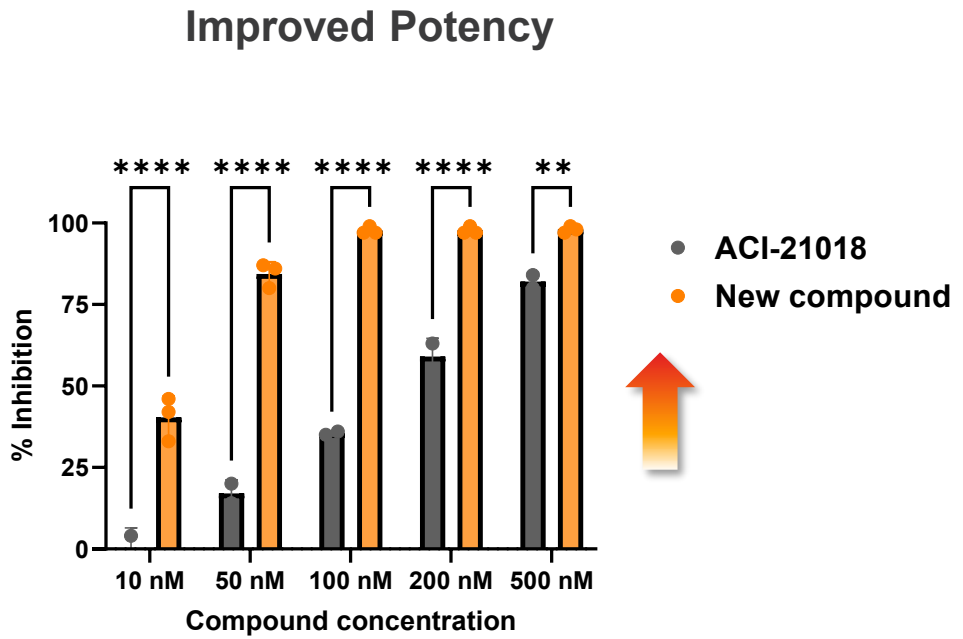
- ACI-21018 treatment resulted in broad neuroprotective effects, reaching levels close to healthy mice
- This neuroprotective effect can be measured by MRI, ensuring high translational value

(1) Magnetic resonance imaging; (2) human a-syn preformed fibrils injected in olfactory nucleus

Continuous Optimization: Next-Generation a-syn Morphomers®

Increased potency to improve development profile





AiC Immune: unpublished data

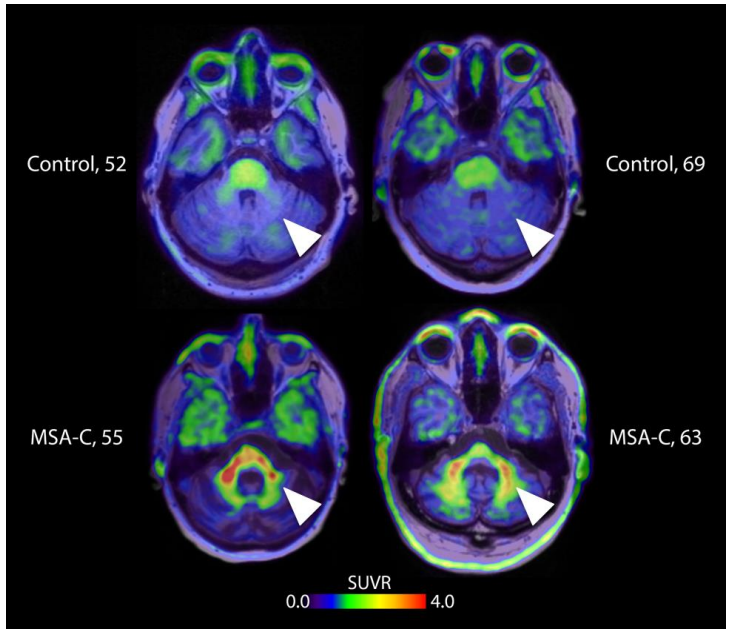
- A thorough MedChem optimization approach delivered compounds with significantly increased potency

(1) phosphoserine 129; **** Two-way ANOVA P-value <0.0001; ** Two-way ANOVA P-value = 0.0035

Accelerating and derisking clinical development in MSA[1]

Unique opportunity to combine AC Immune's a-syn PET[2] tracer and therapeutic Morphomers®

See the disease



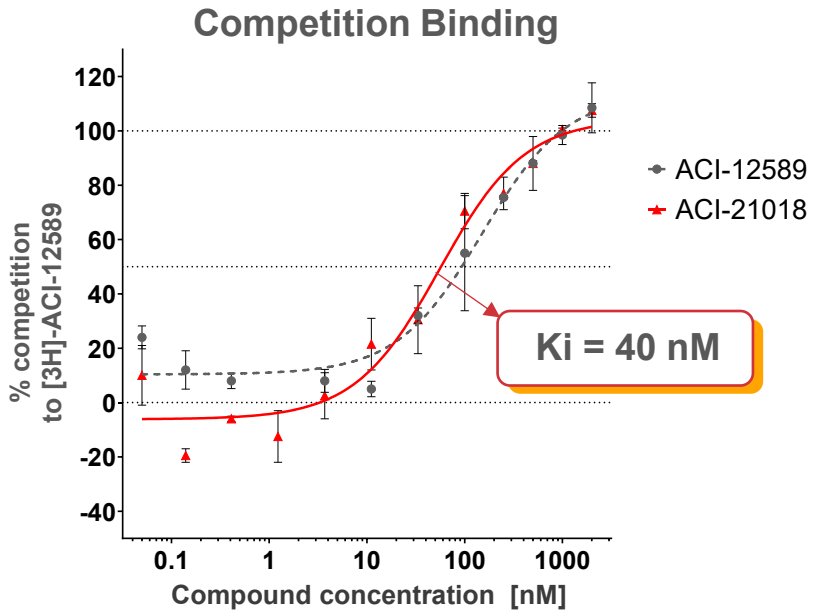
RR. Smith et al., Nat. Com., 2023

ACI-12589: clinically validated a-syn PET tracer

Strategic Advantage: Shared Binding site

1. Select correct patients (pathology confirmed)
2. Measure target engagement in early clinical trials
3. Track reduction of pathology over time

Treat the disease

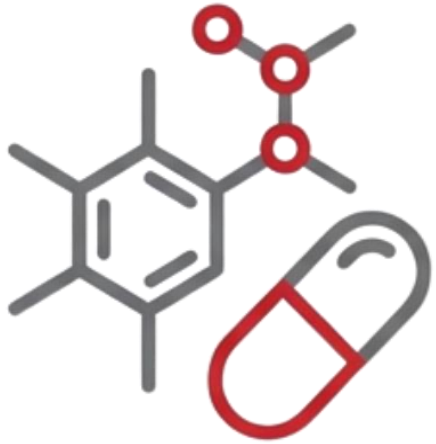


Tsika et al., ADPD™ 2024

ACI-12589 and therapeutic Morphomers® share a common binding site

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

A-syn[1] Morphomers®: A Game-Changing Opportunity



First-in-class

- ✓ **Oral** small molecules
- ✓ Highly CNS penetrant
- ✓ Cell permeable

Intracellular Targeting

Act **"where it matters":**

- ✓ Inhibit aggregation
- ✓ Inhibit seeding
- ✓ Inhibit spreading

Precision Medicine

Therapeutic/Diagnostic synergy: De-risked development via

- ✓ Pathology-based patient selection
- ✓ Early confirmation of target engagement

Therapeutic Potential

Stop disease progression by:

- ✓ Rescue neurons
- ✓ Prevent brain atrophy

(1) alpha-synuclein; Images created with Biorender

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AC Immune

Shifting the treatment paradigm for neurodegenerative disease towards precision medicine and disease prevention


Discussion and Q&A