α-Synuclein as a Target in Neurodegenerative Diseases

NASDAQ: ACIU | KOL Webinar, March 2022

AC Immune

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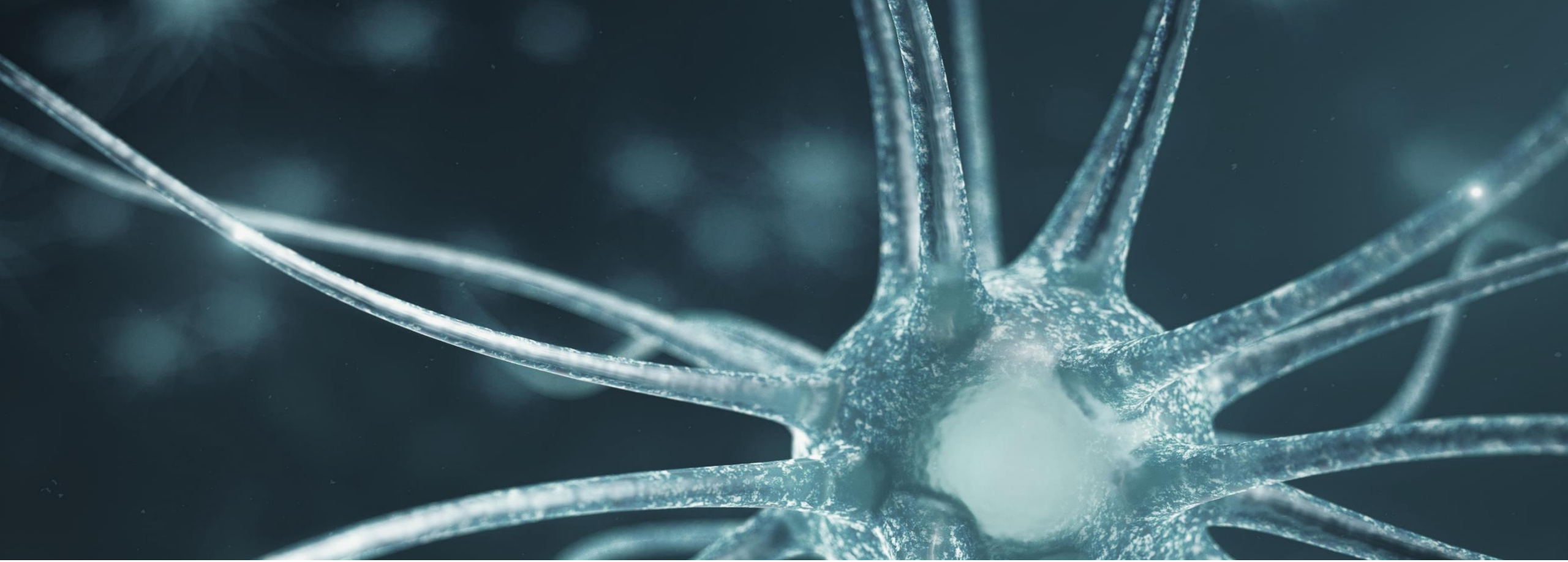
Agenda

Introduction	**Gary Waanders, PhD, MBA** Head of Investor Relations and Communications, AC Immune
Strategy & Pipeline Overview	**Andrea Pfeifer, PhD** Chief Executive Officer, AC Immune
A-syn[1] Introduction	**Marie Kosco-Vilbois, PhD** Chief Scientific Officer, AC Immune
Importance of Biomarkers in NDD[2] **A-syn PET[3] Tracer Clinical Data**	**Oskar Hansson, MD, PhD** Professor of Neurology, Lund University Consulting Neurologist, Skåne University Hospital
A-syn program development plans	**Johannes Streffer, MD** Chief Medical Officer, AC Immune
Conclusion and Q&A	**Andrea Pfeifer, PhD** Chief Executive Officer, AC Immune

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



Strategy and pipeline overview

Andrea Pfeifer, PhD, Chief Executive Officer

Investment highlights

Broad, diversified pipeline in neurodegeneration
Six Phase 2 programs; seven clinical readouts in 2022

Key differentiation: Precision medicine
Integrates therapeutics and diagnostics

Multiple global partnerships
>CHF 3 billion in potential milestones

Clinically validated technology platforms
Best-in-class small molecules and biologics

Strong balance sheet
Funded through Q1 2024

Pioneering precision medicine for neurodegenerative diseases

Growth initiatives for 2022 and beyond

GOALS

Global Leadership	Drives Near and Mid-term Growth		Long-term Growth
Diverse pipeline	**Therapeutics**	**Precision medicine**	**New areas**
Validated programs	5 clinical programs	2 clinical PET[5] tracers	Preclinical programs
Key NDD[1] targets: • Tau • Abeta • A-syn[2] Multiple modalities 4 partnerships	4 clinical readouts in 2022 Tau • 2 Phase 2 (R)[3] Abeta • 1 Phase 2 & 1 Phase 1b (R) A-syn • 1 Phase 2 trial (I)[4]	3 clinical readouts in 2022 Clinical • 2 Tau PET tracer (R) • 1 A-syn PET tracer (R) Discovery • TDP-43[6] PET tracer	Emerging targets in NDD: • A-syn • TDP-43 • NLRP3[7]-ASC[8]

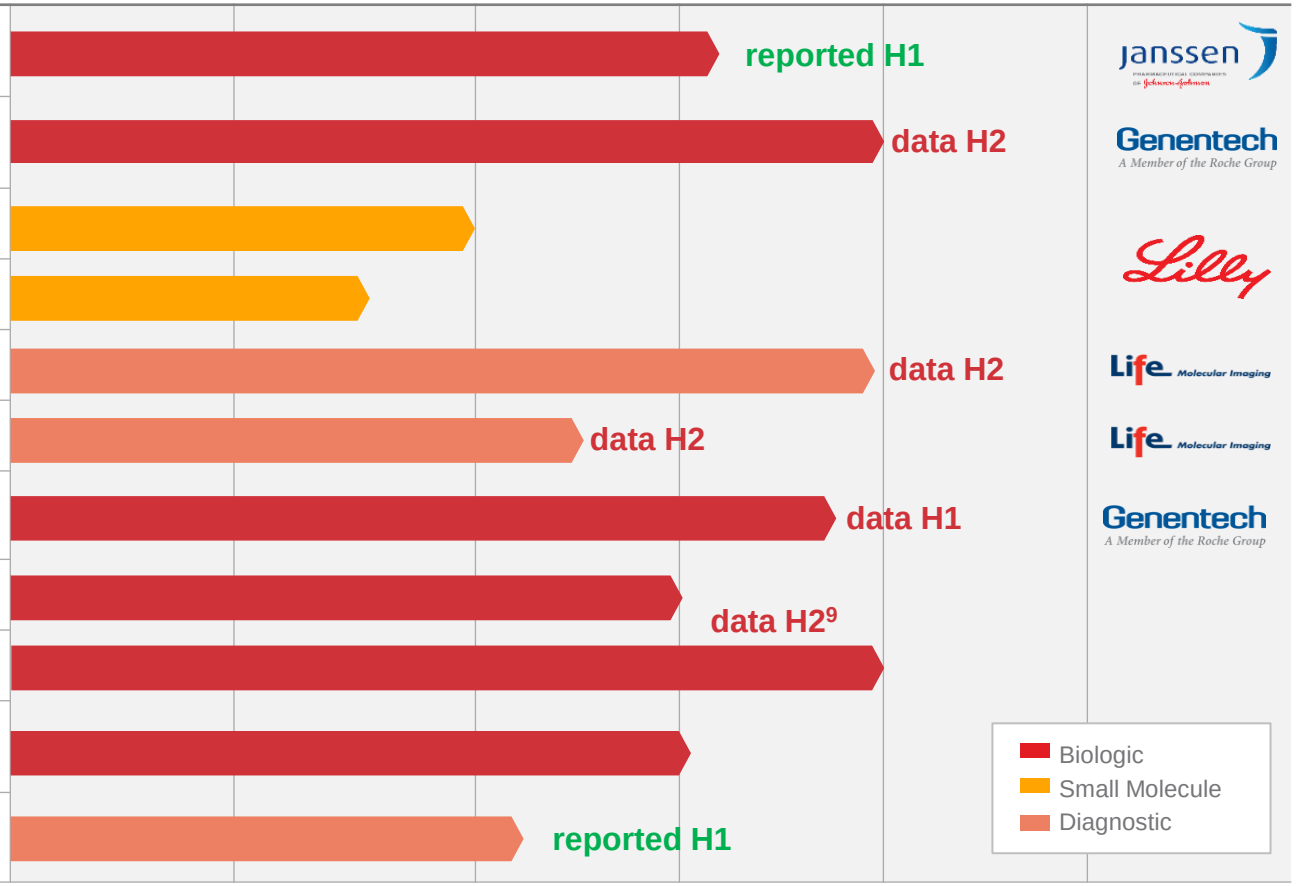
(1) Neurodegenerative disease; (2) Alpha-synuclein; (3) (R) – readout; (4) (I) – initiation; (5) Positron emission tomography; (6) TAR DNA-binding protein 43; (7) (NOD)-like receptor protein 3; (8) Apoptosis-associated speck-like protein containing a CARD, also PYCARD

Broad and robust pipeline in neurodegenerative diseases

Driven by validated proprietary technology platforms for sustained growth

Clinical Stage Programs

TARGET	PRODUCT CANDIDATE	INDICATION	PARTNER
Tau	**ACI-35.030** *(anti-pTau vaccine)*	AD[1] treatment	Janssen
	Semorinemab *(anti-Tau antibody)*	AD treatment *(mild-to-moderate)*[2]	Genentech
	Morphomer® Tau aggregation inhibitor	Rare Tauopathies (ACI-3024)	Lilly
		AD treatment	Lilly
	Tau-PET[3] tracer	AD diagnostic	Life Molecular Imaging
		PSP[4] diagnostic	Life Molecular Imaging
Abeta	**Crenezumab** *(anti-Abeta antibody)*	AD prevention[5]	Genentech
	ACI-24 *(anti-Abeta vaccine)*	AD treatment (*Down syndrome*[6])	
		AD treatment	
a-syn[7]	**ACI-7104** *(anti-a-syn vaccine)*	PD[8], a-synucleinopathies	
	a-syn-PET tracer	a-synucleinopathies (e.g. MSA[10])	



(1) Alzheimer's disease; (2) Open label extension study is ongoing; (3) Positron emission tomography; (4) Progressive supranuclear palsy; (5) Prevention trial API-ADAD in Colombia; (6) Down syndrome-related Alzheimer's disease; (7) alpha-synuclein; (8) Parkinson's disease; (9) Refers to expected readout from a Phase 1b/2 trial of an optimized formulation of ACI-24 in patients with AD and patients with Down syndrome; (10) Multiple system atrophy

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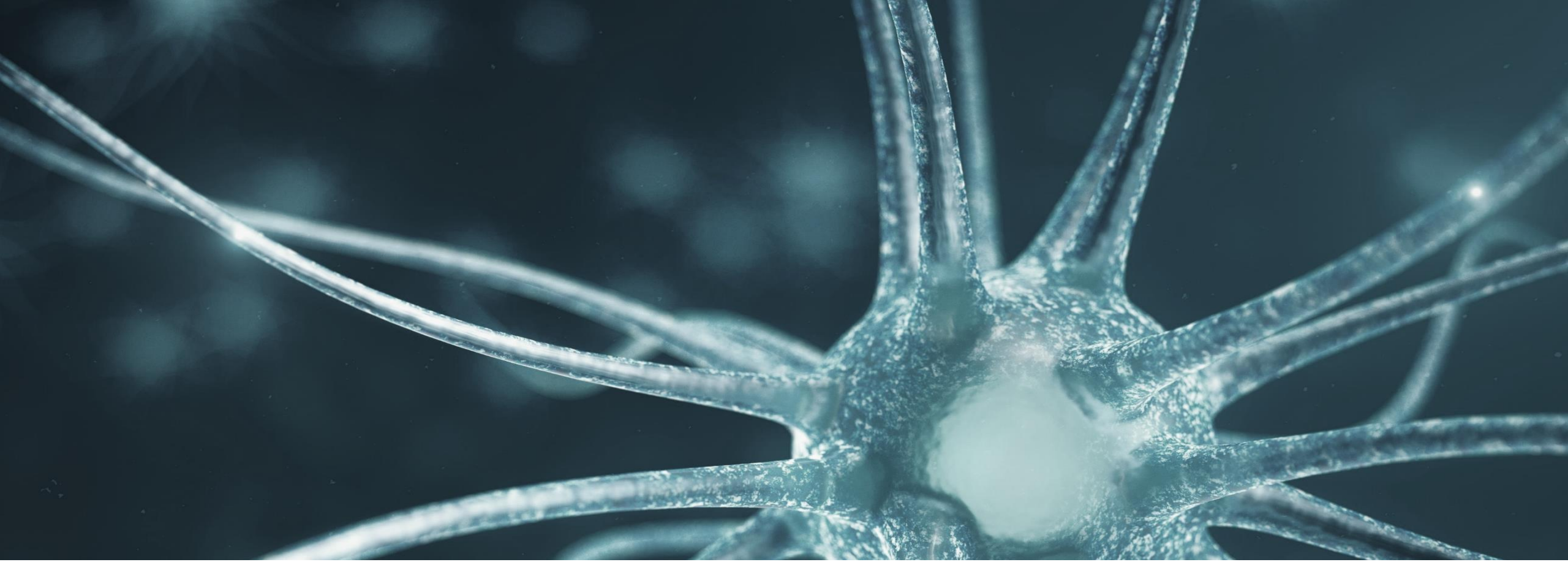
Clinical catalysts to drive further value creation

Seven clinical data readouts expected in 2022

		2022 H1	2022 H2	
Tau	**ACI-35.030 (anti-pTau vaccine)**	✓		**Phase 1b/2a interim analysis (highest dose) of ACI-35.030**
			●	Decision to enter into late-stage development
	Semorinemab (anti-Tau antibody)		●	**Report new Phase 2 Lauriet data (biomarkers)**
	Tau-PET[1] Tracer (PI-2620)		●	**Clinical PET study readout in orphan indication**
			●	**Phase 2 results in AD[2]**
Abeta	**ACI-24 (anti-Abeta vaccine)**	●		ACI-24 (optimized vaccine formulation) Phase 1b/2a First-Patient-In (AD)
			●	**Phase 1b in AD readout and decision to move into DS[3]**
	Crenezumab (anti-Abeta antibody)	●		**Top line results of Phase 2 Alzheimer's prevention trial**
a-syn[4]	ACI-7104 (anti-a-syn vaccine)		●	Phase 2 First-Patient-In
	a-syn-PET tracer	✓		**First clinical proof of concept in alpha-synucleinopathies (e.g. MSA[5])**

(1) Positron emission tomography; (2) Alzheimer's disease; (3) Down syndrome-related AD; (4) alpha-synuclein; (5) Multiple system atrophy



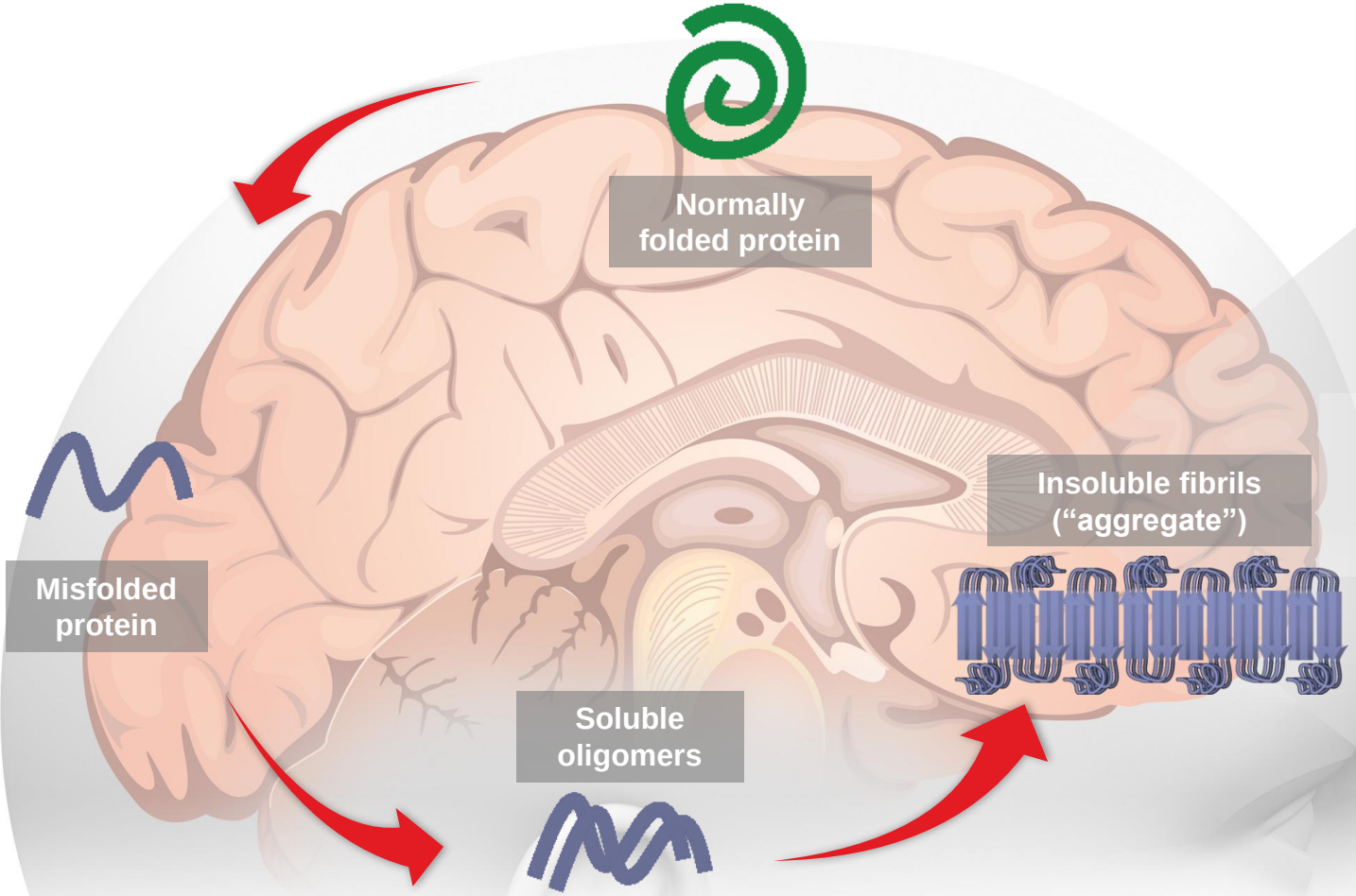
The role of alpha-synuclein in neurodegenerative disease

Marie Kosco-Vilbois, PhD, Chief Scientific Officer

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Misfolded proteins: Leading causes of neurodegenerative diseases

Abeta, Tau, a-synuclein, and TDP-43[1] are important NDD[2] drug targets



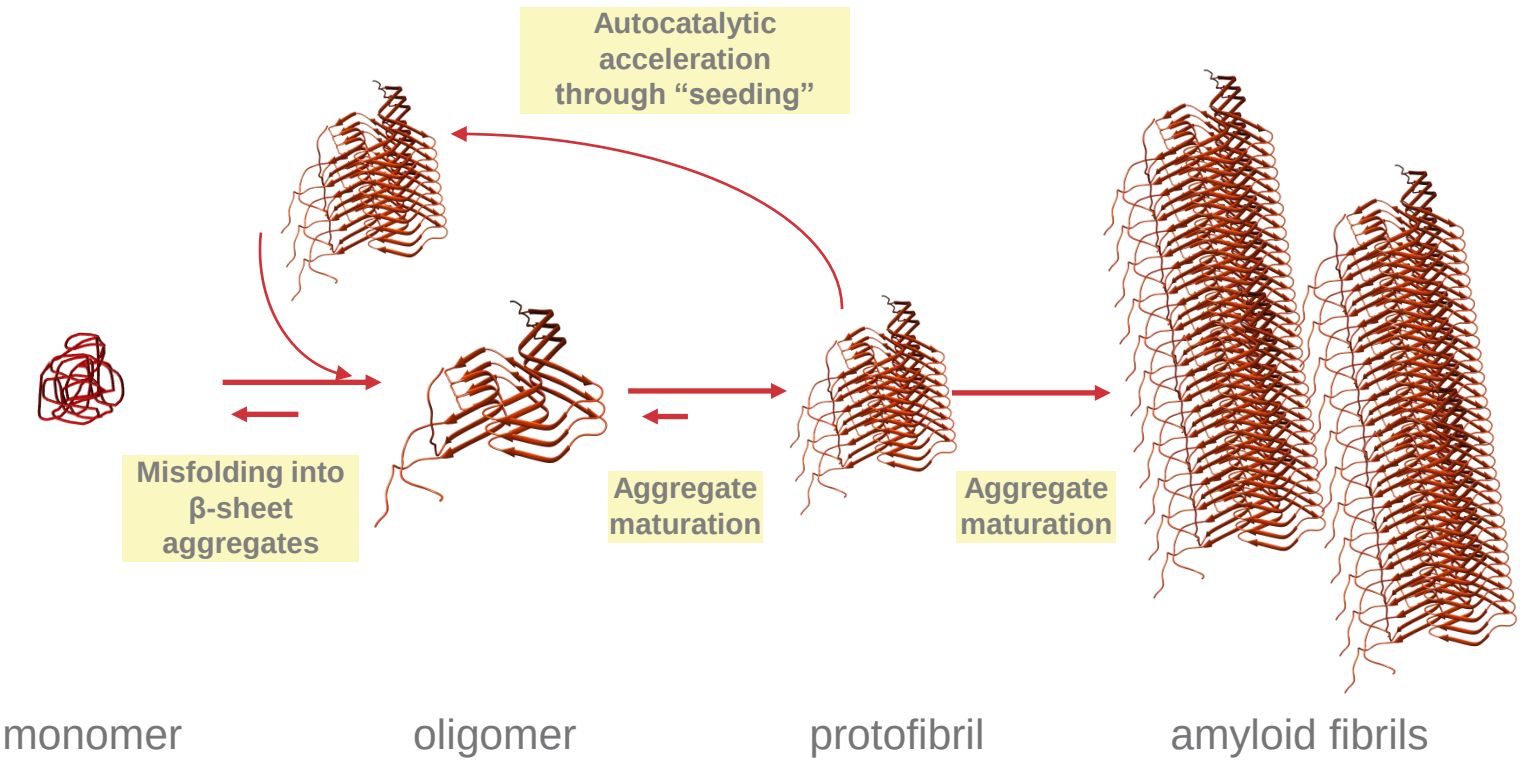
Goal: Remove aggregates or prevent their formation

Aggregate	Disease
Abeta Plaques	Alzheimer's disease
Tau Tangles	Alzheimer's disease
α-synuclein Lewy bodies	Parkinson's disease MSA[4]
TDP-43 Inclusions	LATE[3] dementia ALS[5]

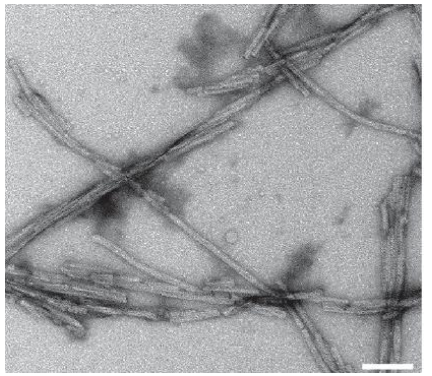
Refs: Soto 2003, http://www.alz.org/brain; Nag *et al.* Acta Neuropathologica Communications (2018) 6:33;
(1) TAR DNA-binding protein 43; (2) Neurodegenerative disease; (3) Limbic-predominant age-related TDP-43 encephalopathy; (4) Multiple system atrophy; (5) Amyotrophic lateral sclerosis

Pathological oligomeric a-syn[1] is causally linked to NDD[2]

Misfolded a-syn monomers mature to form amyloid fibrils

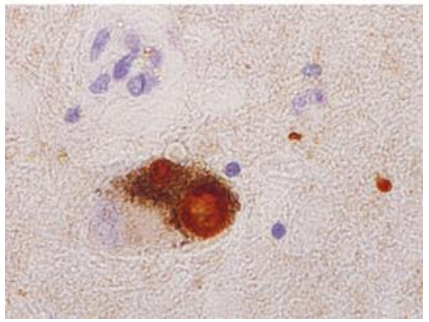


a-syn fibrils



Guerrero-Ferreira et al., 2018

Lewy bodies

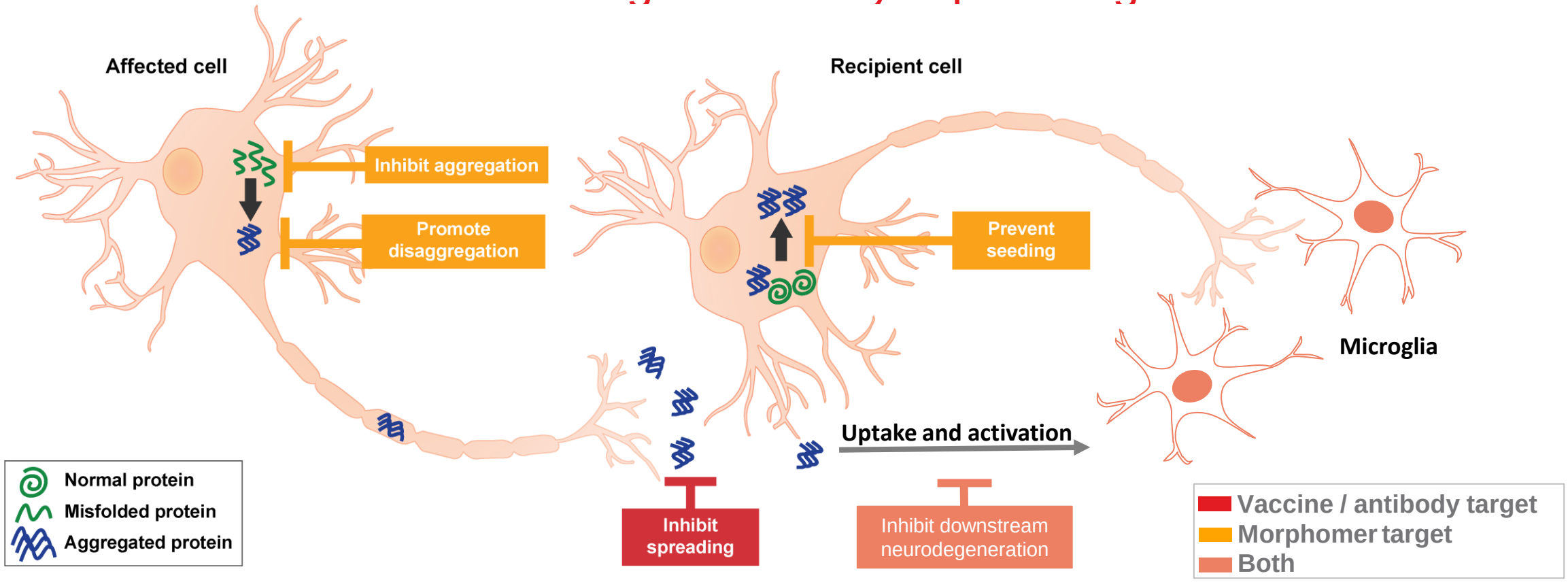


Peng et al., 2017

a-syn misfolding and aggregation are the molecular basis for a-synucleinopathies, e.g. PD, DLB[3] and MSA[4]

(1) Alpha-synuclein; (2) Neurodegenerative disease; (3) Dementia with Lewy bodies; (4) Multiple system atrophy

AC Immune intervention strategies for a-syn[1] pathologies



- Molecular seeding and spreading are potential drivers of disease progression
- AC Immune is targeting each step of a-syn pathology with the SupraAntigen® & Morphomer® platforms

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

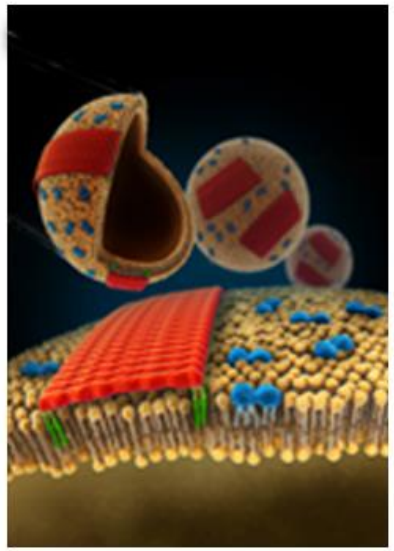
Conformation-specific platforms driving therapeutic and diagnostic pipeline

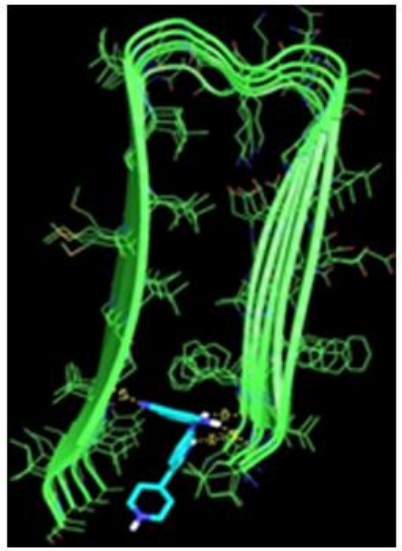
Developing breakthrough mono- and combination therapies for neurodegenerative diseases

Clinically Validated Technology Platforms

SupraAntigen®

Vaccines and antibodies specific to disease causing conformations





Morphomer®

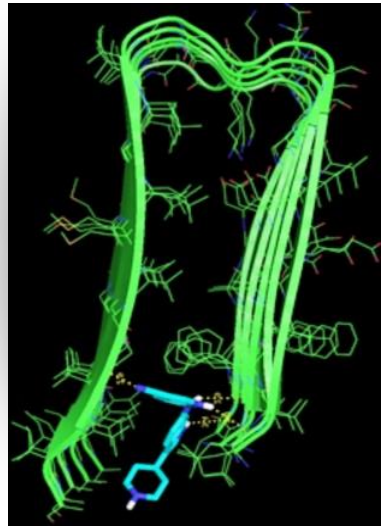
Conformation-sensitive small molecules

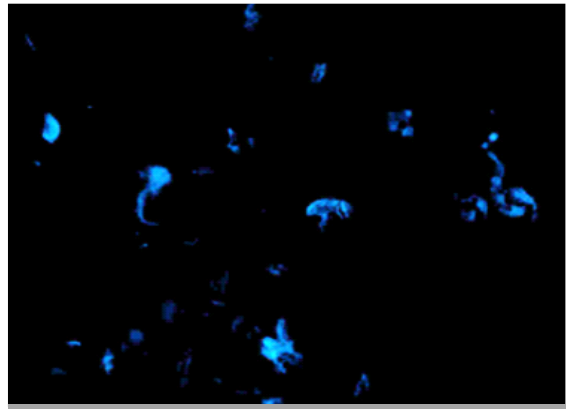
Images: Hickman *et al.*, JBC 2011; Kroth *et al.*, JBC 2012

(1) The goal of precision medicine is to deliver optimally targeted and timed interventions tailored to the individual disease drivers

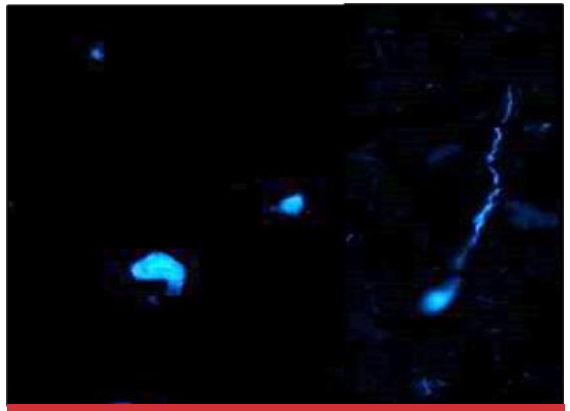
The Morphomer® platform: enables our precision medicine approach

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

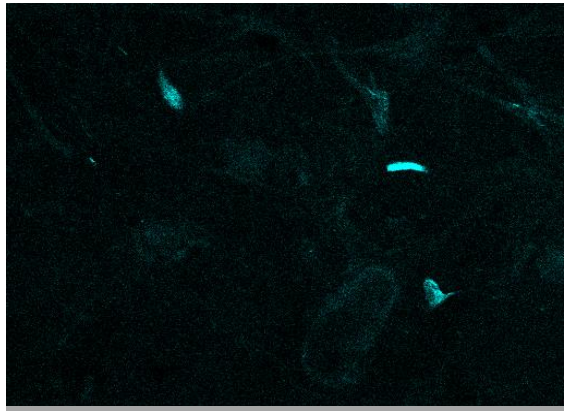




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

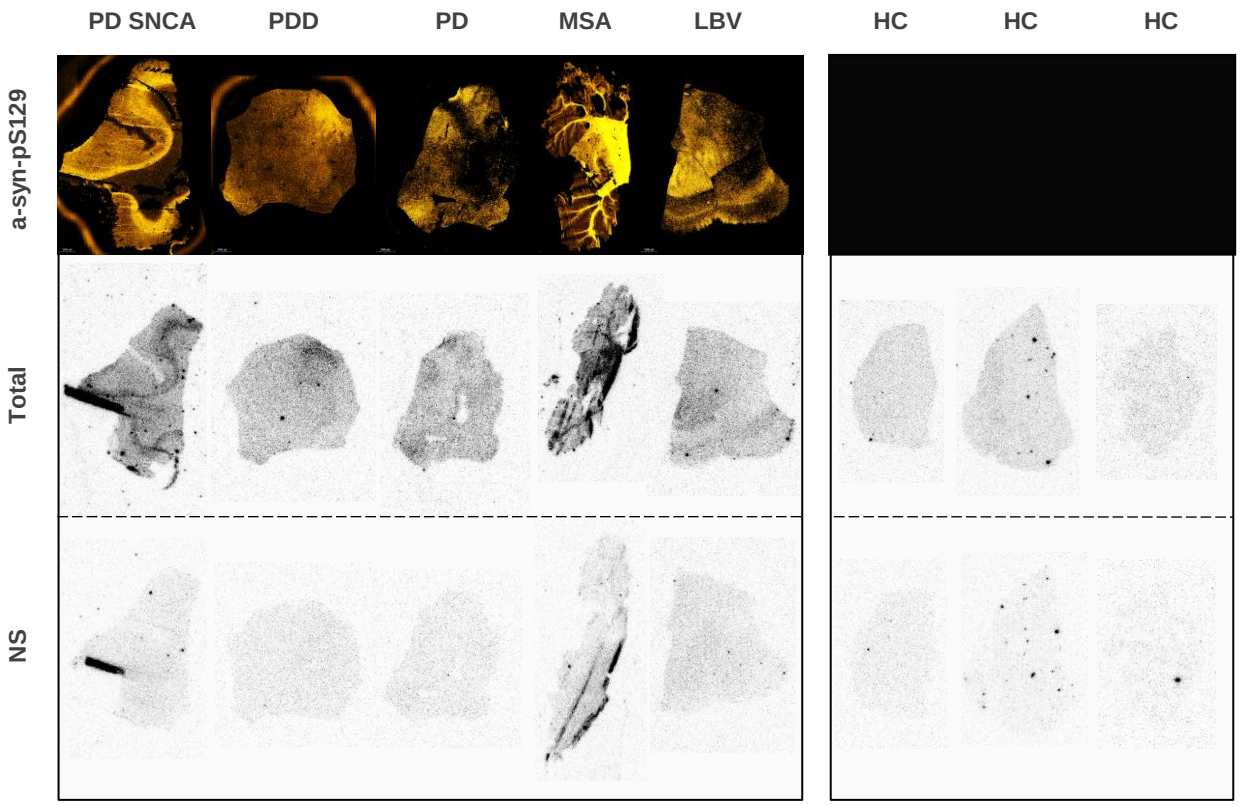
Leverage the Morphomer® small molecule platform:

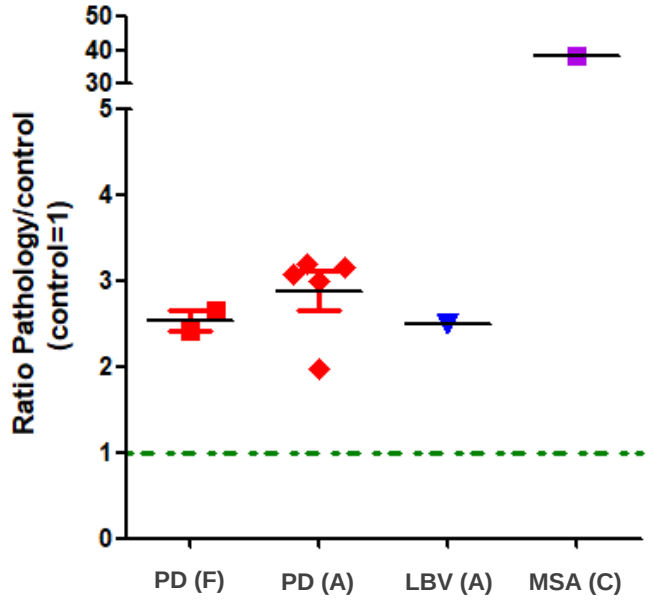
- Non-peptidic, small molecules with CNS[6]-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, TDP-43)
- Pharmacokinetics suitable for brain PET imaging

(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) Alpha-synuclein; (5) TAR DNA binding protein-43 (6) Central nervous system

ACI-12589 shows specific binding in a broad spectrum of a-synucleinopathies

Potential to diagnose a range of a-synucleinopathies





In collaboration with Prof. A. Varrone, Karolinska Institute

Karolinska Institutet

ACI-12589 shows target engagement across a wide range of a-synucleinopathies

PD SNCA, Parkinson's disease with SNCA G51D mutation; **PDD**, Parkinson's disease with dementia; **PD**, idiopathic Parkinson's disease; **MSA**, multiple system atrophy; **LBV**, Lewy body variant of Alzheimer disease; **HC**, healthy control; **(F),** Frontal cortex; **(A)**, amygdala; **(C)**, cerebellum; **Total** = Total binding (1.7nM); **NS** = Non-specific binding (1µM)

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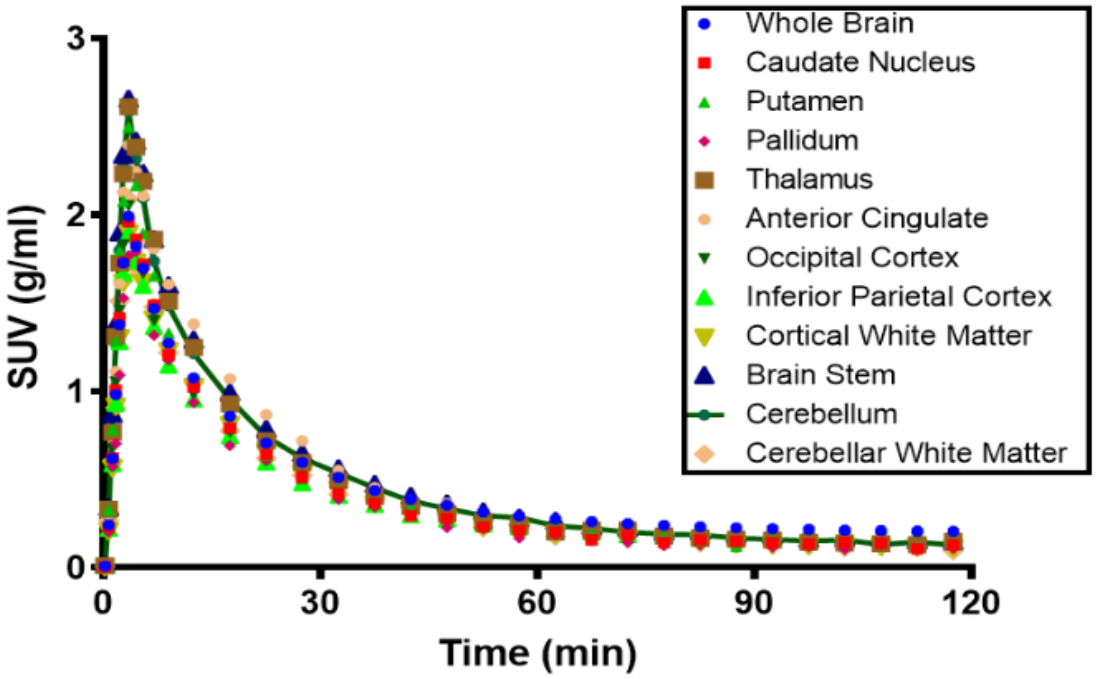
ACI-12589 has suitable PK[1] profile for a brain PET[2] tracer

ACI-12589 PK profile in non-human primates (NHP)

Time-activity curves in different brain regions



NHP ID	Brain Uptake (min to C_{max})	Brain Uptake (% ID/g)	Peak(half peak (min)	Remaining at 120 min (% of C_{max})
Target	< 10	>3	<30	<10
ACI-12589	3.5	4.4	14	10

NHP PK shows rapid brain uptake, homogeneous distribution, and rapid and complete washout

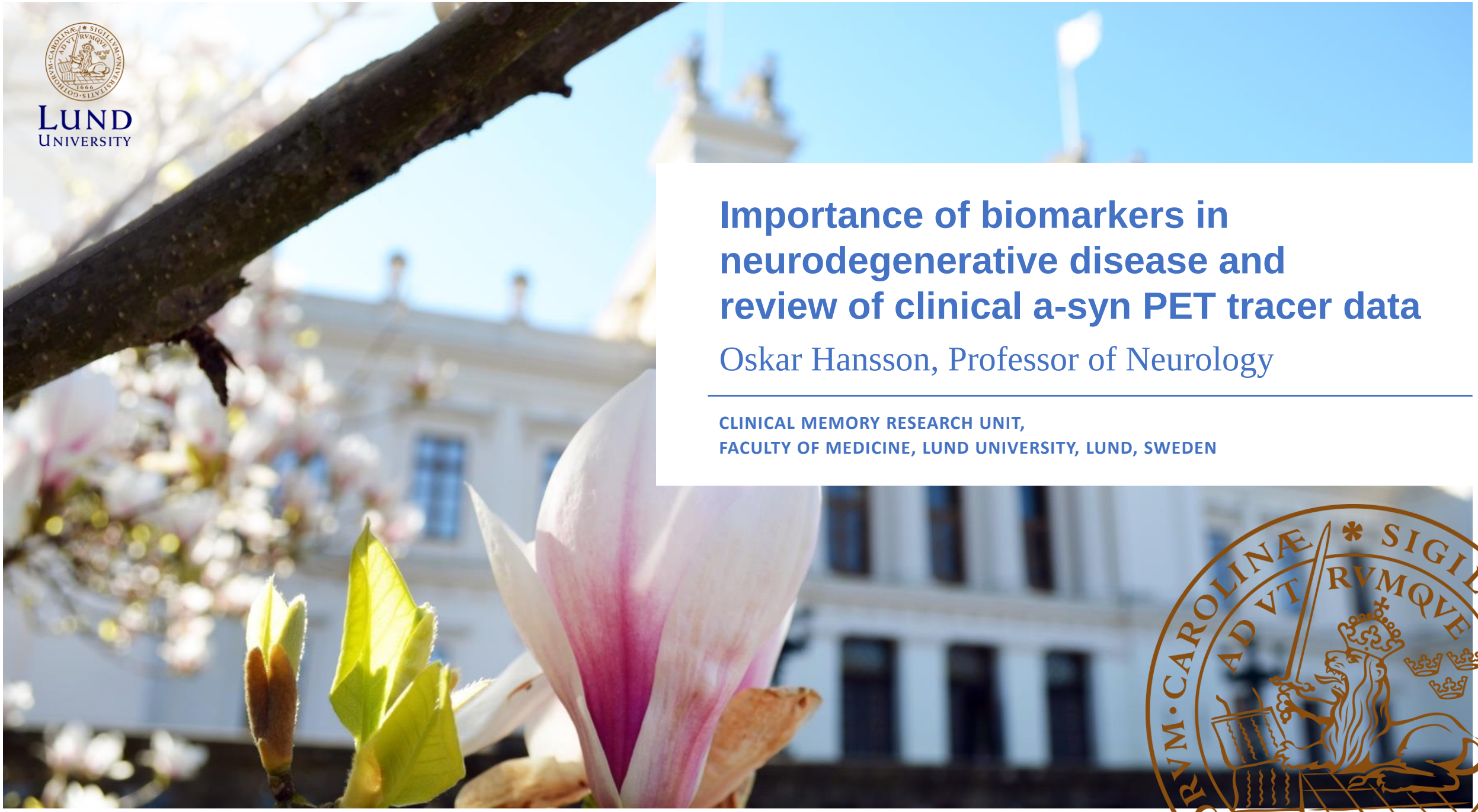
(1) Pharmacokinetic (2) Positron emission tomography

Conclusion on preclinical data package

1. **Morphomer® platform delivered** the first a-syn[1] targeting PET[2] tracer candidate, ACI-12589
2. **Screening system optimized** for high-performance imaging molecules
3. **Selected tracers with CNS[3]-drug profiles** suitable for brain penetration and PET imaging
4. **ACI-12589 selective for pathological a-syn** with minimal activity across co-pathologies
5. **ACI-12589 advanced** into clinical development as first-in-class a-syn PET tracer

Pioneering precision medicine for neurodegenerative diseases

(1) Alpha-synuclein; (2) Positron emission tomography; (3) Central nervous system



Importance of biomarkers in neurodegenerative disease and review of clinical a-syn PET tracer data

Oskar Hansson, Professor of Neurology

CLINICAL MEMORY RESEARCH UNIT,
FACULTY OF MEDICINE, LUND UNIVERSITY, LUND, SWEDEN

Biomarkers to improve clinical practice

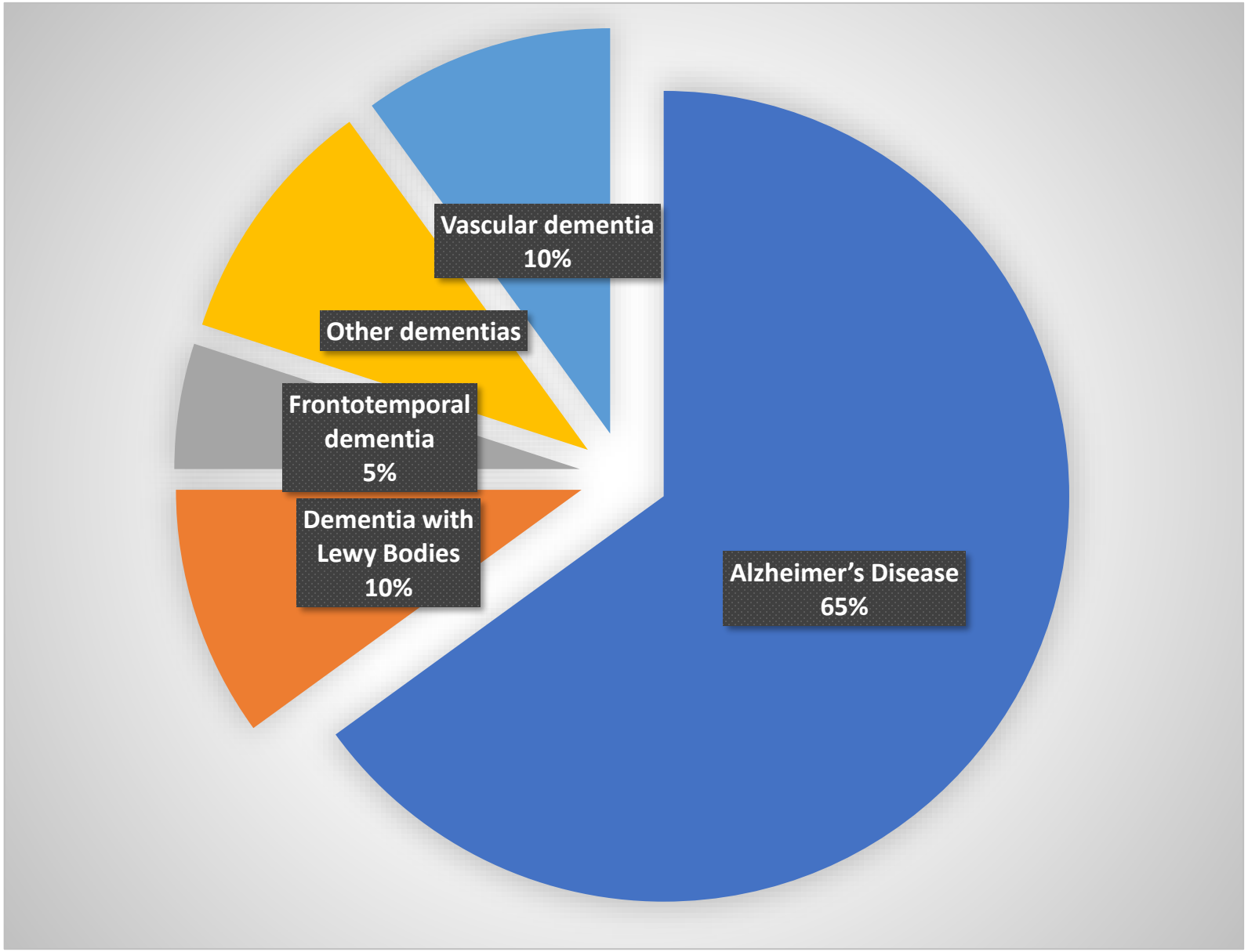
- The clinical diagnosis of most neurodegenerative diseases is mediocre
  - Often 20-40% of the patients are misdiagnosed in specialized clinics
  - >50% are misdiagnosed in primary care

- Misdiagnosis results in suboptimal treatment and care
  - Delayed or incorrect symptomatic therapies
  - Incorrect information about disease and prognosis

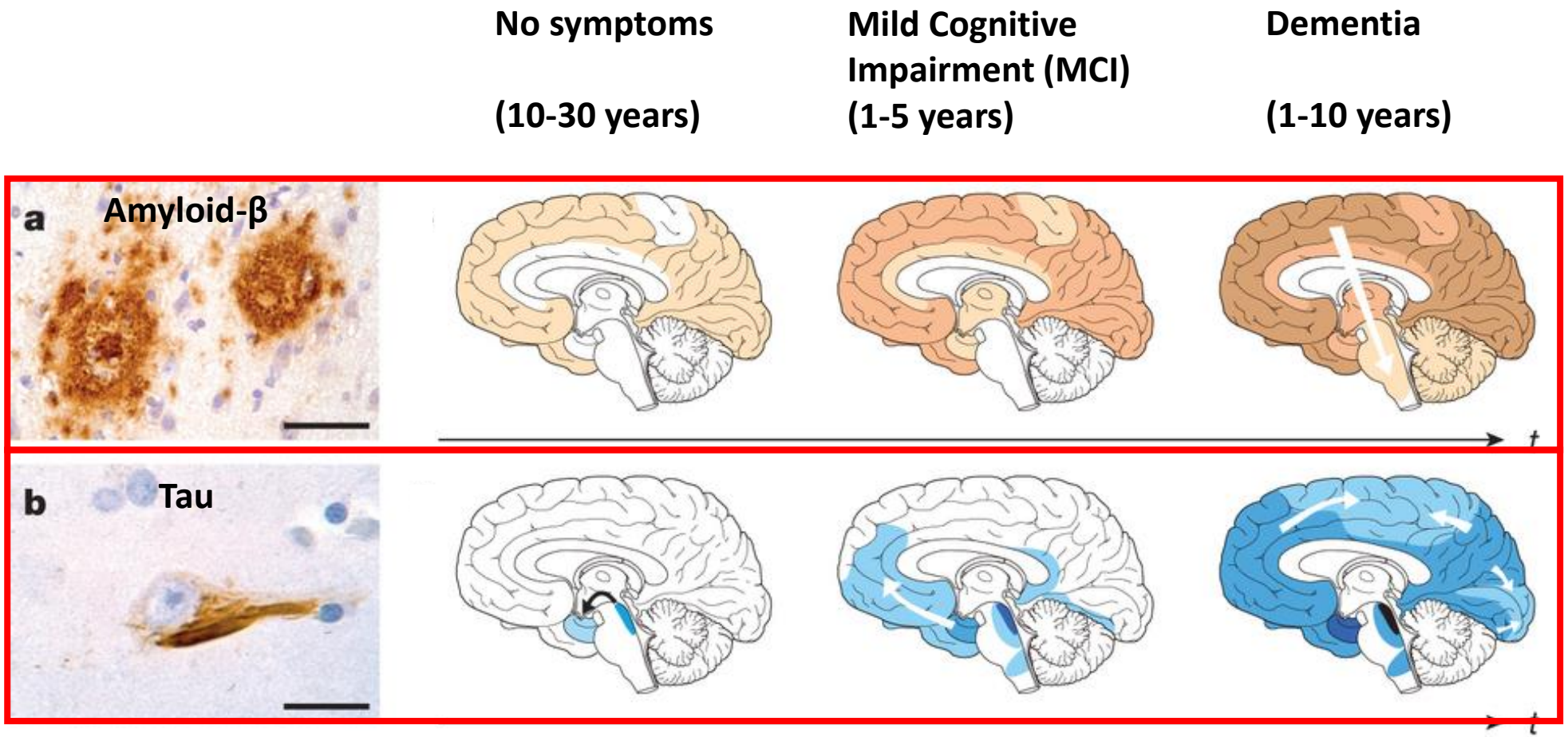
Biomarkers to improve drug development

- Enable early diagnosis – Selection of individuals with preclinical or prodromal disease
- Identify relevant subgroups – Disease stratification depending on therapy
- Ensure relevant target engagement – Select most promising drugs candidates
- Monitor downstream disease processes – Surrogate biomarkers (slow clinical progression)
- Improve knowledge about pathogenesis – New drug targets or combinations of targets

Dementia disorders



Key pathologies in Alzheimer's disease



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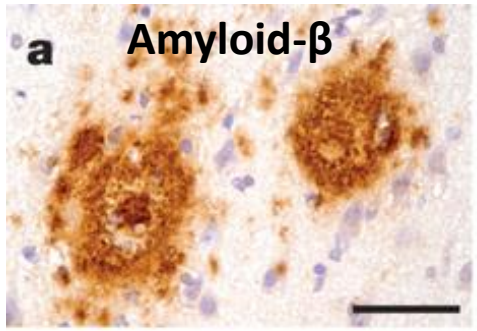
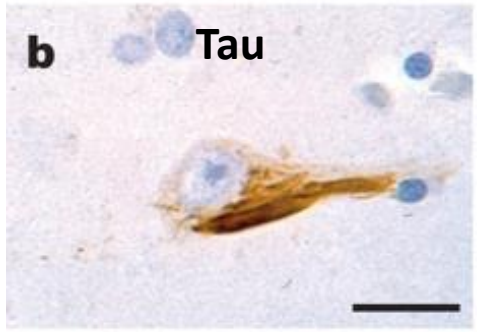
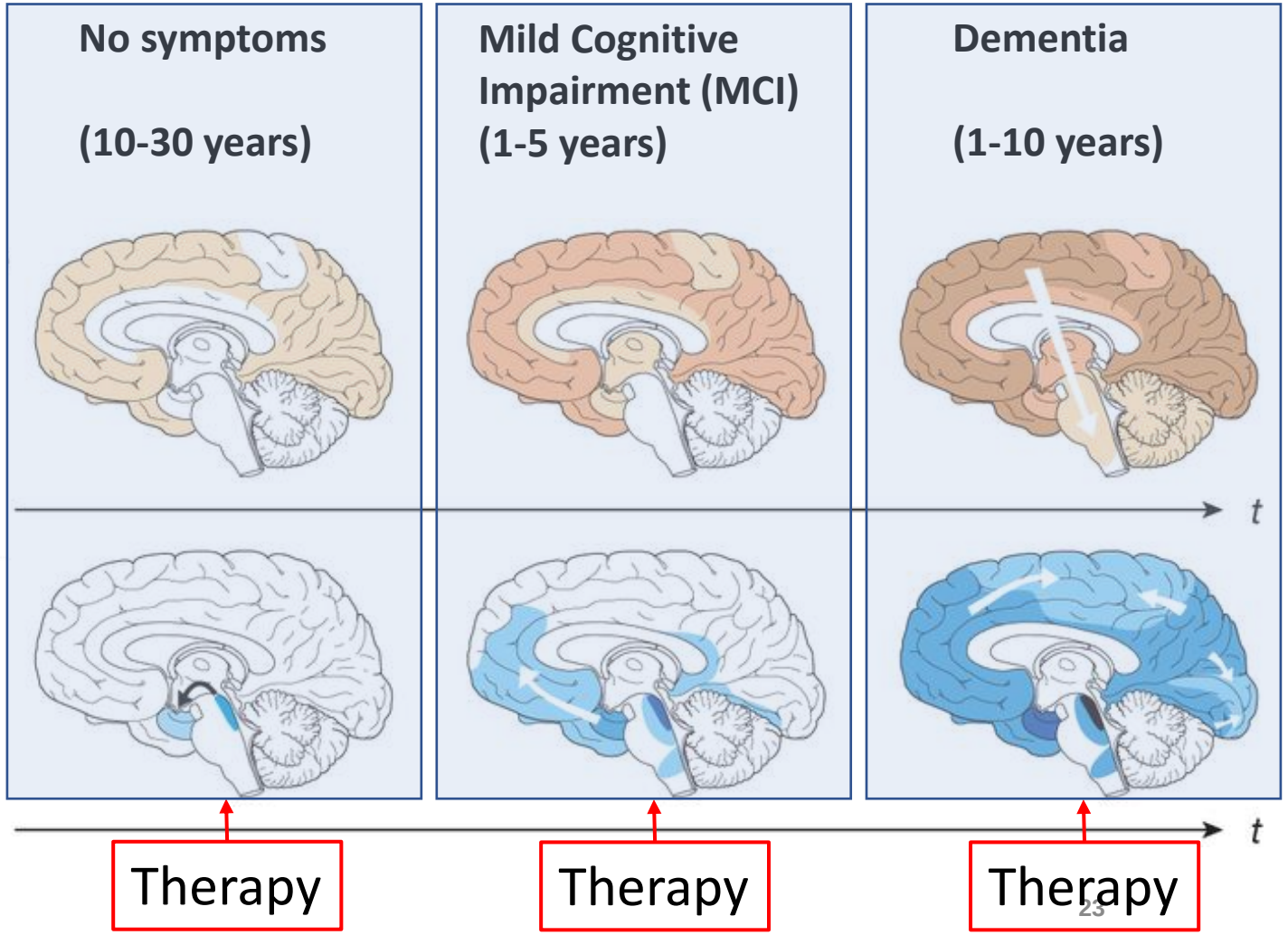
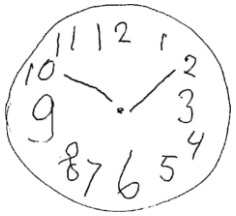


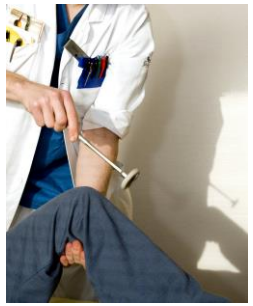


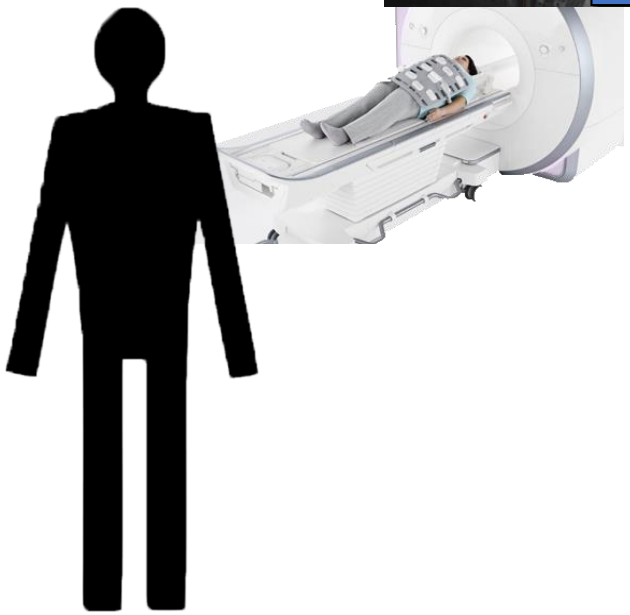


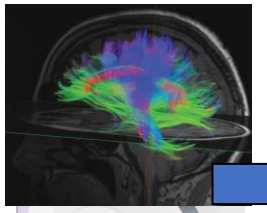
Alzheimer diagnostics – a multidisciplinary approach

Clinical assessments
- Cognitive tests
- Psychiatric & neurological assessments
- ADL function









MRI or CT
- Exclude other pathologies
- Regional atrophy patterns
- Cerebrovascular disease
- (Microbleeds)

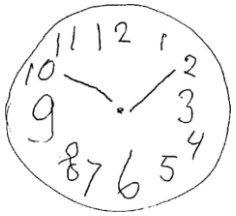
Concordance between clinical diagnosis of AD dementia and neuropathology is not good (sensitivity 70-80% and specificity 50-70%)

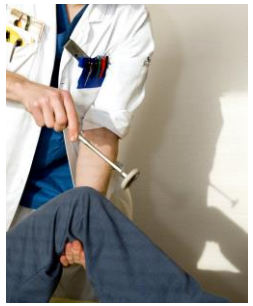
Even lower diagnostic accuracy in patients with ”MCI due to AD”

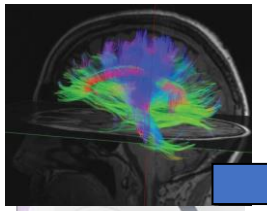
Beach et al., JNEN, 2012
Knopman et al., Neurology, 2001

Alzheimer diagnostics – a multidisciplinary approach

Clinical assessments
- Cognitive tests
- Psychiatric & neurological assessments
- ADL function

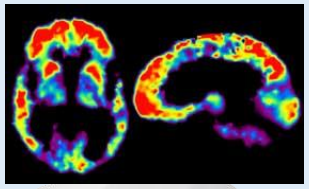


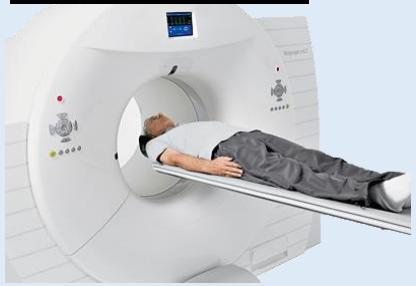


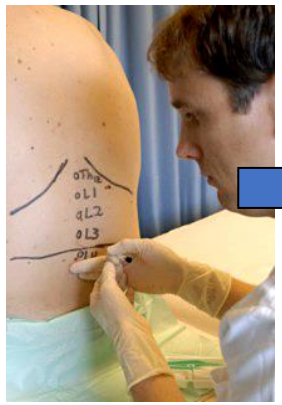


MRI or CT
- Exclude other pathologies
- Regional atrophy patterns
- Cerebrovascular disease
- (Microbleeds)

PET-imaging
- Aβ
- Tau



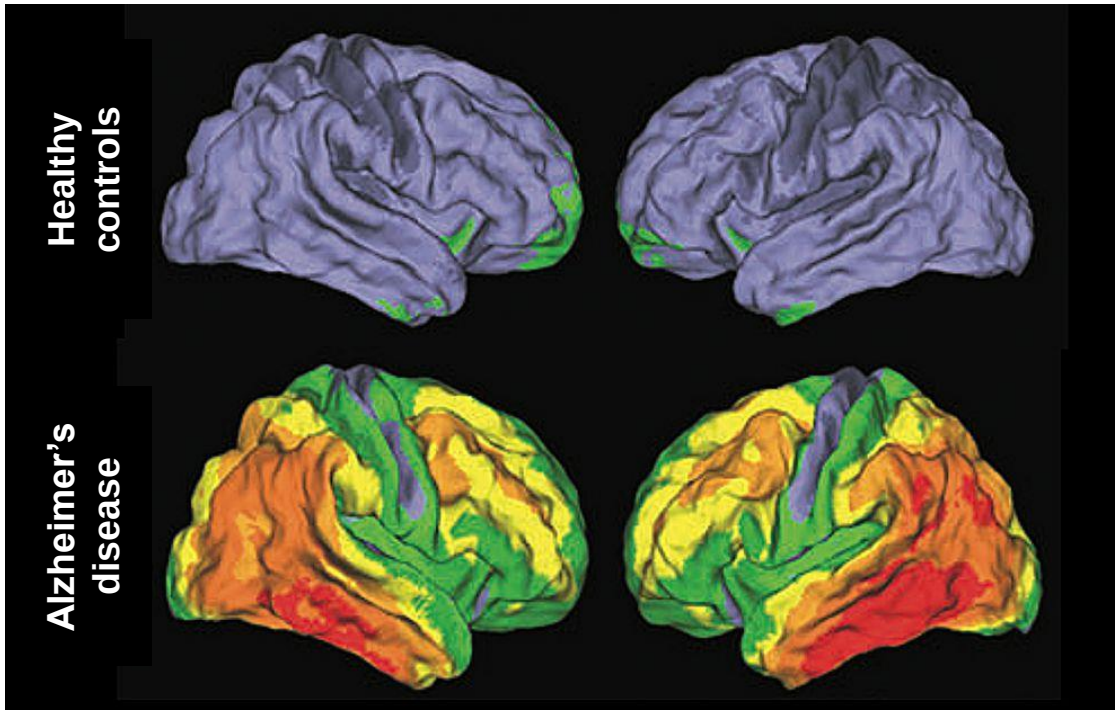




Cerebrospinal fluid (CSF)
- Aβ
- T-tau
- P-tau
- NfL

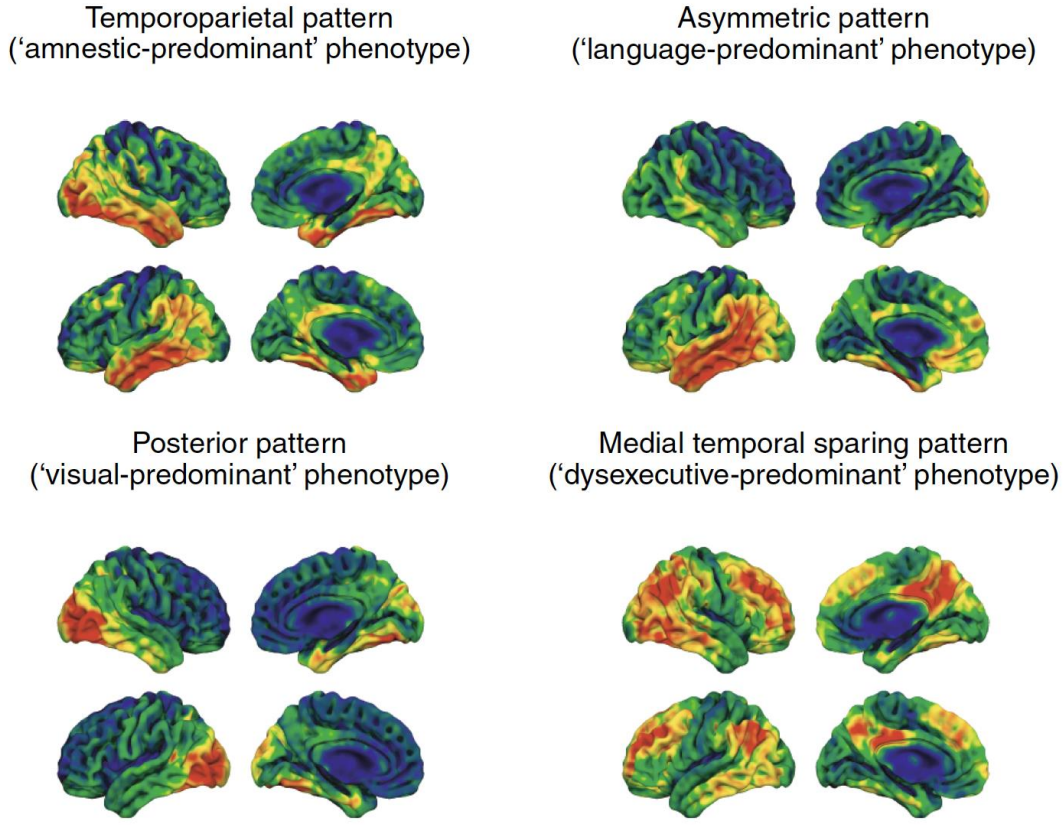
PET imaging of Tau in Alzheimer's disease

Tau-PET can distinguish between Alzheimer and all other neurodegenerative diseases



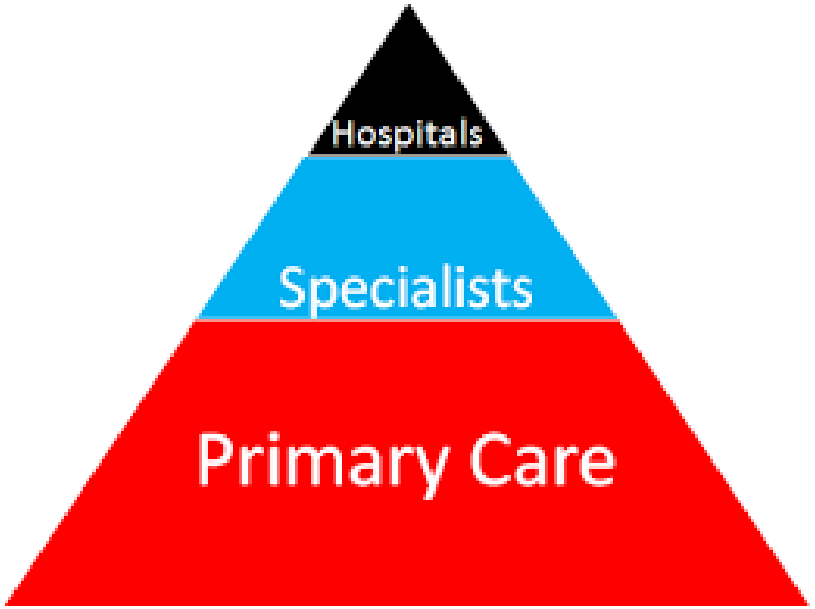
Ossenkoppele et al.
JAMA, 2018.

Tau-PET can detect 4 different subtypes of Alzheimer's disease



Vogel et al.
Nature Medicine, 2021.

Alzheimer diagnostics – Primary care



50-70% of demented subjects are not correctly diagnosed today in primary care

Blood-based biomarkers might improve the diagnostic work-up of AD

Novel blood test for Alzheimer!

"All the News That's Fit to Print"

The New York Times

Late Edition

Today, mostly sunny, hot, a bit less humid, high 90. Tonight, clear to partly cloudy, low 75. Tomorrow, mostly sunny, hot once again, high 91. Weather map is on Page C8.

VOL. CLXIX . . . No. 58,769 © 2020 The New York Times Company NEW YORK, WEDNESDAY, JULY 29, 2020 $3.00

POOL PHOTO BY ERIN SCHAFF/EPA-EFE

Attorney General William P. Barr defended the government's protest response on Tuesday before the House Judiciary Committee.

At Start, F.B.I. Saw Protesters As Threatening

Memo Talks of 'Inciters' and 'Instigators'

This article is by ***Zolan Kanno-Youngs, Sergio Olmos, Mike Baker*** *and* ***Adam Goldman.***

WASHINGTON — From the earliest days of the recent protests against police brutality and racism, some top federal law enforcement officials viewed the demonstrators with alarm and called for an aggressive federal response that two months later continues to escalate.

A memo from the deputy director of the F.B.I., dated June 2, demanded an immediate mobilization as protests gathered after George Floyd's death while in police custody a week earlier. David L. Bowdich, the F.B.I.'s No. 2, declared the situation "a national crisis," and wrote that in addition to investigating "violent protesters, instigators" and "inciters," bureau leaders should collect information with "robust social media exploitation teams" and examine what appeared to be "highly organized behavior."

Mr. Bowdich suggested that the bureau could make use of the Hobbs Act, put into place in the 1940s to punish racketeering in labor groups, to charge the protesters.

"When 9/11 occurred, our folks did not quibble about whether there was danger ahead for them," he wrote, telling aides that the continuing coronavirus pandemic should not hold them back. "They ran head-on into peril."

The memo came after a weekend in which protests gave way to looting in some cities and the day after federal agents forcibly cleared peaceful protesters from the White House so President Trump could walk through Lafayette Square. Since then, the federal response has become a focal point of the Trump administration and of Mr. Trump's re-election campaign. The Bowdich memo

Continued on Page A14

UNDER FIRE, BARR DEFENDS ACTIONS AGAINST PROTESTS

HEARING TURNS HOSTILE

House Democrats Accuse Attorney General of Abusing Power

By NICHOLAS FANDOS and CHARLIE SAVAGE

Attorney General William P. Barr vigorously defended the federal response to nationwide protests and civil unrest in a combative congressional hearing on Tuesday where Democrats accused him and other Trump administration officials of suppressing protesters' rights in an overly violent crackdown.

The attorney general also insisted that he intervened in the criminal cases of President Trump's allies Roger J. Stone Jr. and Michael T. Flynn to uphold the rule of law, not to do Mr. Trump's bidding.

Mr. Barr's defenses punctuated an outright hostile election-season oversight hearing before the House Judiciary Committee. Democrats tried to portray him as a dangerous errand boy for the president. But Mr. Barr insisted he was trying to enforce the law against what he characterized as rioters using demonstrations as cover to commit crimes. He also said of the criminal cases that grew out of the Russia investigation that he wanted to be fair to Mr. Trump's former advisers.

"The president's friends don't deserve special breaks, but they also don't deserve to be treated more harshly than other people," he said. "And sometimes that's a difficult decision to make, especially when you know you're going to be castigated for it."

The five-hour hearing, Mr. Barr's first on Capitol Hill in more than a year, grew increasingly heated as Democrats spoke over his attempts to respond to their

Continued on Page A15

Trump Family Legacy: Empathy Is for the Weak

Nation's Crises Are Met With an Inability to Feel Others' Pain

By ANNIE KARNI and KATIE ROGERS

WASHINGTON — The Marble Collegiate Church on Fifth Avenue in Manhattan was packed with developers, politicians and New York celebrities, more than 600 in all, for the funeral of Fred C. Trump, the builder whose no-frills brick rental towers transformed Brooklyn and Queens.

Three of his four living children, who had grown up listening to the sermons of the church's most famous minister, Norman Vincent Peale, offered loving eulogies to their father. Then it was Donald Trump's turn.

He began by talking about himself.

He had learned of his father's death, he told the crowd that day in June 1999, just moments after reading a front-page New York Times article about his biggest development to date, Trump Place.

"Donald started his eulogy by saying, 'I was having the greatest year of my business career, and I was sitting having breakfast thinking of how well things were going for me,'" when he learned of his father's death, said Alan Marcus, a former public-relations consultant for the Trump Organization. "Donald's eulogy was all about Donald, and everybody in Vincent Peale's church knew it."

Gwenda Blair, a Trump family biographer, also attended the funeral. She, too, could not help but take note of the eulogy, which she described in her book "The Trumps."

"Was it surprising?" Ms. Blair said in an interview. "No. Was it stunning? Yes."

Whether he is dealing with the loss of a family member, the deaths of nearly 150,000 Americans in a surging pandemic, more than 30 million people out of work or the racial unrest brought on by the killings of African-Americans by white police officers, President

Continued on Page A18

Biden Marries Racial Equity To a Recovery

By THOMAS KAPLAN and KATIE GLUECK

WILMINGTON, Del. — Joseph R. Biden Jr. unveiled wide-ranging plans on Tuesday to address systemic racism in the nation's economy, saying this year's election was about "understanding people's struggles" and pledging to tear down barriers for minority-owned businesses.

In an address near his home in Wilmington, Mr. Biden made the argument that racial justice is central to his overall policy vision in areas like housing, infrastructure and support for small businesses, while aiming to draw a stark contrast with a president who has regularly inflamed racial tensions.

"This election is not just about voting against Donald Trump," Mr. Biden said, standing before four American flags in a community center gym. "It's about rising to this moment of crisis, understanding people's struggles and building a future worthy of their courage and their ambition to overcome."

Mr. Biden's plan is the fourth piece of his "Build Back Better" proposal, an economic agenda that also encompasses manufacturing, climate and infrastructure and caregiving plans, and takes aim at Mr. Trump's stewardship of the economy and his impact on working families, a potential vulnerability that has emerged during the coronavirus crisis.

The speech on Tuesday came with just under 100 days until Election Day, amid a searing national debate over racism in American society. Mr. Biden continues to hold a substantial lead

Continued on Page A19

TAMIR KALIFA FOR THE NEW YORK TIMES

An Overwhelming Toll

Covid-19 has funeral homes in South Texas fighting to keep up. Above, in Brownsville. Page A5.

MASON TRINCA FOR THE NEW YORK TIMES

Federal agents outside a courthouse in Portland, Ore., on Tuesday.

New York City Hailed Contact-Tracing Corps; Workers Saw Chaos

Mayor Alters Project After a Rocky Start

By SHARON OTTERMAN

It was only a few weeks into the rollout of New York City's much-heralded contact-tracing program, a vital initiative in the effort to contain the coronavirus and to reopen the local economy. But in private messaging channels, the newly hired contact tracers were already expressing growing misgivings about their work.

One said the city was "putting out propaganda" about the program's effectiveness.

Another wrote, "I don't think this is the type of job we should just 'wing it,' and that's the sense I've been getting sometimes."

A third tracer said, "The lack of communication and organization is crazy."

The authorities around the world — especially in East Asia and Western Europe — have rapidly enacted contact-tracing programs, which are used to identify and then isolate groups of people who may be infected with the coronavirus.

Mayor Bill de Blasio has declared that the city's new Test and Trace Corps, which has hired about 3,000 contact tracers, who monitors and others, will make a difference in curbing the virus now that the outbreak that devastated New York in the spring has waned.

But contact-tracing programs have presented an array of challenges to government officials everywhere, including difficul

Continued on Page A6

Blood Test Is 'Big Step Forward' In Early Detection of Alzheimer's

Giving Accurate Results With Low-Cost Tools, a Longtime Goal

By PAM BELLUCK

A newly developed blood test for Alzheimer's has diagnosed the disease as accurately as methods that are far more expensive or invasive, scientists reported on Tuesday, a significant step toward a longtime goal for patients, doctors and dementia researchers. The test has the potential to make diagnosis simpler, more affordable and widely available.

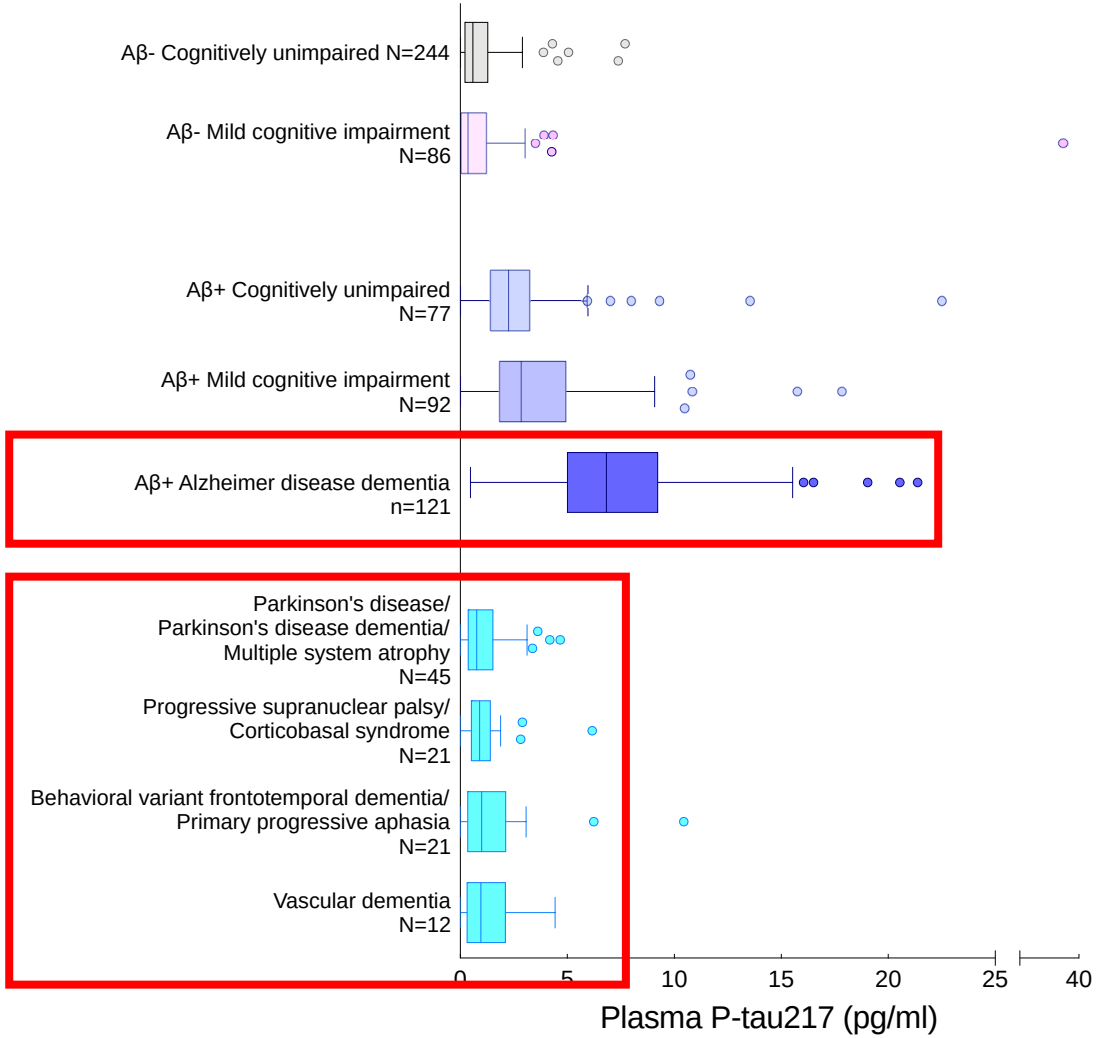
The test determined whether people with dementia had Alzheimer's instead of another condition. And it identified signs of the degenerative, deadly disease 20 years before memory and thinking problems were expected in people with a genetic mutation that causes Alzheimer's, according to research published in JAMA and presented at the Alzheimer's Association International Conference.

Such a test could be available for clinical use in as little as two to three years, the researchers and other experts estimated, providing a readily accessible way to diagnose whether people with cognitive issues were experiencing Alzheimer's, rather than another type of dementia that might require different treatment or have a different prognosis. A blood test like this might also eventually be used to predict whether someone with no symptoms would develop

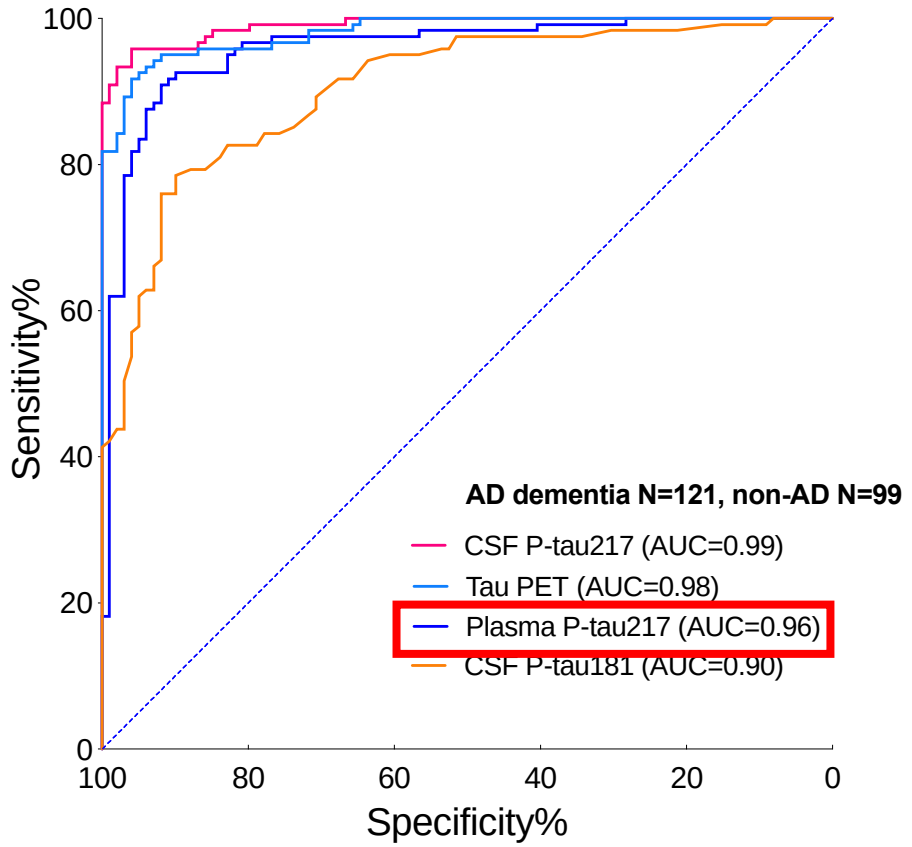
Continued on Page A20

Plasma P-tau can distinguish Alzheimer's disease from other dementia disorders

Plasma P-tau217 levels are increased by 500-700% in AD dementia

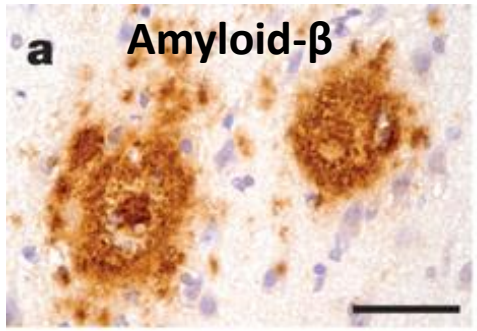


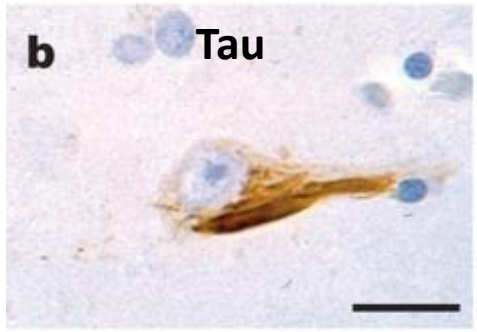
Plasma P-tau can differentiate AD from non-AD diseases similar to Tau-PET and CSF P-tau

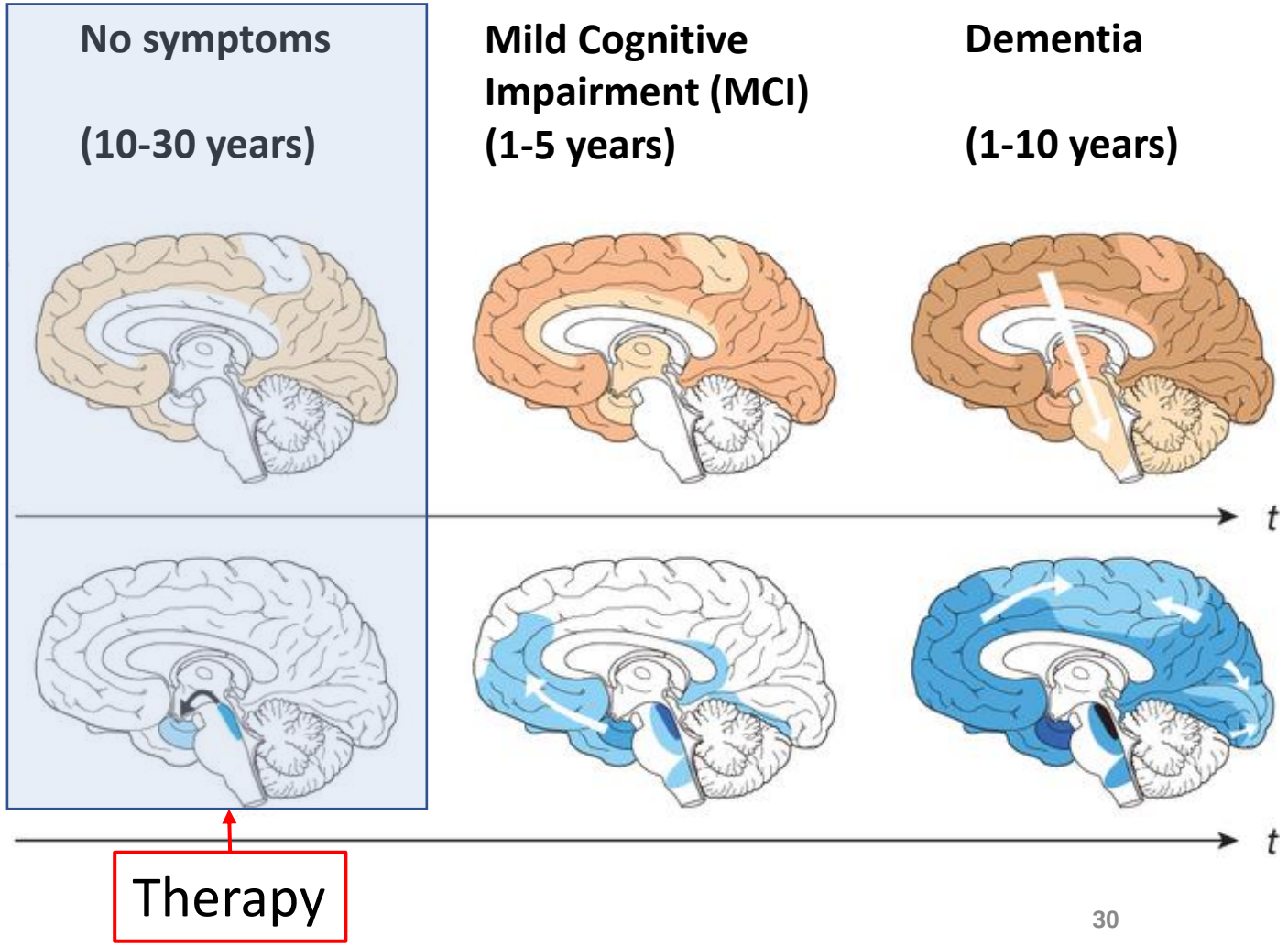


Palmqvist S, Janelidze S* et al, JAMA, 2020*

Plasma biomarkers and **pre-symptomatic AD**

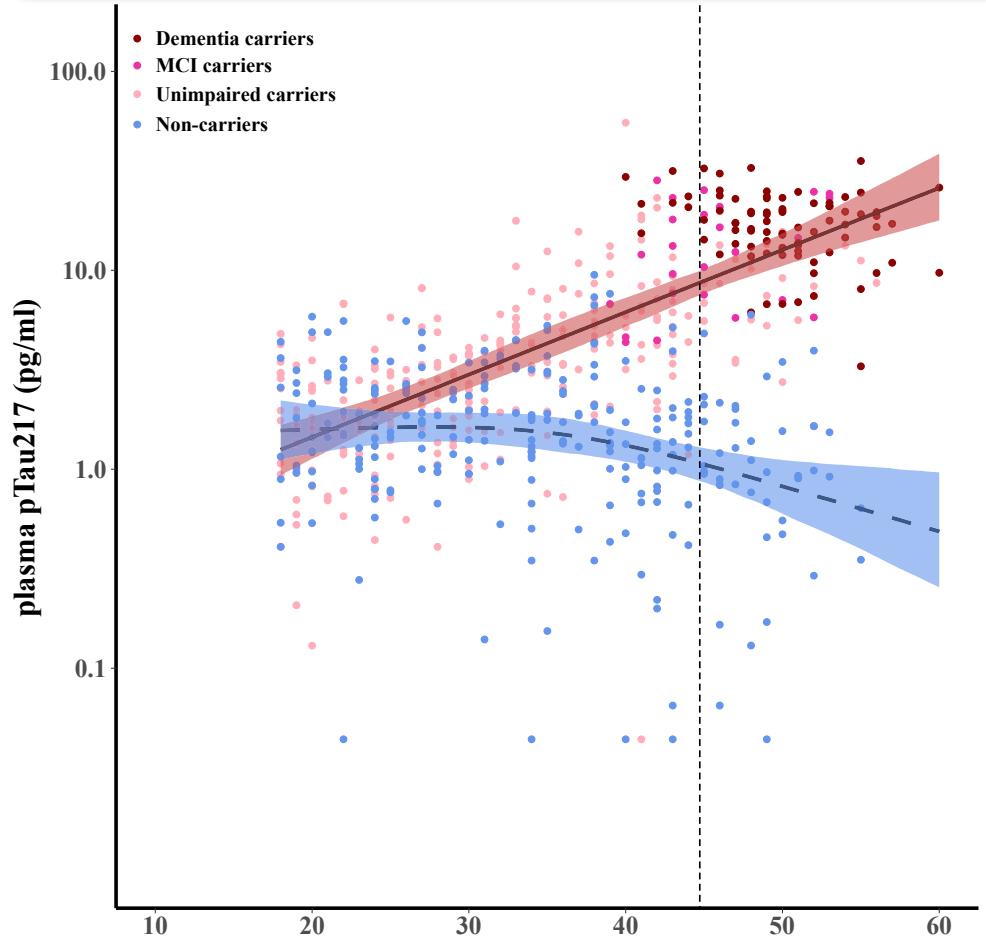






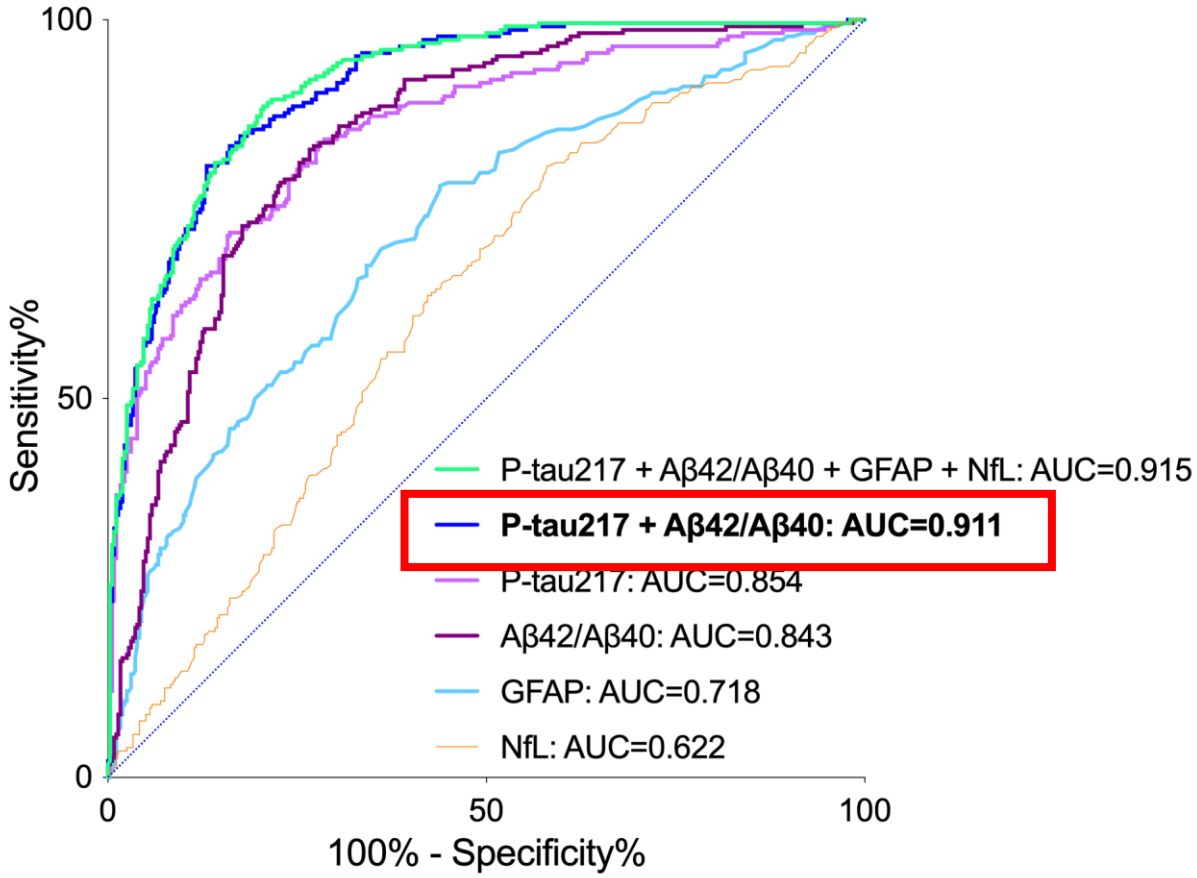
Detection of **pre-symptomatic** Alzheimer's disease using plasma tests

Plasma P-tau changes 20 years before onset of cognitive impairment



Palmqvist S, Janelidze S* et al, JAMA, 2020*

A combination of plasma Aβ42/40 and P-tau can predict cerebral Aβ pathology

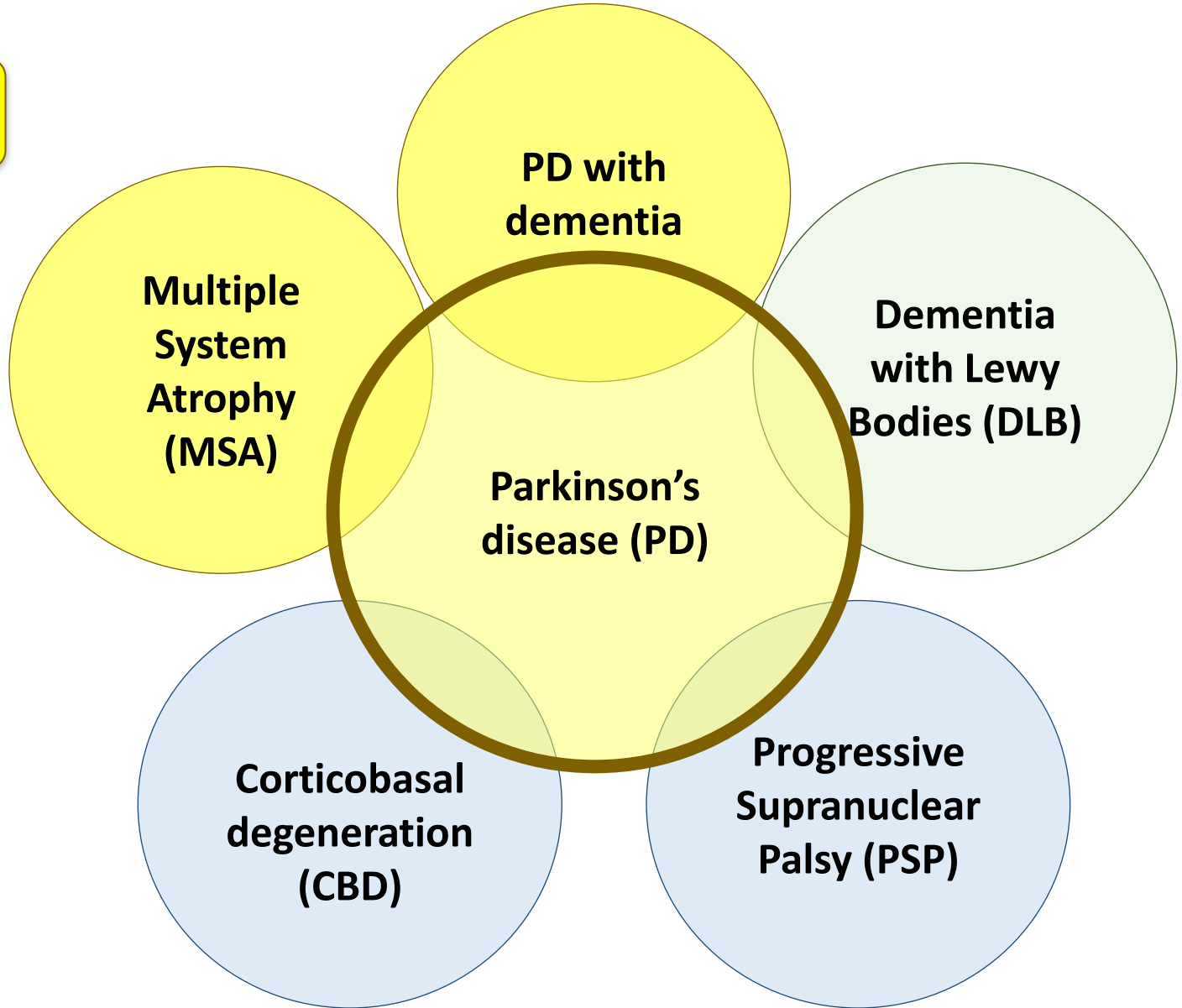


Janelidze et al, unpublished

Diseases causing Parkinsonian Syndromes

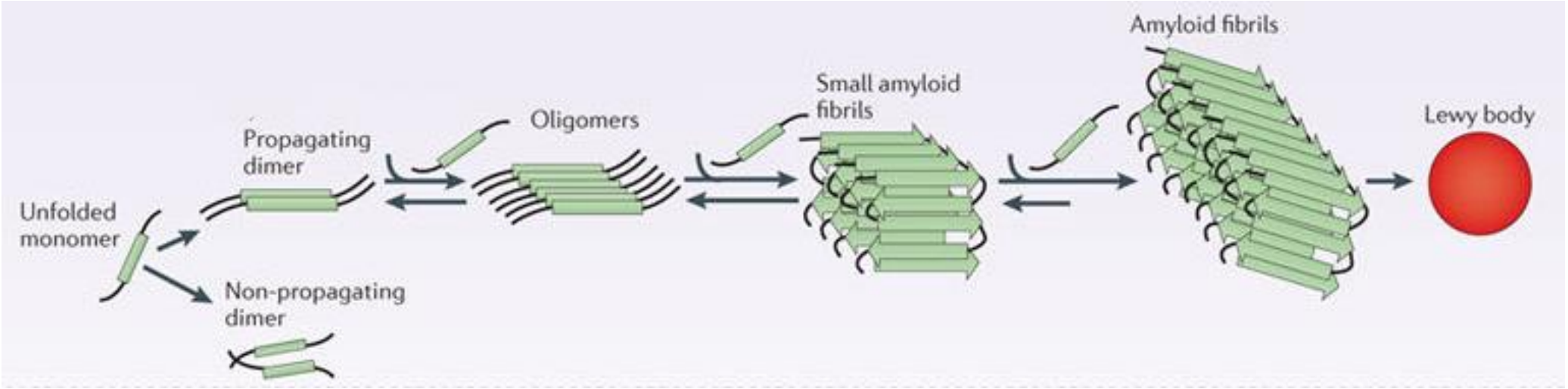
α-Synuclein

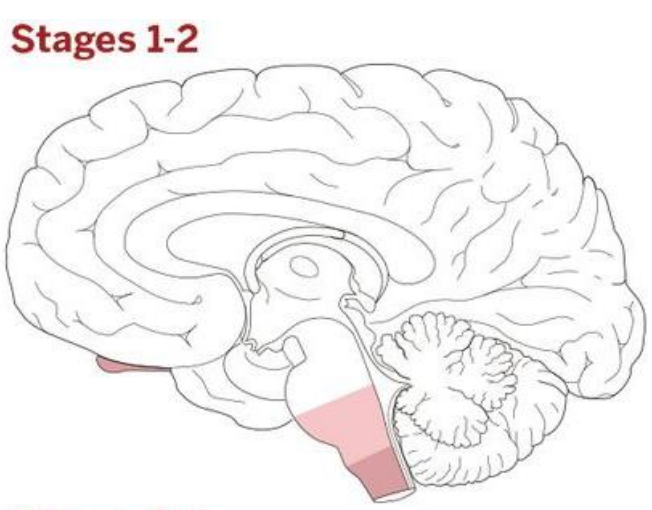
α-Synuclein & Tau

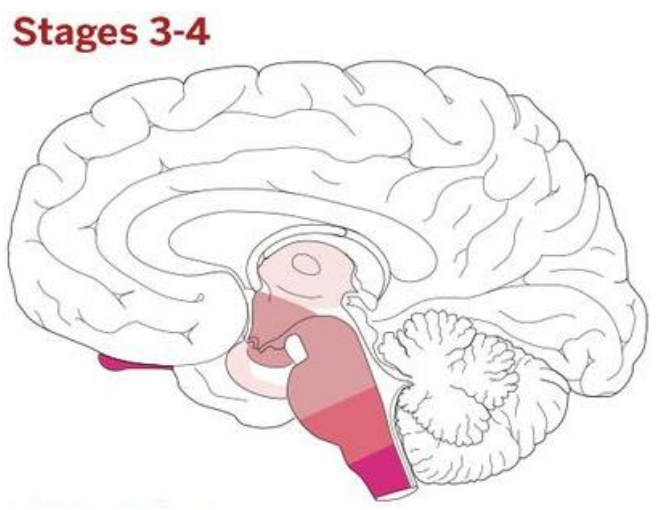


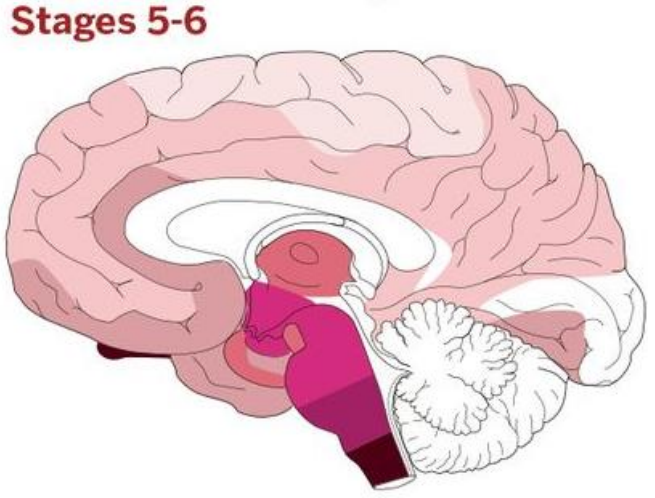
Tau

α-Synuclein aggregates and spreads in the brain in Parkinson's disease





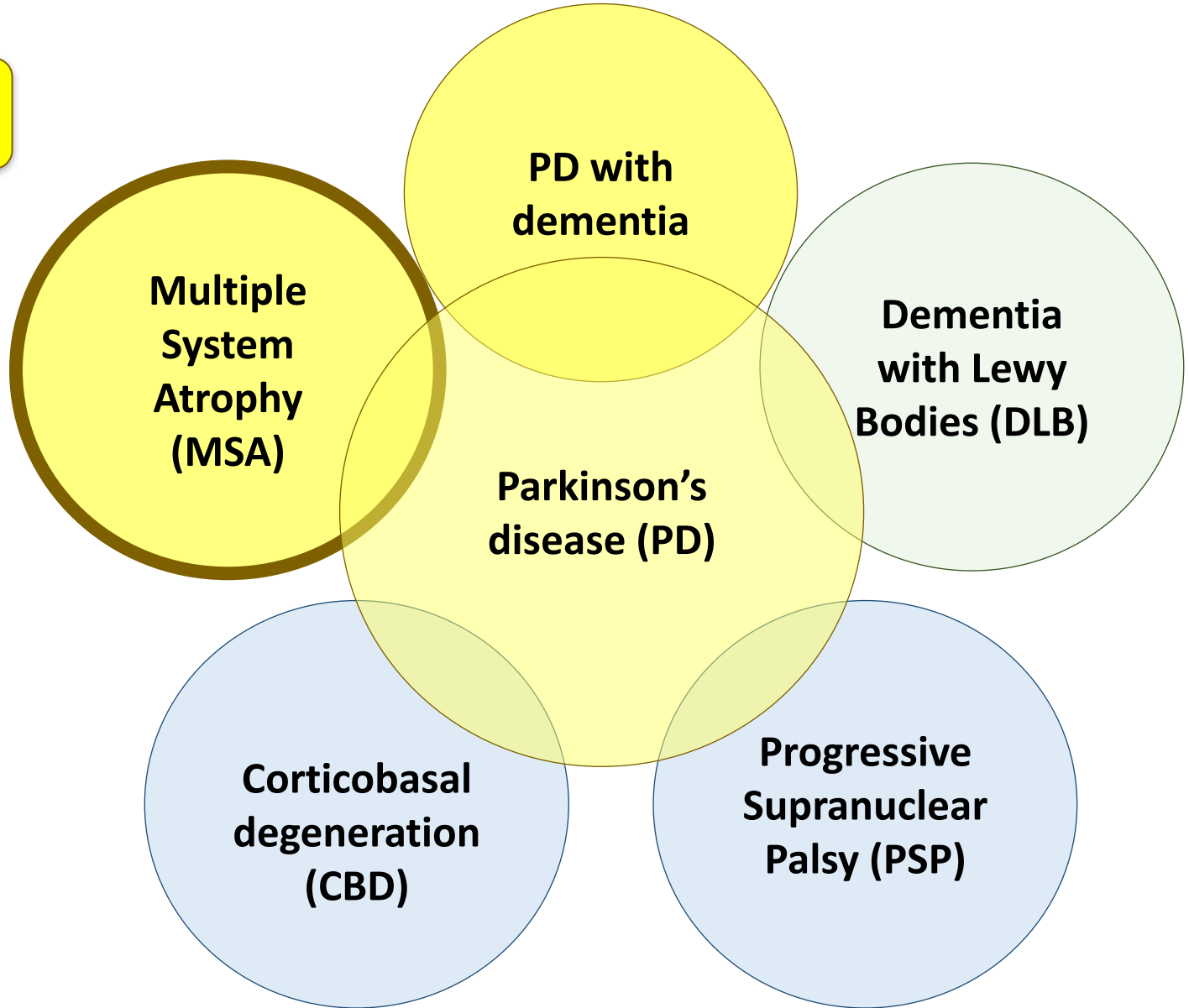




Diseases causing Parkinsonian Syndromes

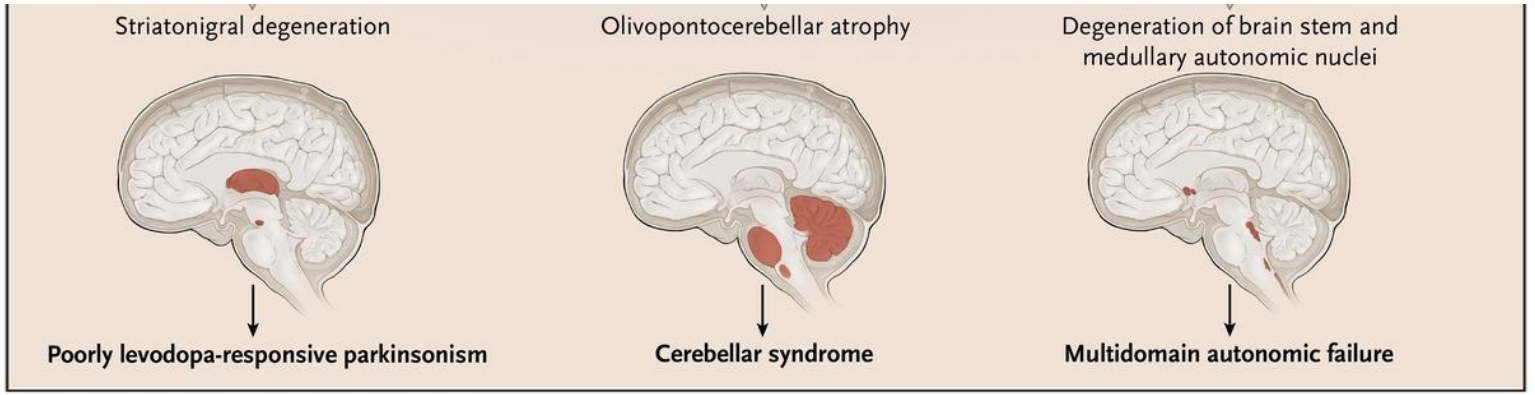
α-Synuclein

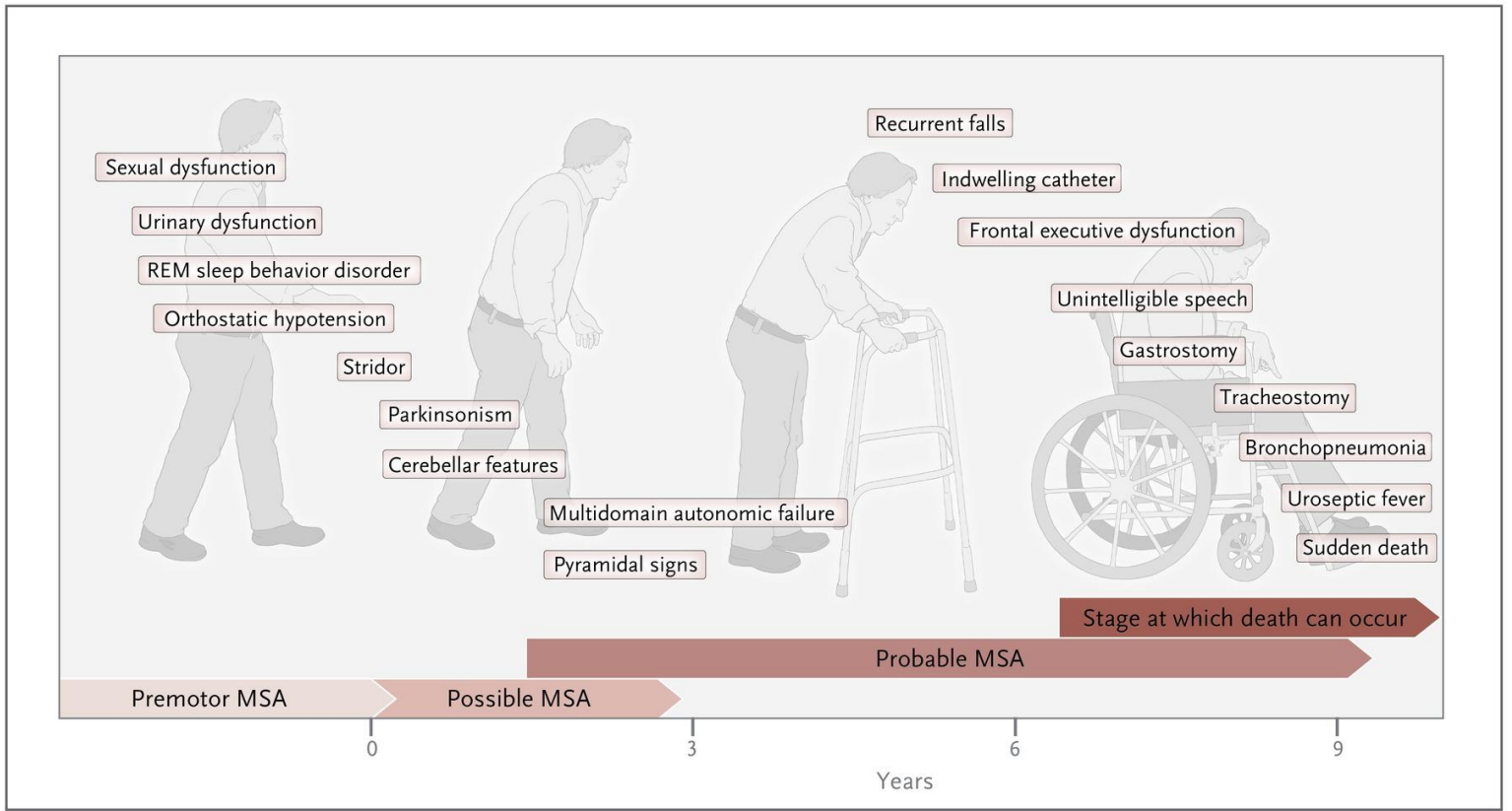
α-Synuclein & Tau



Tau

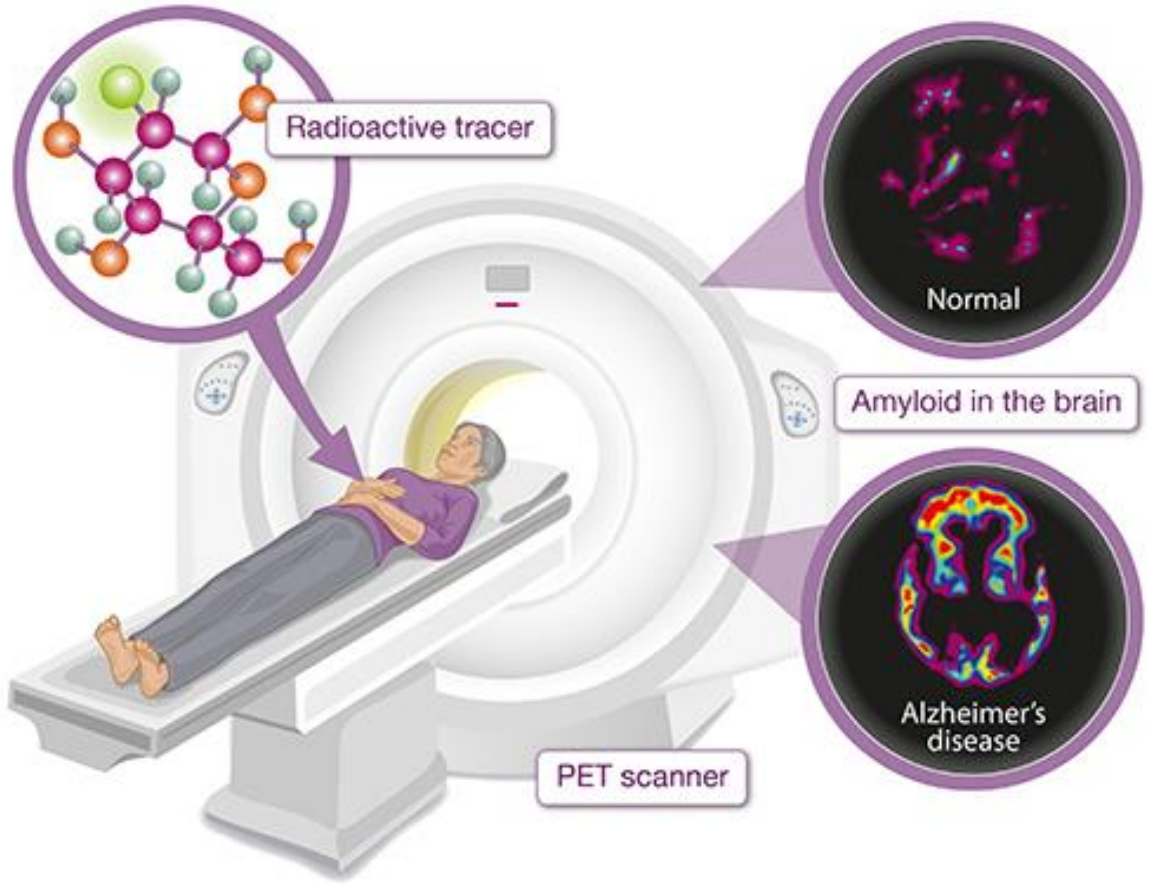
Multiple-System Atrophy (MSA)





Fanciulli et al. NEJM, 2015

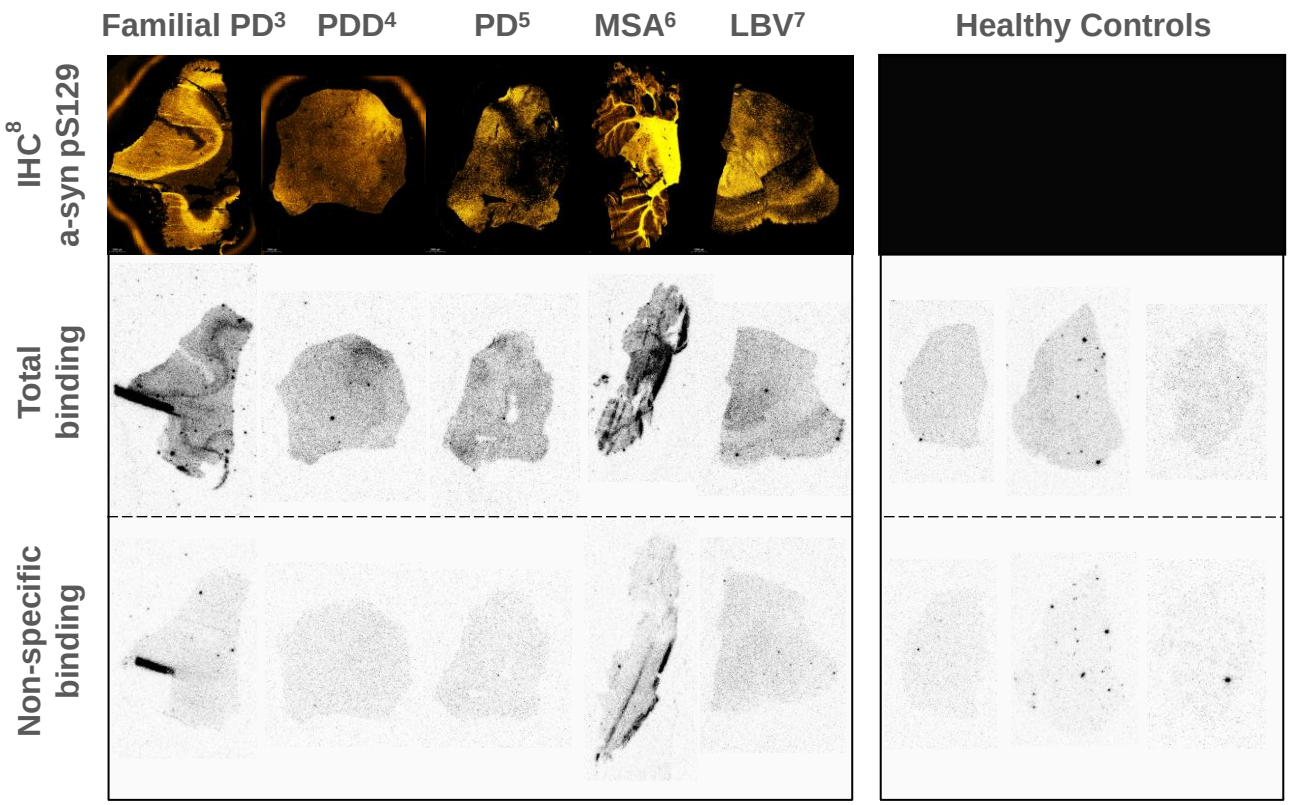
α-Synuclein PET imaging

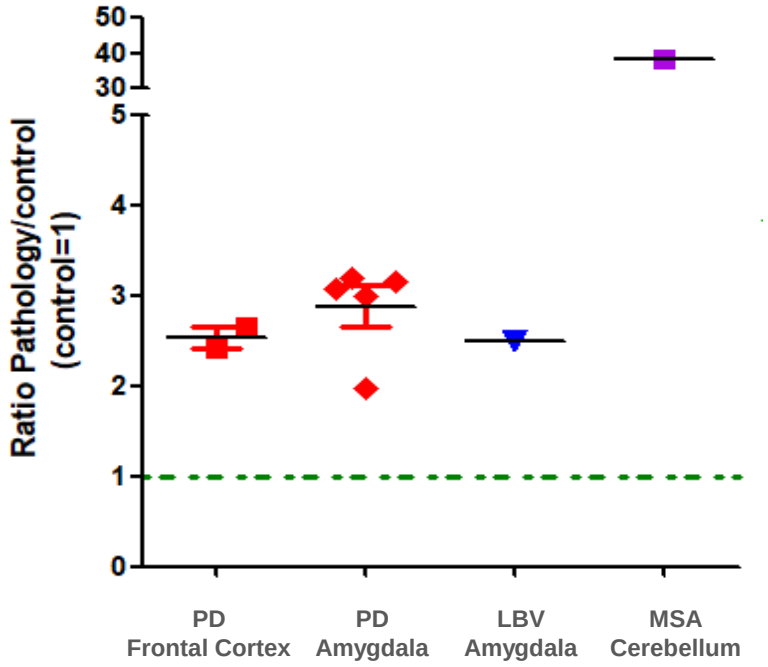


- Improved diagnosis in clinical practice of Parkinsonian disorders
- Drug development against toxic α-synuclein
  - Target engagement
  - Diagnosis
  - Subtypes

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

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





In collaboration with Prof. A. Varrone, Karolinska Institute

Karolinska Institutet

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

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

AC Immune

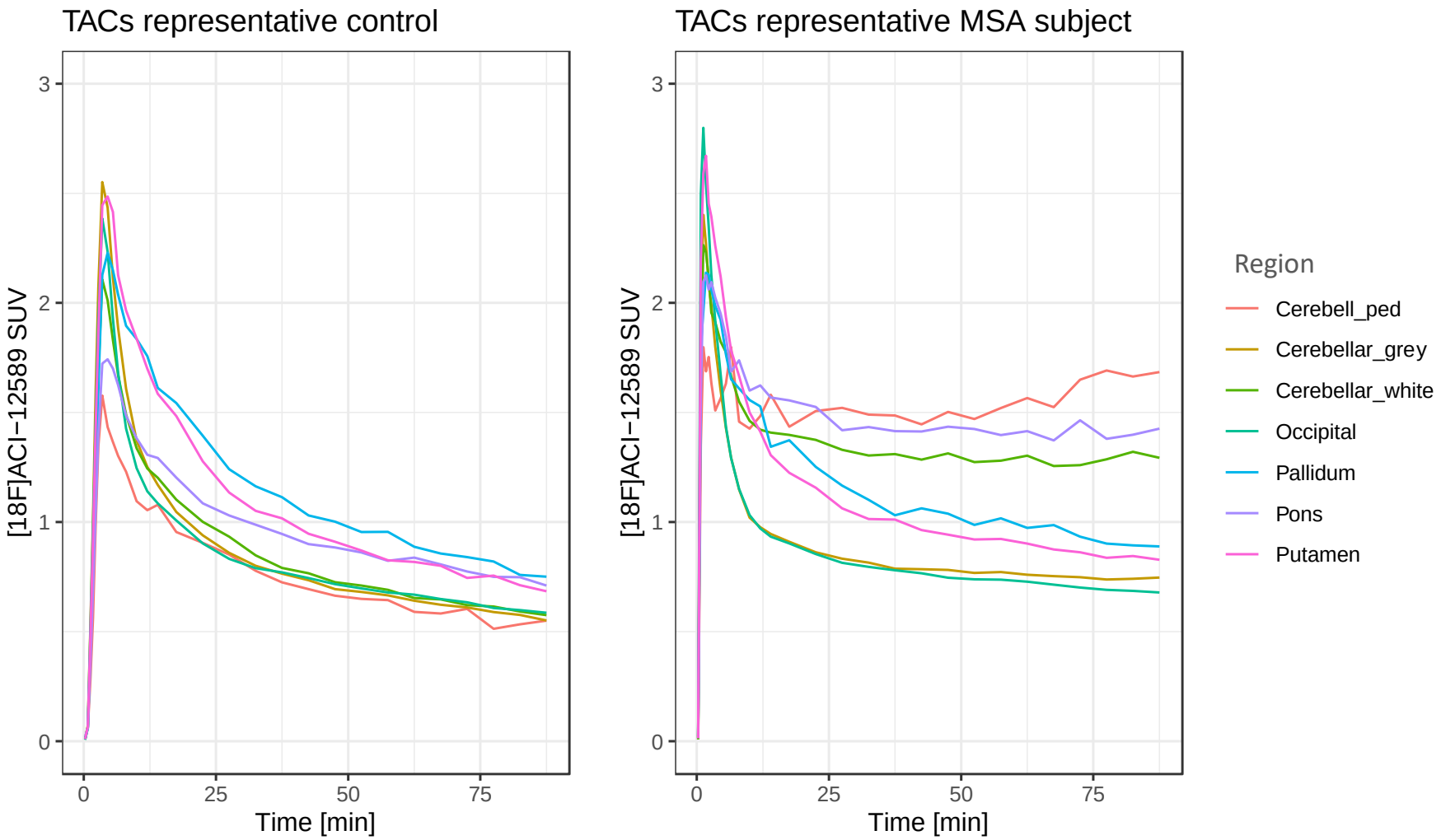
Participant characteristics

25 participants with a-synuclein related disorders scanned

Dynamic 0-90 min scans with arterial blood sampling

	Control	PD	MSA	DLB
n	8	7	8	2
Sex (M/F)	5/3	6/1	3/5	2/0
Age (± SD)	63±11	67±7	62±8	81±1
Inj Dose (MBq)	314±39	311±60	297±15	289±1
UMSARS I + II	N/A	N/A	50±24	N/A
UPDRS-III	N/A	65±16	N/A	N/A

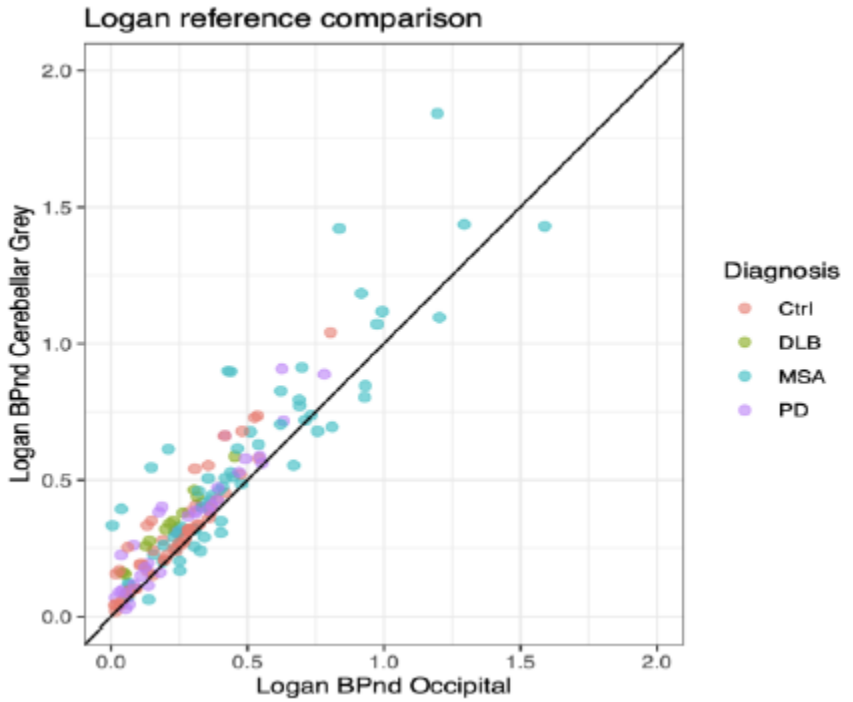
Kinetic modelling –Time Activity Curves



Cerebell_ped = Cerebellar peduncles; MSA = Multiple system atrophy; SUV = Standardized Uptake Value Ratio; TAC – Time activity curve

Kinetic modelling - reference regions

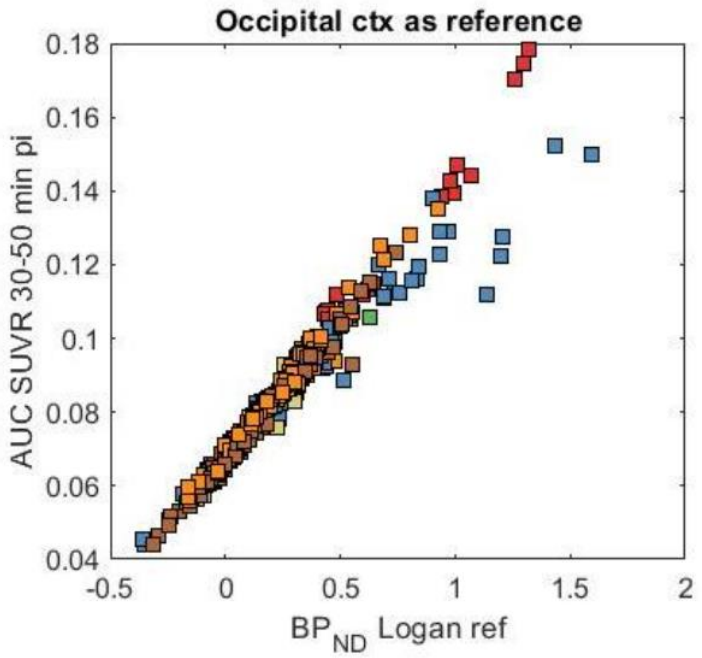
- No difference in cerebellar grey matter or occipital cortex V_Ts between diagnostic groups
- High correlation between data derived using cerebellar grey matter and occipital cortex reference regions



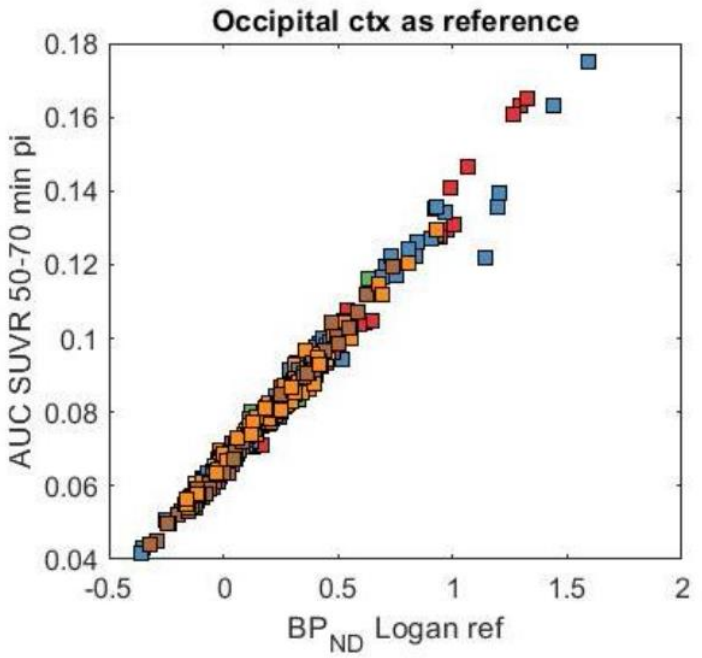
Both cerebellar cortex and occipital cortex suitable reference regions

Kinetic modelling - SUVR

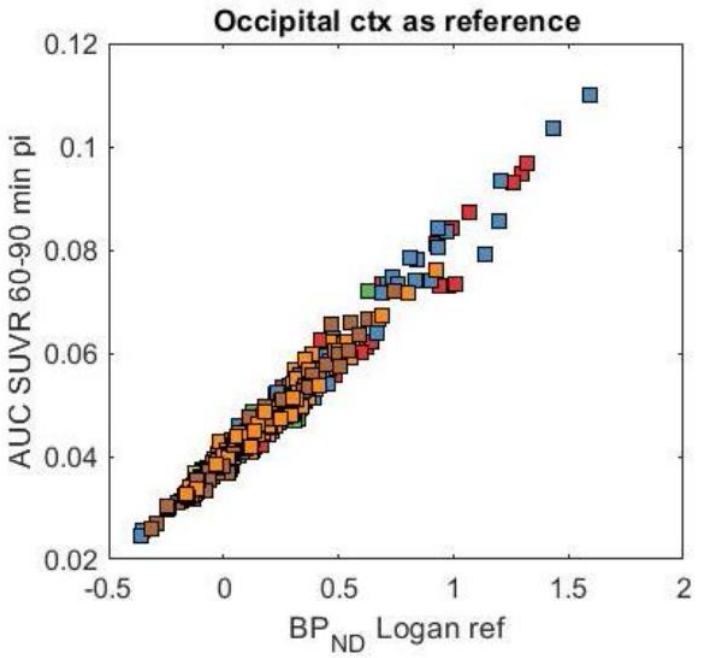
- Strong correlations between SUVR values and Logan ref BP_{ND}s (and MA1 BP_{ND}s). Best at 50-70 min and 60-90 min intervals



30-50 min



50-70 min



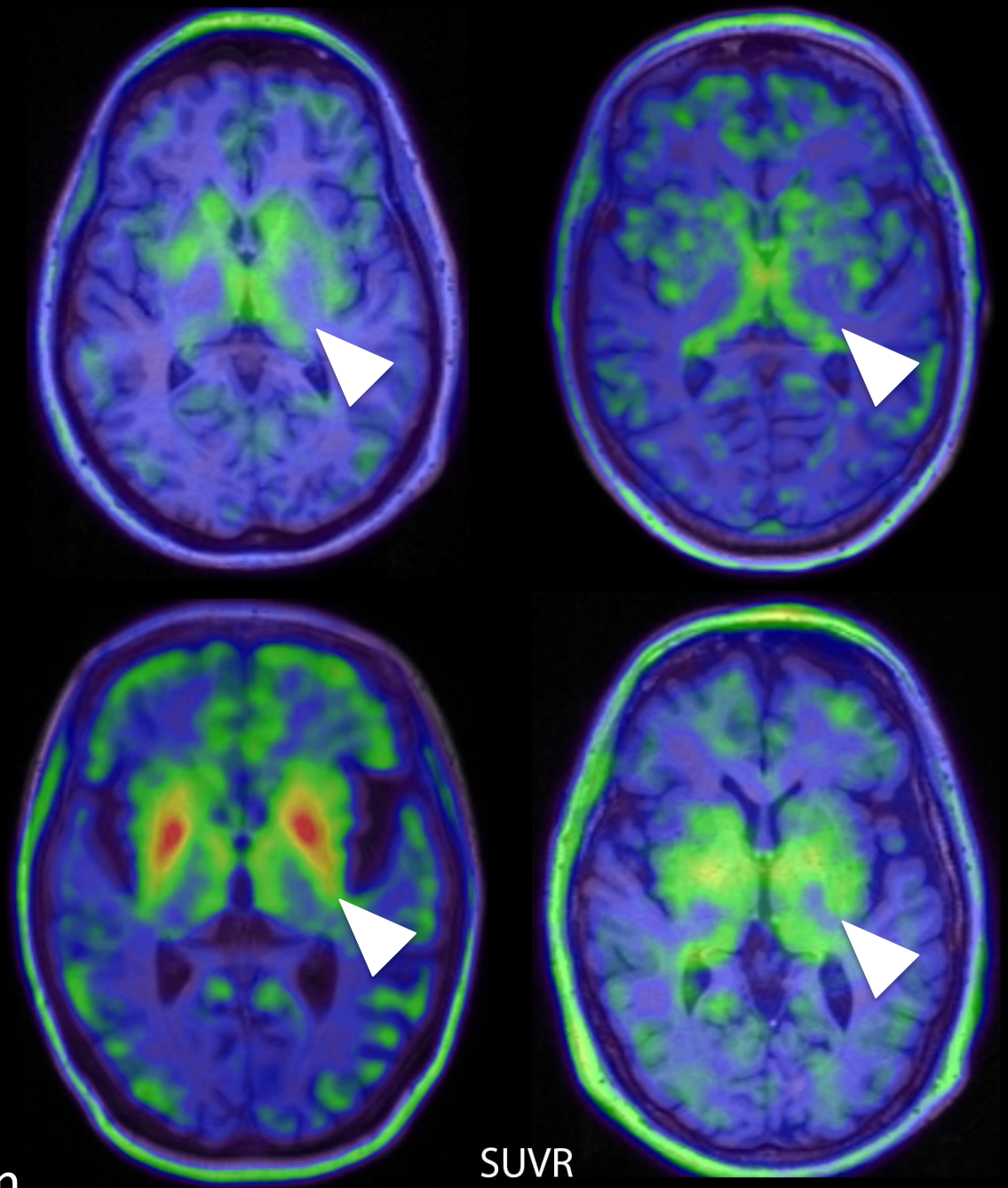
60-90 min

Control, 52

Control, 68

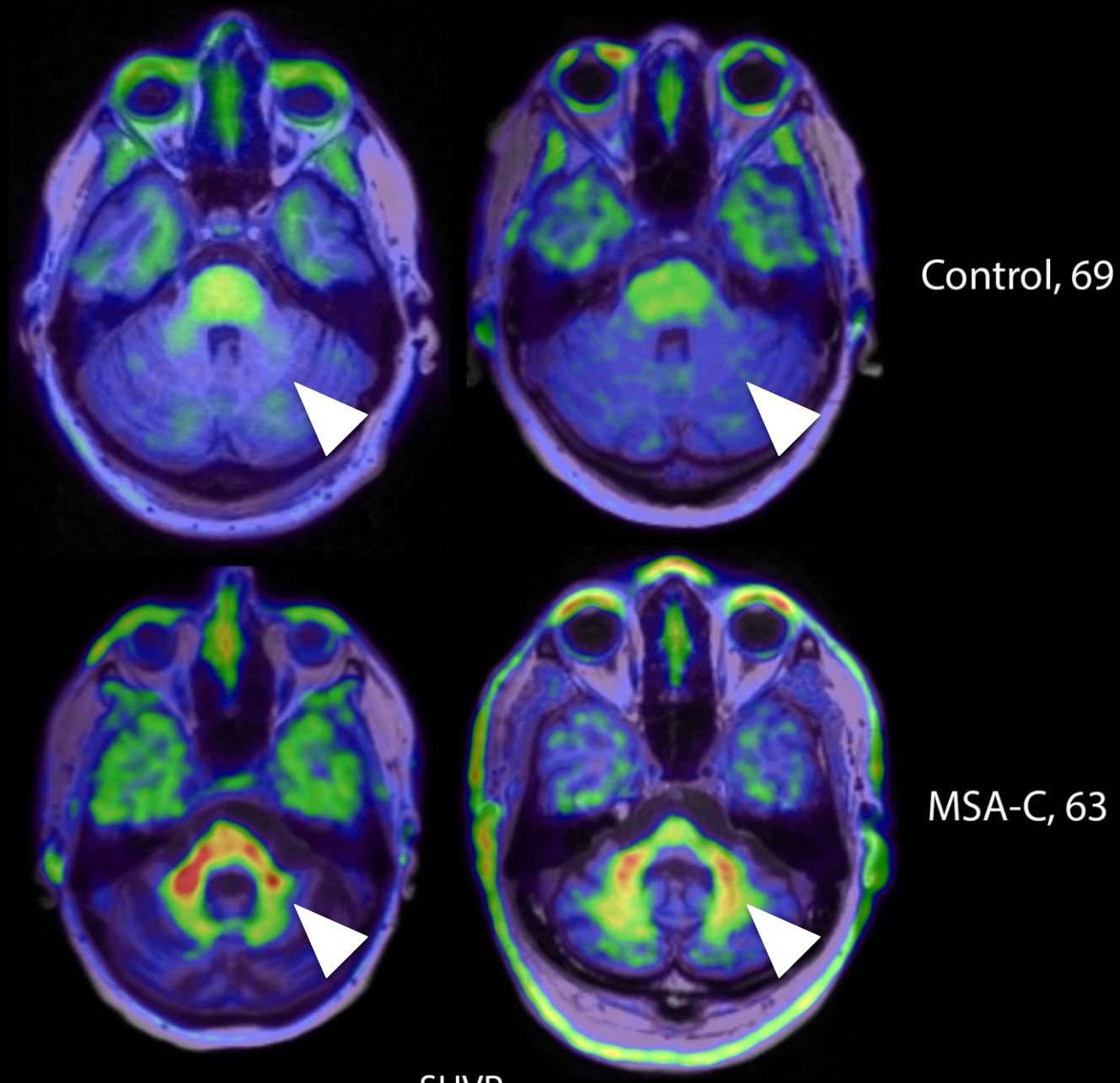
MSA-P, 54

PD, 73



SUVRs 60-90 min

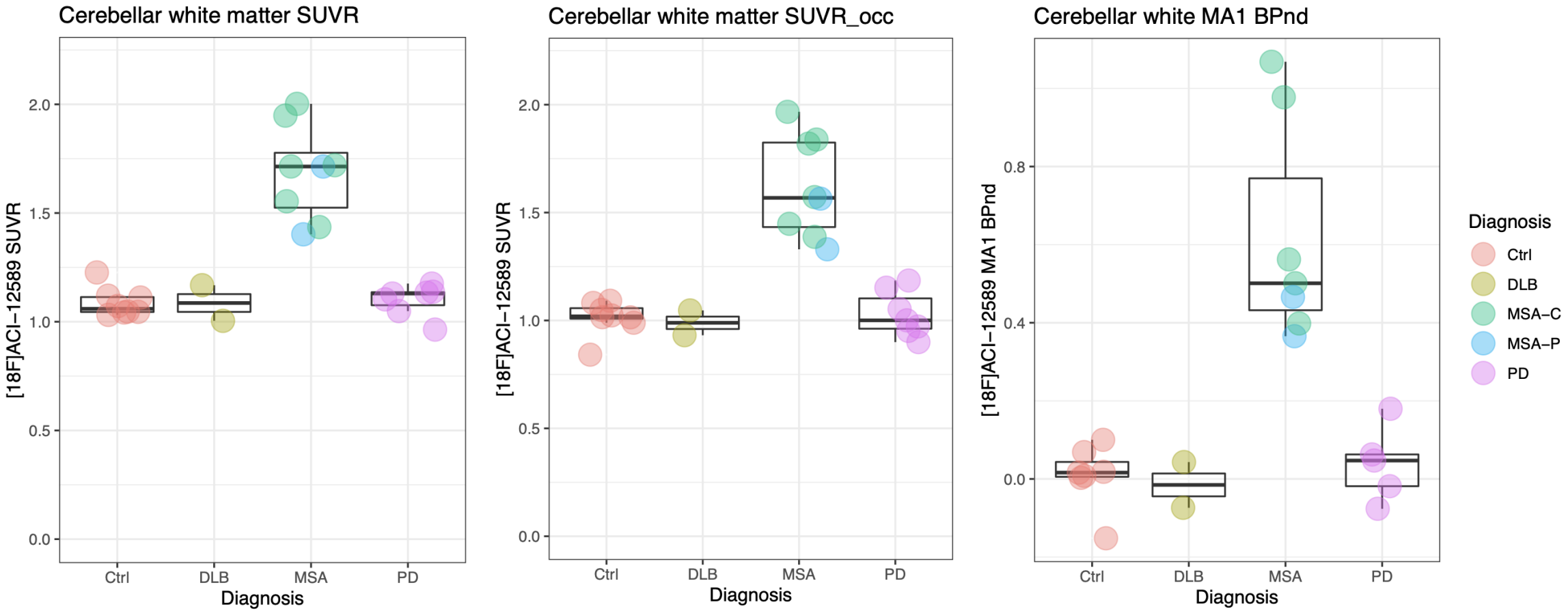
Increased basal ganglia uptake in MSA-P patients. Some unspecific uptake in controls



Clear increase in retention in MSA patients in cerebellar white matter and cerebellar peduncles

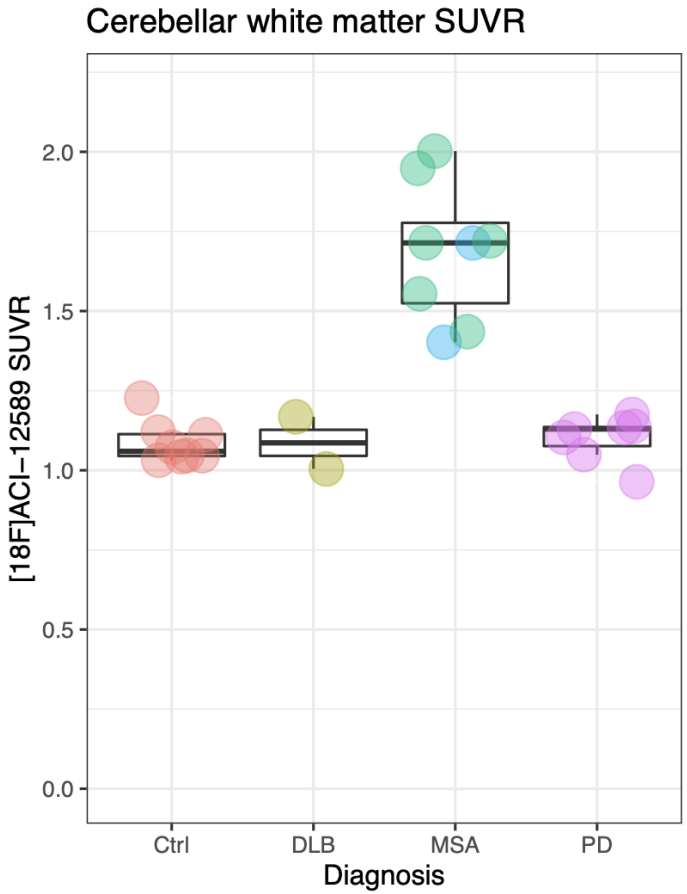
SUVRs 60-90 min

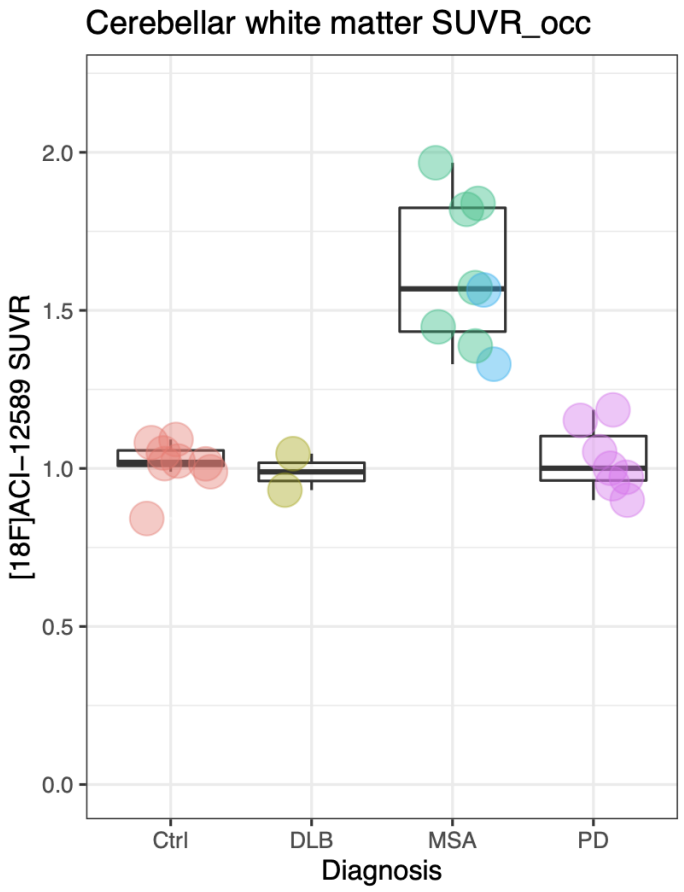
Cerebellar white matter [^{18}F]ACI-12589 retention

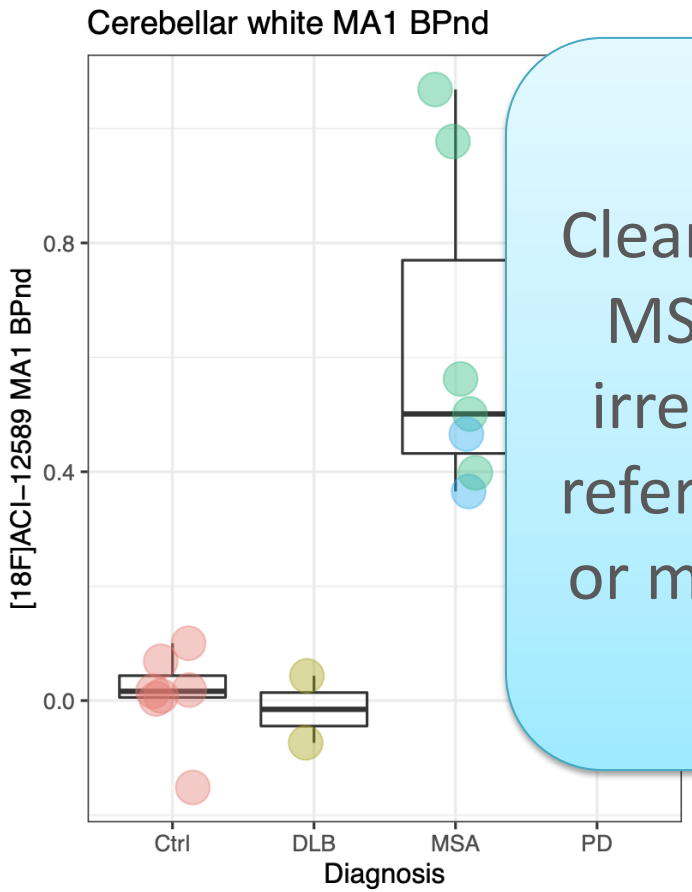


BPnd = Binding Potential, non-displaceable; Ctrl = Control; DLB = Dementia with Lewy Bodies; MA1 = Ichise multilinear analysis; MSA-C = Multiple system atrophy – cerebellar phenotype; MSA-P = Multiple system atrophy – parkinsonian phenotype; PD = Parkinson's Disease; SUVR = Standardized Uptake Value Ratio

Cerebellar white matter [^{18}F]ACI-12589 retention







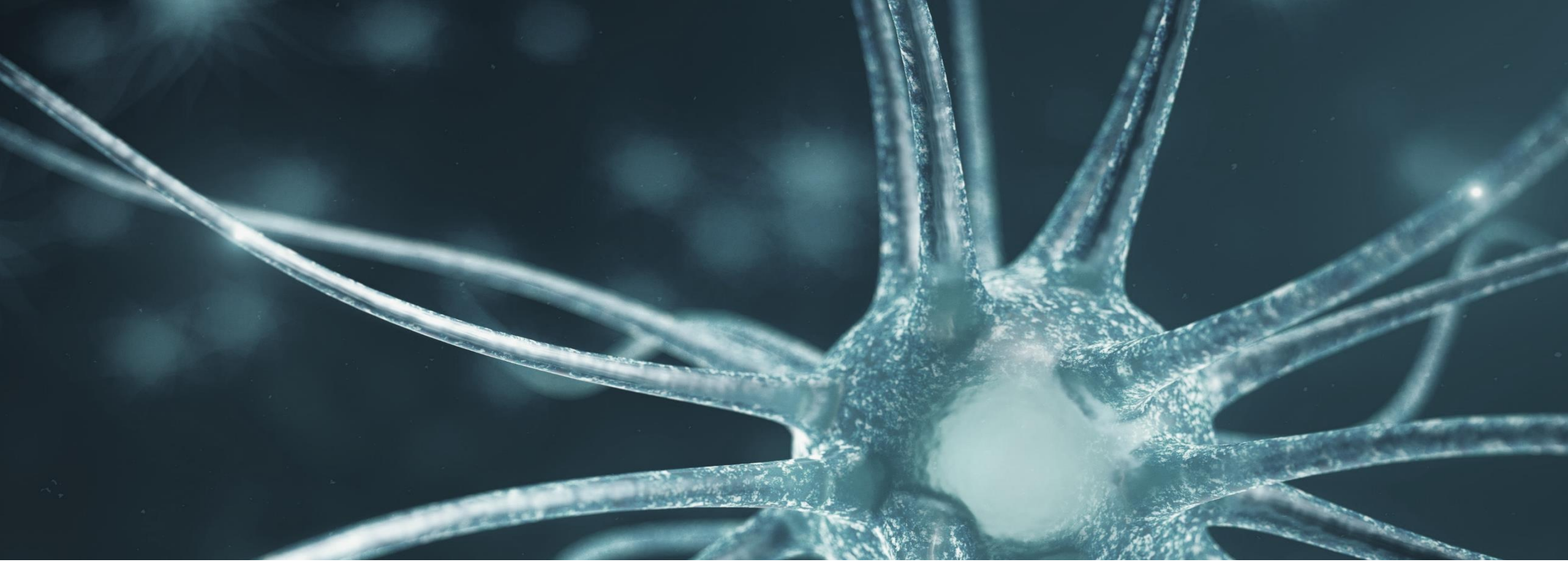
Clear increase in MSA patients irrespective of reference region or method used

BPnd = Binding Potential, non-displaceable; Ctrl = Control; DLB = Dementia with Lewy Bodies; MA1 = Ichise multilinear analysis; MSA-C = Multiple system atrophy – cerebellar phenotype; MSA-P = Multiple system atrophy – parkinsonian phenotype; PD = Parkinson's Disease; SUVR = Standardized Uptake Value Ratio

Conclusions

- [^{18}F]ACI-12589 shows a rapid brain uptake and fast signal equilibrium.
- SUVR can be used with occipital or cerebellar grey reference region.
- No relevant binding to MAO-B in cerebellar white matter

- Strong binding in expected regions in MSA
- Completely separates MSA from other synucleinopathies and controls
- [^{18}F]ACI12589 is a promising radiotracer for supporting a diagnosis of MSA and α-synuclein drug target engagement
- Further studies needed in Parkinson's Disease



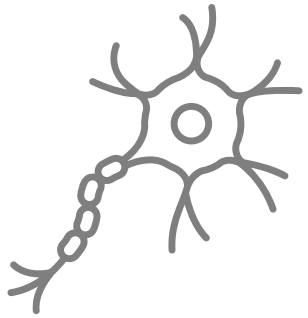
Clinical development plans for programs targeting alpha-synuclein

Johannes Streffer, MD, Chief Medical Officer

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

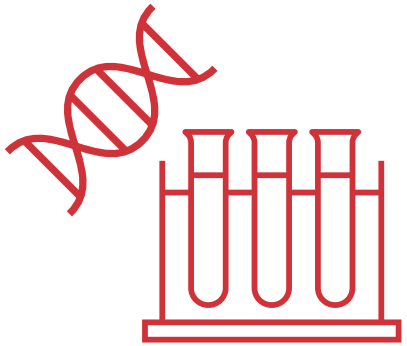
An effective PET tracer is needed to best enable precision medicine for a-synucleinopathies

Early Diagnosis and Treatment is Key in NDD



- Once neurons are damaged, they cannot be repaired or replaced with current therapies

Early diagnosis of a-syn-opathies[4] is not possible with current techniques



- Dopaminergic imaging correlates poorly with disease severity
- Genetic testing is ineffective in most cases
- Low abundance of a-syn limits utility of fluid biomarkers

Benefits of PET tracers for imaging have been validated

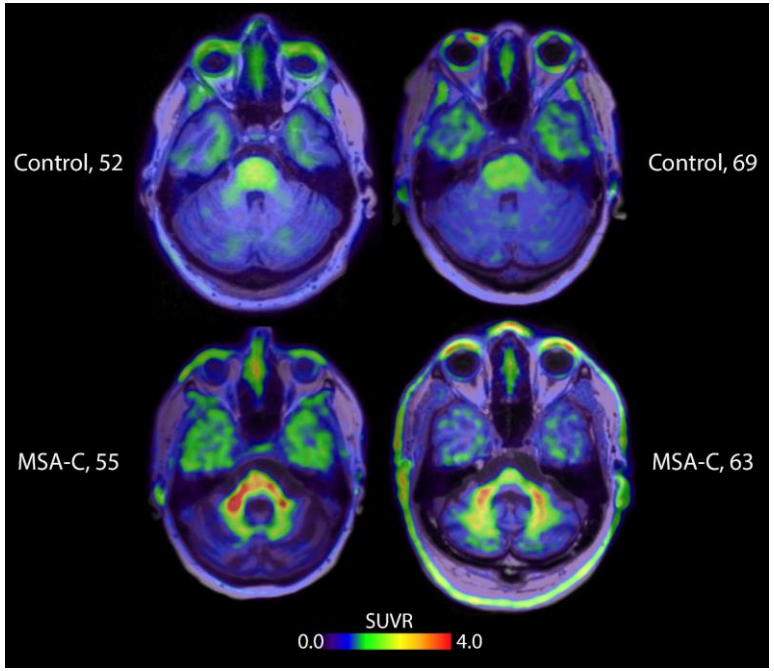
- Patient stratification
- Better clinical trials when focused using PET tracer for recruitment and monitoring
- May enable combination treatment of co-pathologies

(1) Alpha-synuclein; (2) Positron emission tomography; (3) Neurodegenerative disease; (4) Alpha-synucleinopathies; (5) Alzheimer's disease

ACI-12589: First clinically-validated a-syn[1] PET[2] tracer

First clinical PoC[3] for ACI-12589 opens new avenues in translational medicine

1. ACI-12589 effectively detected a-syn in human brains and distinguished MSA[4] from healthy controls and other a-syn-opathies[5]
2. ACI-12589 has the potential to enable the early diagnosis of MSA, which is extremely challenging with current techniques
3. First clinical PoC opens regulatory pathway to discuss biomarker-based development for an orphan indication
4. Learnings from development in MSA may allow for future applications in PD[6] with ACI-12589 or next-generation tracers



ACI-12589 is taking the first step towards a-syn-based precision medicine

(1) Alpha-synuclein; (2) Positron emission tomography; (3) Proof-of-concept; (4) Multiple system atrophy; (5) Alpha-synucleinopathies; (6) Parkinson's disease;

Next steps for ACI-12589 a-syn[1] PET[2] tracer development

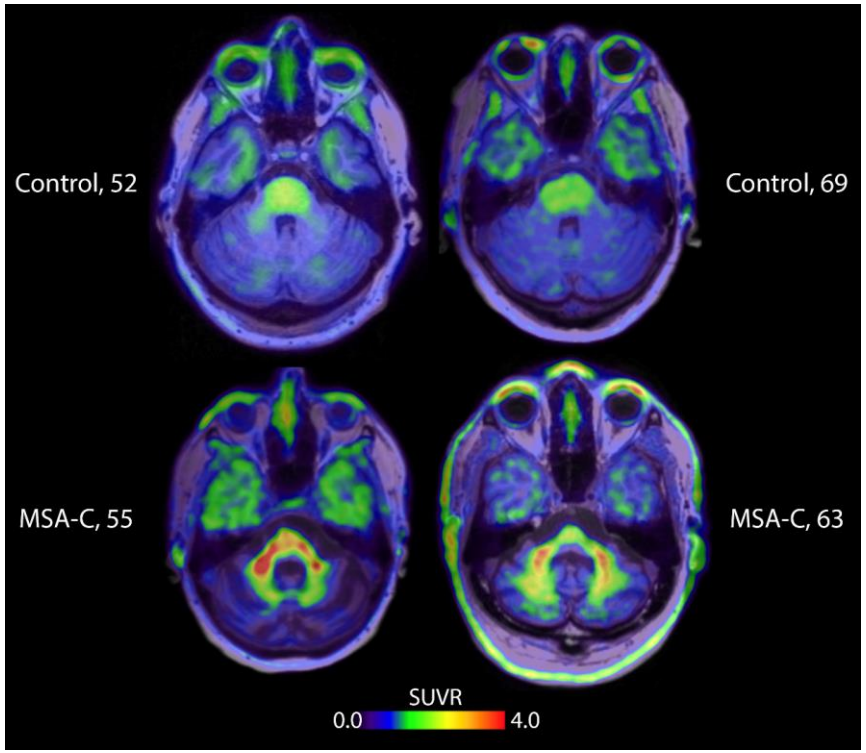
1 **Clinical Proof-of-Concept data in Multiple system atrophy (MSA) at AD/PD™ 2022**

2 **MSA (Orphan) – planned studies**

- Dosimetry
- Test – Retest
- Longitudinal progression
- Pharmacodynamic marker establishment

3 **Evaluation in Parkinson's and other neurodegenerative diseases**

4 **Collaboration and partnership discussions**



Indication	U.S. Patient Population	Global Patient Population
MSA (Orphan)	15,000-50,000[4]	~316,000[6]
PD[3]	960,000[5]	>6.1M[5]

(1) alpha-synuclein; (2) Positron emission tomography; (3) Parkinson's disease; (4) NINDS Multiple System Atrophy Fact Sheet; (5) GBD 2016 Parkinson's Disease Collaborators Lancet Neurology 2018; (6) Vanacore et al., Neurological Sciences 22: 97–99 (2001)

AC Immune's precision medicine approach to Parkinson's disease

Complementary portfolio covers full spectrum of treatment modalities targeting a-syn[1]

Product candidates	Leading therapies and diagnostics:			
	vaccine	diagnostic	antibody	small molecule
				
Current focus[2]	PD[3]	a-synucleinopathies	PD, NeuroOrphan	PD
Status	**Preparing adaptive Phase 2 study**	**First clinical PoC[4] (MSA[5] specific)**	**Preclinical**	**Discovery**

Initiation of dosing in Phase 2 vaccine study expected in H2 2022

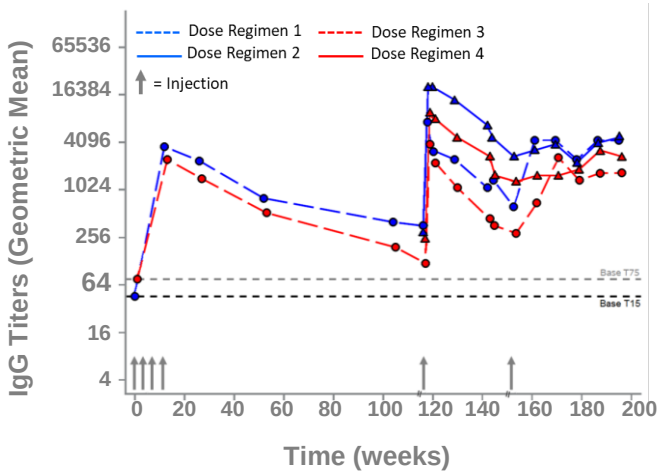
(1) Alpha-synuclein; (2) Programs can be expanded into additional a-synucleinopathies, (3) Parkinson's disease; (4) Proof of concept; (5) Multiple system atrophy

Anti-a-syn[1] vaccine is clinically validated[2] in Parkinson's disease

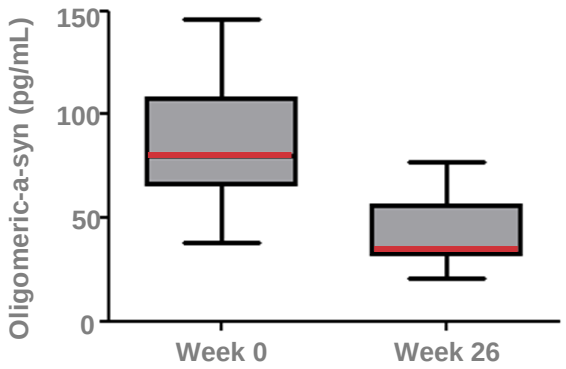
Phase 1 results in *The Lancet Neurology* support best-in-class profile

THE LANCET Neurology

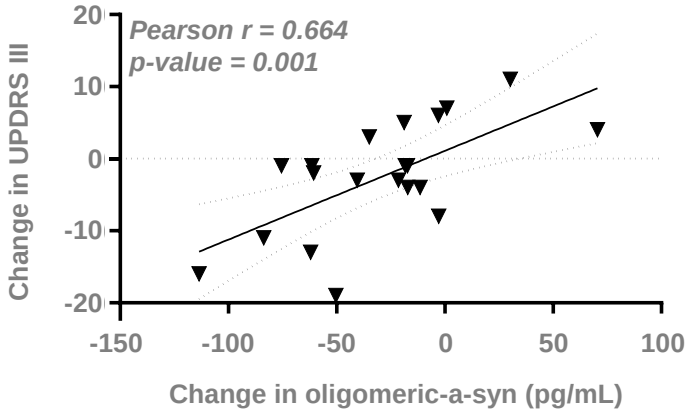
Strong and boostable antibody response



50% reduction[3] of pathological a-syn in CSF[4]



Changes[5] in oligo-a-syn and UPDRS III correlate



1 Safe and well tolerated with no safety concerns noted in patients followed for more than 3.5 years

2 Strong and boostable antibody responses

3 Target engagement evidence: 50% reduction in pathological (oligomeric) a-syn in the CSF

4 Signal of clinical efficacy: stabilization of UPDRS[6] III scores correlated with reductions in oligomeric a-syn

(1) alpha-synuclein; (2) Volc *et al.*, Lancet Neurol. 2020; (3) Data from 75 µg dose group; (4) Cerebrospinal fluid; (5) Change in oligomeric a-syn calculated at week 26, change in UPDRS III calculated at week 100; (6) Unified Parkinson's Disease Rating Scale

AC Immune

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

Placebo-controlled Phase 2 Study Overview

Inclusion criteria

- Idiopathic PD untreated or treated with MAO-B[2] inhibitor
- A diagnosis of PD for 2 years or less at screening (not demented / no cognitive impairment)
- Dopaminergic deficit by DaT SPECT[3]

Study design

- Seamless transition
  - All participants from Part 1 will contribute to final analysis
- Biomarker based interim analyses
  - Early immunogenicity to tailor dose and/or dose regimen
  - Understand biological signal for early transition to filing

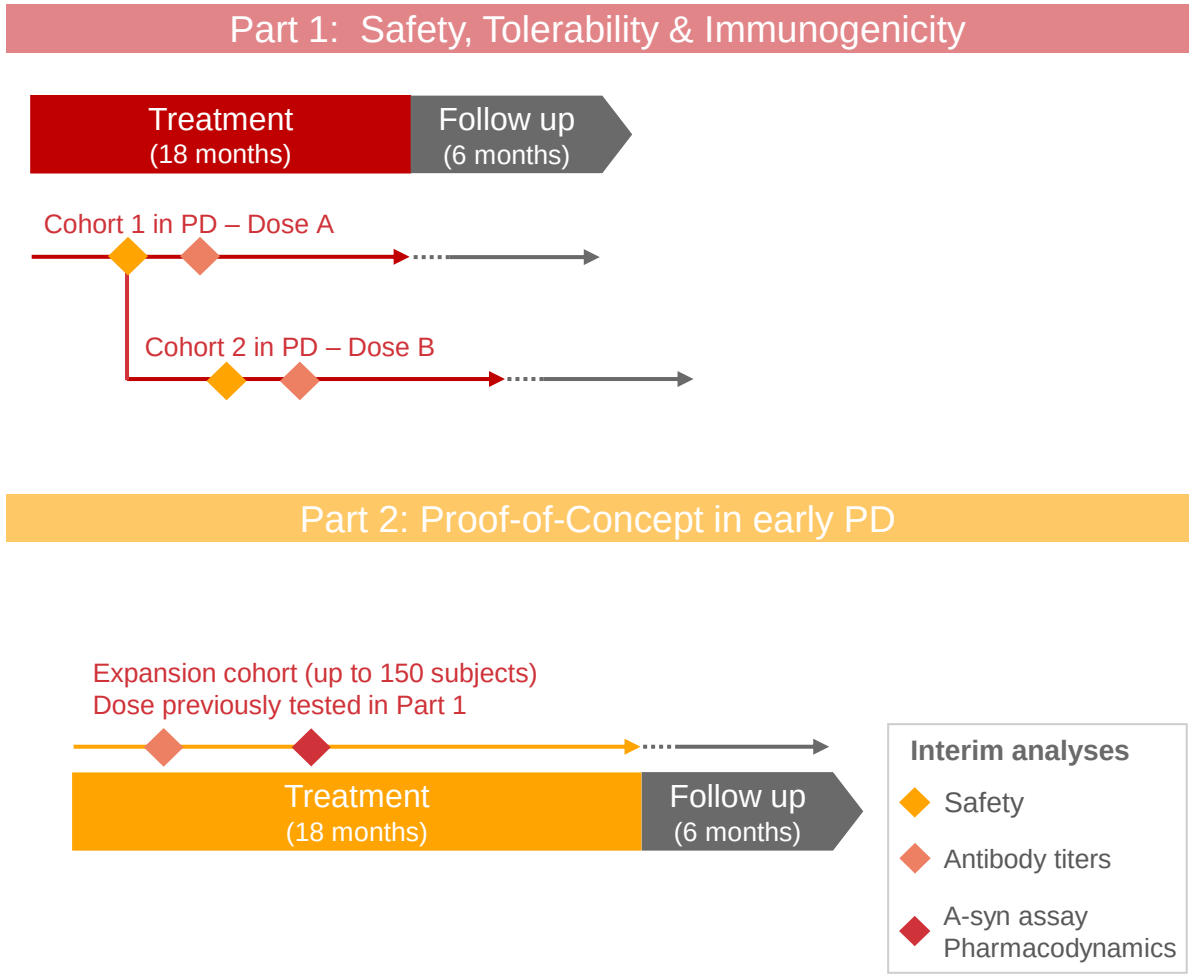
Part 1: Safety & PK/PD[4]

- Key immunogenicity measures
- Measures of pathological a-syn[5] and a-syn aggregation (phospho-a-syn and a-syn oligomers)

Part 2: PoC[6] in early PD

- Motor and Non-Motor Functioning (UPDRS[7] based)
- Neurodegeneration of dopaminergic terminals (DaT SPECT or VMAT2[8] imaging)
- Digital biomarkers of motor and non-motor function
- Advanced MRI (including ASL[9] and DTI[10])
- Functional and patient reported outcomes

Dosing Schematic



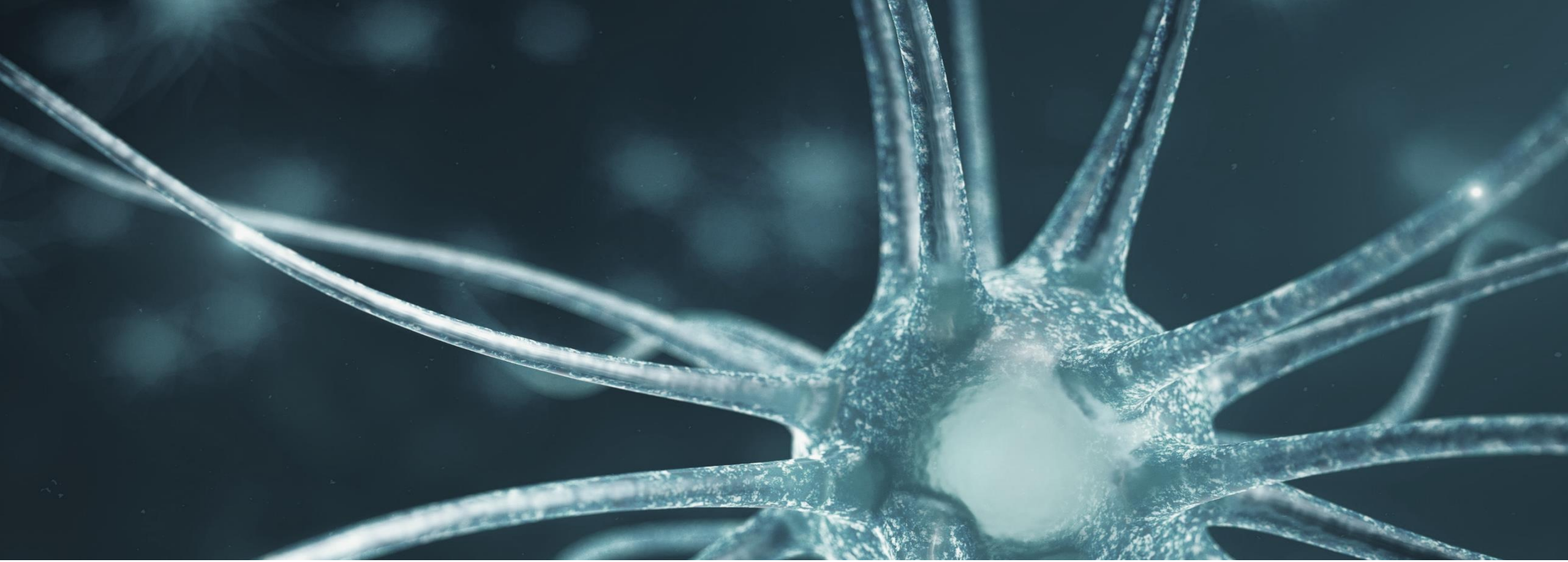
(1) Parkinson's disease; (2) Monoamine Oxidase Type B; (3) Dopamine Transporter Single Photon Emission Computed Tomography; (4) Pharmacokinetics and Pharmacodynamics; (5) alpha-synuclein; (6) Proof-of-concept; (7) Unified Parkinson's disease rating scale; (8) Vesicular monoamine transporter 2; (9) Arterial spin labeling; (10) Diffusion tensor imaging

Summary

1. **Breakthrough in a-syn[1] PET[2] imaging** demonstrates the excellence of our Morphomer® platform
2. **a-syn PET tracer distinguished MSA[3]** from healthy controls and other a-synucleinopathies
3. **Effective a-syn PET imaging** to accelerate clinical trials of a-syn therapeutics in biomarker-based studies
4. **Development of next-gen[4] a-syn PET tracers** for other a-synucleinopathies informed by experience in MSA
5. **AC Immune leadership in a-syn and NDD[5]** underscored by broad pipeline of best-in-class agents

Pioneering precision medicine for neurodegenerative diseases

(1) Alpha-synuclein; (2) Positron emission tomography; (3) Multiple system atrophy; (4) Next generation; (5) Neurodegenerative diseases



Q&A

Andrea Pfeifer, PhD, Chief Executive Officer