Morphomer™: platform and pipeline review

NASDAQ: ACIU | March 31, 2021

AC Immune

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Welcome

Today we will provide a comprehensive overview of AC Immune's

clinically validated Morphomer™ small molecule technology platform

and our pipeline of Morphomer-derived therapeutic and diagnostic candidates

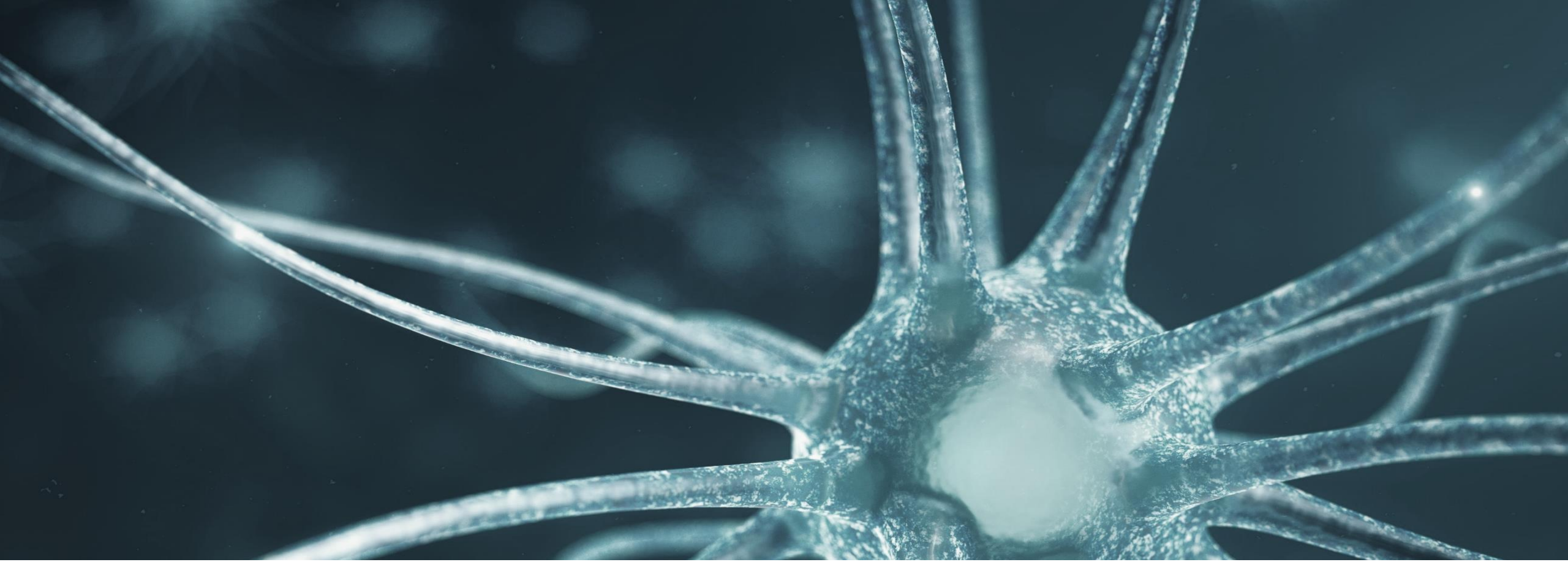
Driving progress toward precision medicine

for neurodegenerative diseases

Agenda

Introduction	**Joshua Drumm, PhD** Head of Investor Relations
Strategy & Pipeline Overview	**Andrea Pfeifer, PhD** Chief Executive Officer
Morphomer™ Platform Introduction	**Marie Kosco-Vilbois, PhD** Chief Scientific Officer
Therapeutic CNS[1] Molecules	**Sonia Poli, PhD** Life Cycle Leader
PET[2] Imaging Agents	**Francesca Capotosti, PhD** Group Leader *In Vivo* Pharmacology and Non-Clinical Safety
Conclusion and Q&A	**Andrea Pfeifer, PhD** Chief Executive Officer

(1) Central nervous system; (2) Positron emission tomography



Strategy and pipeline overview

Andrea Pfeifer, PhD, Chief Executive Officer

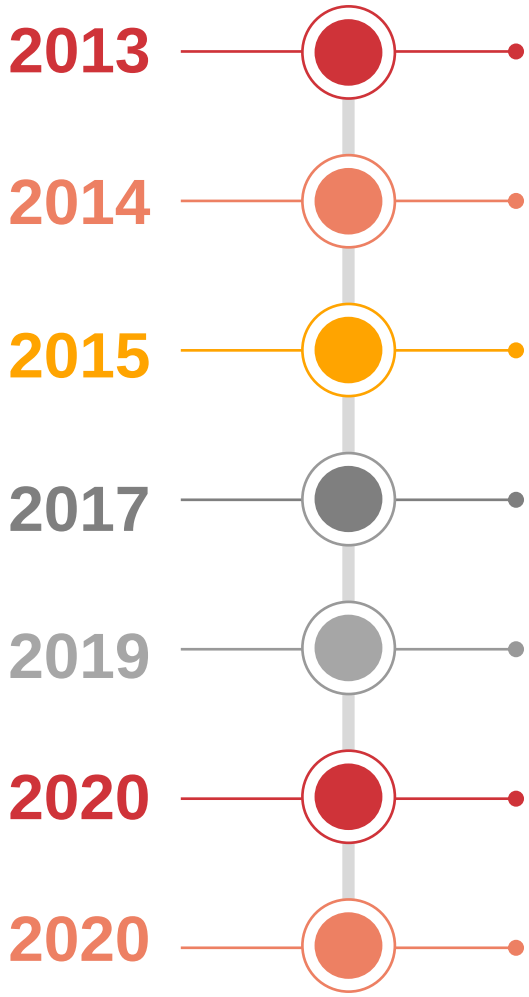
AC Immune investment highlights

Pioneering precision medicine for neurodegenerative diseases

- Largest healthcare market
  - Diversified approach targeting traditional and novel targets; five Phase 2 candidates
  - Multiple near-term catalysts in large and orphan indications
- Validating partnerships
  - Generated CHF 334 million to date; more than raised from investors
  - CHF 3 billion in total potential milestones plus royalties
  - Genentech[1], Janssen and Eli Lilly deals and five prestigious grants validate platform technologies
- Clinically validated SupraAntigen™ and Morphomer™ platforms
  - Fuel proprietary pipeline – e.g. preclinical assets: **a-syn[2], TDP-43[3], NLRP3[4]**
  - Drive value creation from existing and future partnerships
  - Enable precision medicine
- Precision medicine strategy
  - First- and/or best-in-class companion diagnostic products
  - Better clinical trials due to selection of defined patient populations
- CHF 225.9 million in cash funds operations through Q1 2024[5]
  - Multiple meaningful value inflection points
  - Continuous investment into newly validated targets

(1) A member of the Roche group; (2) Alpha-synuclein; (3) TAR DNA-binding protein 43; (4) (NOD)-like receptor protein 3; (5) As of December 31, 2020

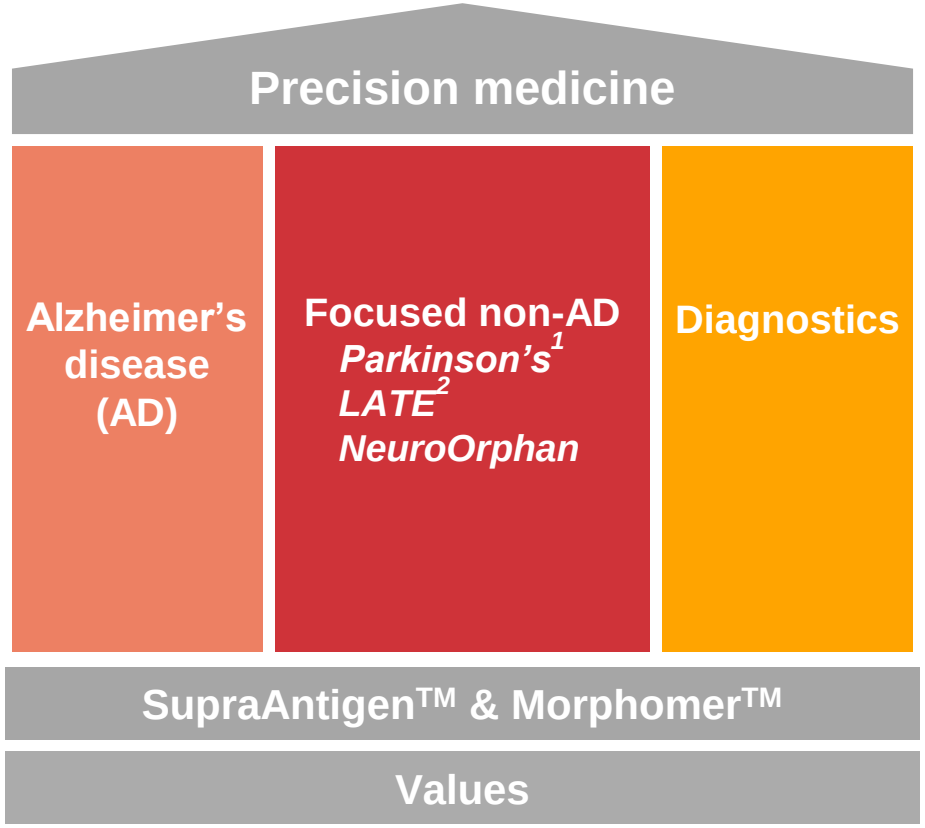
“Firsts” reflect ACIU’s leadership in NDD[1]



2013	1st	Prevention trial in AD[2] (crenezumab)
2014	1st	Anti-pTau[3] vaccine clinical trial in AD
2015	1st	Clinical vaccine trial in Down syndrome (Abeta vaccine)
2017	1st	Clinical data for Tau PET[4]-imaging tracer in PSP[5]
2019	1st	Morphomer™ Tau[6] clinical trial (ACI-3024)
2020	1st	Anti-TDP-43[7] antibody shown to mitigate TDP-43 neuropathology
2020	1st	Anti-Tau antibody Phase 2 readout in AD

(1) Neurodegenerative diseases; (2) Alzheimer's disease; (3) Phosphorylated Tau; (4) Positron emission tomography; (5) Progressive supranuclear palsy; (6) Small molecule Tau-specific aggregation inhibitor; (7) TAR DNA binding protein-43

Execution of our three-pillar strategy: the 2021 focus



Alzheimer's disease

- Accelerate development of phospho-Tau vaccine with partner Janssen
- Prioritize development of small molecule Tau aggregation inhibitor with partner Lilly

Non-AD and NeuroOrphans

- Advance Abeta vaccine in Down syndrome[3] to late stage; seek partner for AD
- Advance anti-TDP-43[4] mAb[5] in NeuroOrphan indications (ALS[6], FTLD-TDP[7])
- Accelerate a-syn[8] small molecule in Parkinson's disease
- Develop NLRP3[9] assets in CNS[10] and non-CNS indications

Diagnostics for precision medicine

- Advance differentiated diagnostic pipeline (Tau, a-syn, TDP-43) to late stage
- Early detection, improved clinical trials and marked differentiation

(1) Parkinson's disease; (2) Limbic-predominant age-related TDP-43 encephalopathy, a TDP-43-dependent dementia that affects 20%-50% of individuals >80 years old; (3) Down syndrome- related Alzheimer's disease; (4) TAR DNA-binding protein 43; (5) Monoclonal antibody; (6) Amyotrophic lateral sclerosis; (7) Frontotemporal lobar degeneration with TDP-43 pathology; (8) Alpha-synuclein; (9) (NOD)-like receptor protein 3; (10) Central nervous system

Morphomer™ and SupraAntigen™ platforms

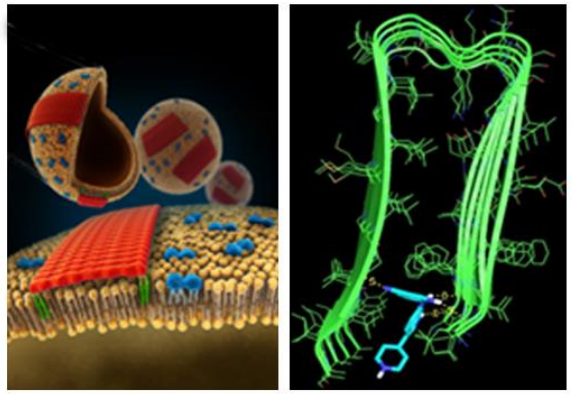
An integrated approach to CNS[1]-specific therapies

CNS-optimized

- Rapid generation of therapeutics and diagnostics for novel CNS targets
  - Small molecules with excellent BBB[2] passage and intracellular mechanism of action
  - Safe, T-cell-independent vaccines
  - Highly specific (low nM to pM) monoclonal antibodies

Conformation specific

- High selectivity for pathological forms of target proteins
- Strong safety profile



Clinically validated

- 2 Monoclonal antibodies
- 2 Liposomal vaccines
- 1 Small molecule
- 2 PET[3] tracers

Precision medicine enabling

- First-/best-in-class companion diagnostics
  - Earlier, more reliable diagnosis
  - Treatment according to underlying pathology
  - Prevention through early, safe intervention

(1) Central nervous system; (2) Blood-brain barrier; (3) Positron emission tomography

Positioned for precision medicine

Suite of novel therapeutics and diagnostics enable differentiated approach

2

Clinically validated technology platforms fuelling future growth

9

Therapeutic product candidates

3

Diagnostic product candidates

5

Key molecular targets addressed

6

Candidates in clinical trials

4

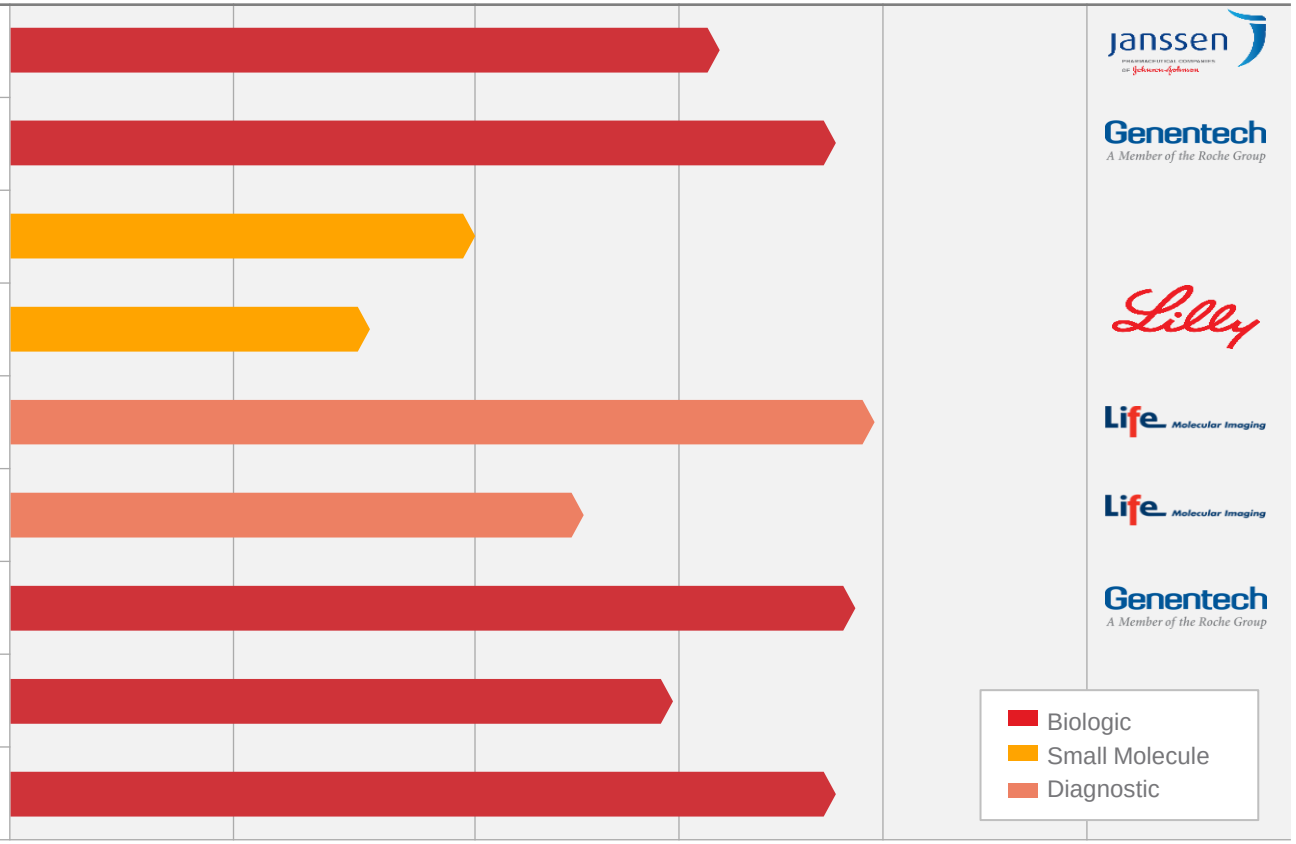
Collaborations with major pharmaceutical companies

Broad and robust pipeline in neurodegenerative diseases

Driven by validated proprietary technology platforms for sustained growth

Established Targets Pipeline

TARGET	PRODUCT CANDIDATE	INDICATION	PARTNER
Tau	**ACI-35.030** *(anti-pTau vaccine)*	AD[1] treatment	Janssen
	Semorinemab *(anti-Tau antibody)*	AD treatment (*moderate*)	Genentech
	Morphomer™ Tau aggregation inhibitor	Rare Tauopathies (ACI-3024)	Lilly
		AD treatment	
	Tau-PET[2] tracer	AD diagnostic	Life Molecular Imaging
		PSP[3] diagnostic	Life Molecular Imaging
Abeta	**Crenezumab** *(anti-Abeta antibody)*	AD prevention[4]	Genentech
	ACI-24 *(anti-Abeta vaccine)*	AD treatment (*Down syndrome[5]*)	
		AD treatment	



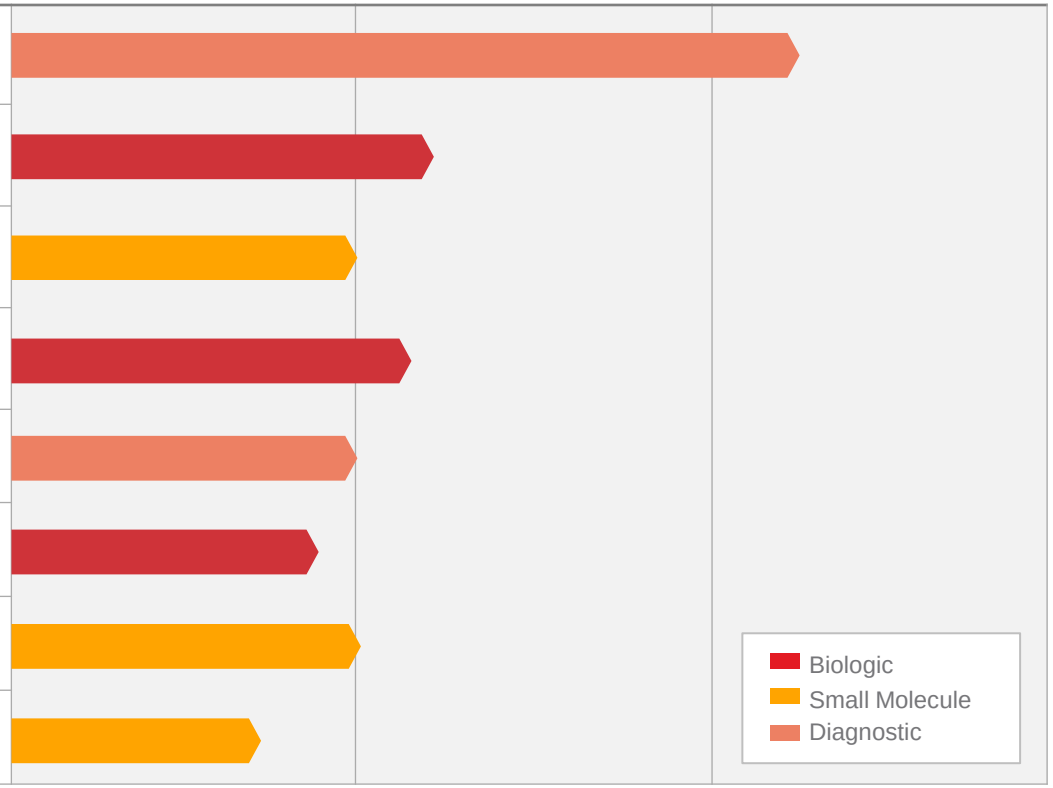
(1) Alzheimer's disease; (2) Positron emission tomography; (3) Progressive supranuclear palsy; (4) Prevention trial API-ADAD in Colombia; (5) Down syndrome-related Alzheimer's disease

Broad and robust pipeline in neurodegenerative diseases

Diversification into non-AD[1] and non-CNS[2] diseases

Novel Targets Pipeline

TARGET	PRODUCT CANDIDATE	INDICATION
a-synuclein (a-syn)	**A-syn-PET[3] tracer**	PD[4], a-synucleinopathies
	Anti-a-syn antibody	PD, NeuroOrphan
	Morphomer™ a-syn *(a-syn inhibitor)*	PD, a-synucleinopathies
TDP-43	**Anti-TDP-43[5] antibody**	LATE[6], NeuroOrphan
	TDP-43-PET tracer	TDP-43-opathies
Inflammasome	**Anti-NLRP3[7]-ASC[8] antibody**	NeuroOrphan
	Morphomer NLRP3-ASC	Non-CNS
	Morphomer NLRP3-ASC	NeuroOrphan



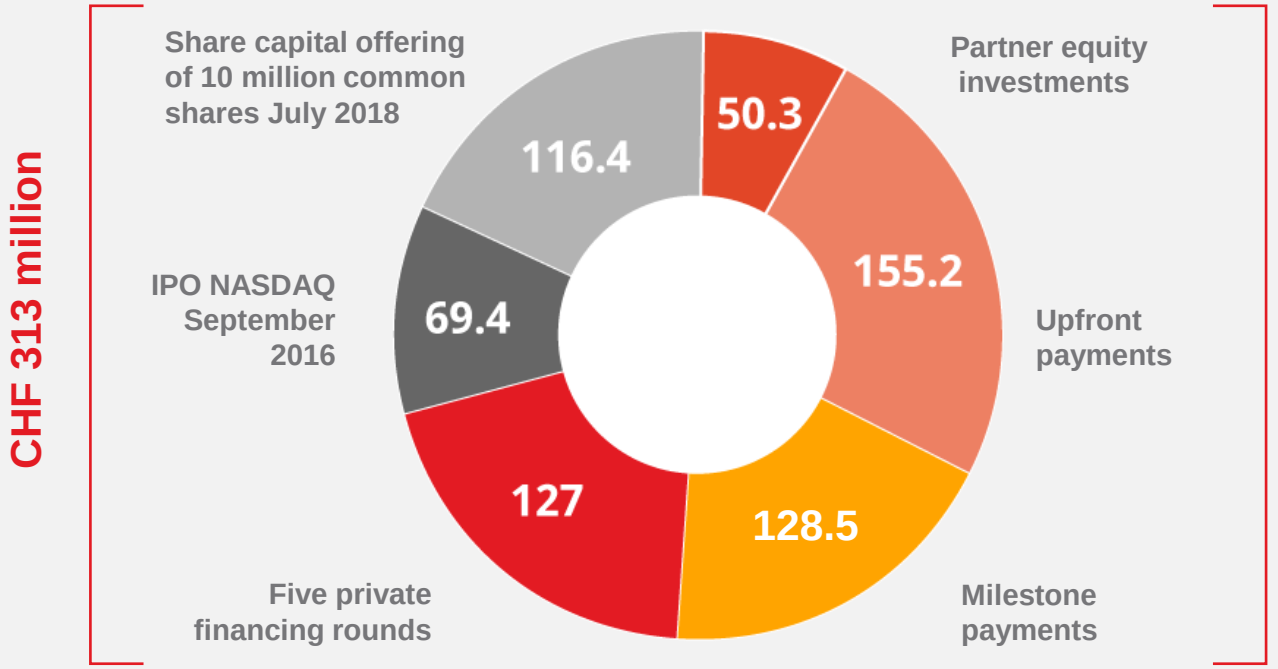
(1) Alzheimer's disease; (2) Central nervous system; (3) Positron emission tomography; (4) Parkinson's disease; (5) TAR DNA-binding protein 43; (6) Limbic-predominant age-related TDP-43 encephalopathy; (7) (NOD)-like receptor protein 3; (8) Apoptosis-associated speck-like protein containing a CARD, also PYCARD

Substantial funds from partnerships complement equity investments

Distinguished institutional investors[1]

B.A:M:
Fidelity INVESTMENTS
BlackRock
LSP
INVUS
BVF PARTNERS L.P.
TEKLA Capital Management LLC
PROSIGHT CAPITAL
TEMASEK

Corporate funding to date[2] (in CHF millions)



- CHF 313 million from investor funds
- CHF 334 million in partnering related funds[3,4]
- CHF 3 billion in total potential payments plus potential royalties outstanding

(1) Based on latest schedule 13G and 13F filings; (2) Converted to CHF based on exchange rates at times of receipt; (3) Milestone payments as of June 30, 2020; (4) With Lilly convertible loan

AC Immune

Broadest anti-Tau pipeline has generated CHF 264 million in cash

Product candidates	Therapies and Diagnostics:			
	antibody	vaccine	small molecule	diagnostic
				
Current focus[1]	AD[2]	AD	AD, NeuroOrphan	AD, PSP[3]
Partner	Genentech A Member of the Roche Group	janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson	Lilly	Life Molecular Imaging
Cash received	**CHF 59 million**	**CHF 31 million**	**CHF 170 million**	**EUR 3.5 million**

(1) Programs can be expanded into additional Tauopathies; (2) Alzheimer's disease; (3) Progressive supranuclear palsy

Spotlight on key Morphomer™ licensing deals[1]

Proprietary pipeline assets carry substantial future deal value

Therapeutic: Tau Morphomer small molecules (in millions)	
Total value	CHF 1,860
Upfront payment	CHF 80 + USD 50 equity investment
Milestones received to date	CHF 40
Next milestone	CHF 60 at Phase 2 start
Royalties	Low-double digits to mid-teens
Partner	Lilly

Diagnostic: Tau PET imaging agent (in millions)	
Total value (millions)	EUR 160
Upfront payment	EUR 0.5
Milestone received to date	EUR 3
Royalties	Mid-single digits to low teens
Partner	Life Molecular Imaging

(1) Disclosure limited due to confidentiality agreements with collaboration partners

Substantial market & partnership opportunities for novel targets pipeline

Combination of very large and NeuroOrphan indications

Large Indications		
Alzheimer's disease	**Parkinson's disease**	**LATE[5]**
Prevalence: Affects 50M globally[1]	Prevalence: >6.1M globally[4]	Prevalence: 20-50% of individuals over age 80[6]
Tau, NLRP3[2]-ASC[3]	a-synuclein, NLRP3-ASC	TDP-43[7]
Partner (Tau): Lilly NLRP3-ASC: AC Immune	Therapeutic: Diagnostic: AC Immune	Therapeutic: Diagnostic: AC Immune

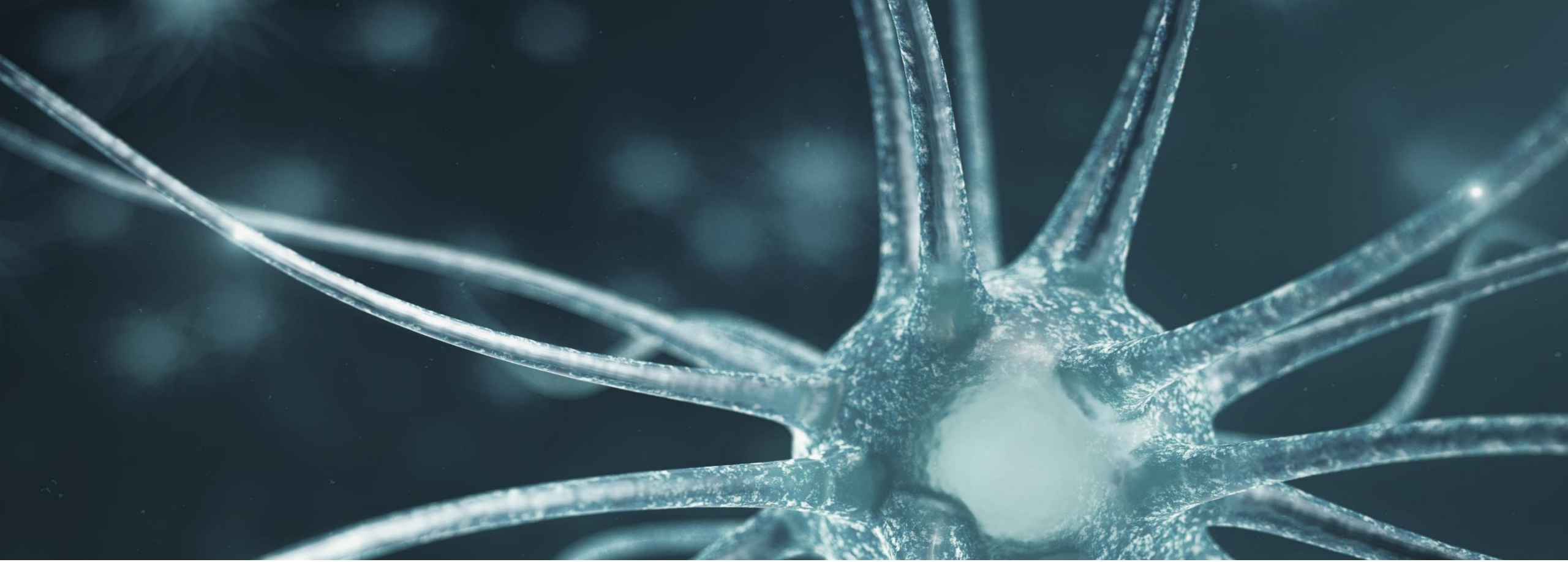
NeuroOrphan Indications			
Progressive Supranuclear Palsy	**Multiple System Atrophy**	**Amyotrophic Lateral Sclerosis**	**Frontotemporal Lobar Degeneration**
Prevalence: ~20K in U.S.[8]	Prevalence: 15-50 K in U.S.[9]	Prevalence: 15-30K in U.S.[10,11]	Prevalence: 20-30K in U.S.[12]
Tau	a-synuclein	TDP-43	TDP-43
Therapeutic: with partners Partner (diagnostic): Life Molecular Imaging	Therapeutic: Diagnostic: AC Immune	Therapeutic: Diagnostic: AC Immune	Therapeutic: Diagnostic: AC Immune

(1) The World Alzheimer Report 2019; (2) (NOD)-like receptor protein 3; (3) Apoptosis-associated speck-like protein containing a CARD, also called PYCARD (4) GBD 2016 Parkinson's Disease Collaborators *Lancet Neurology* 2018; (5) Limbic-predominant age-related TDP-43 encephalopathy; (6) Nelson et al. *Brain* 2019; (7) TAR DNA-binding protein 43; (8) National Institute of Neurological Disorders and Stroke (NINDS) Progressive Supranuclear Palsy Fact Sheet; (9) NINDS Multiple System Atrophy Fact Sheet; (10) ALS Association *Rare Disease* 2013; (11) NINDS Amyotrophic Lateral Sclerosis Fact Sheet; (12) Knopman and Roberts *J. Mol. Neurosci.* 2011

Drivers of value creation in 2021 and beyond

Accelerate late-stage clinical development	▪ ACI-35.030 in Alzheimer's disease (partnered with Janssen) ▪ ACI-24 in Down syndrome (wholly owned)
Focus on NeuroOrphans	▪ Accelerate development of anti-TDP-43[1] antibodies and small molecule Tau aggregation inhibitor candidates in NeuroOrphan indications
Expand Morphomer™ Platform	▪ Prioritize development of small molecule portfolio, e.g. a-syn[2] ▪ Generate companion diagnostic for precision medicine
Advance neuroinflammation	▪ Maximize value of neuroinflammation programs ▪ Expand strategic focus within and beyond CNS[3]
Sustained financial strength	▪ Further enhance financial strength ▪ Explore regional / global partnerships in specific programs

(1) TAR DNA-binding protein 43; (2) Alpha-synuclein; (3) Central nervous system

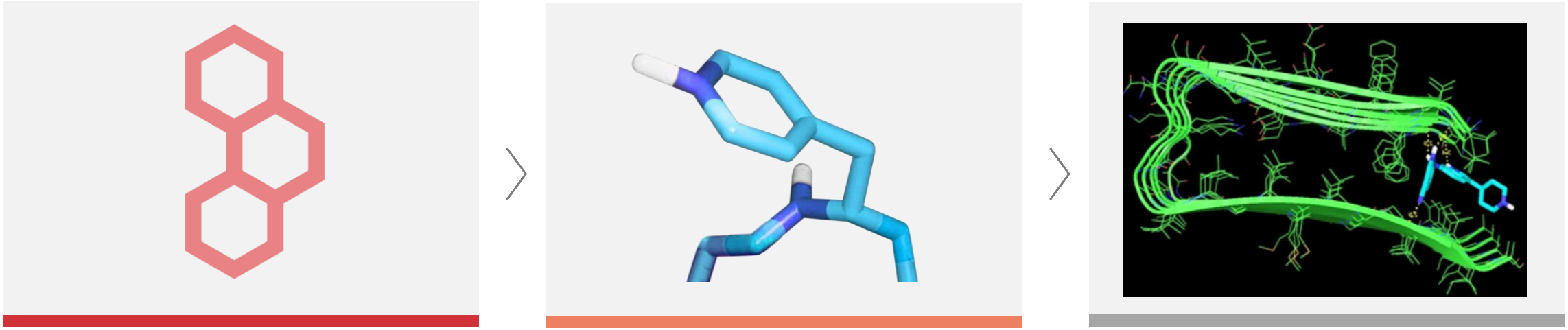


Morphomer™ platform introduction

Marie Kosco-Vilbois, PhD, Chief Scientific Officer

Proprietary Morphomer™ technology

CNS[1] drug discovery and development platform



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

(1) Central nervous system

Morphomer™ pipeline in neurodegenerative diseases

Enables multiple high-value therapeutic and diagnostic opportunities

Morphomer™ programs

TARGET	PRODUCT CANDIDATE	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	PARTNER
Tau	**Morphomer™ Tau aggregation inhibitor**	Rare Tauopathies (ACI-3024)						Lilly
		AD[1] treatment						
	Tau-PET[2] tracer	AD diagnostic						Life Molecular Imaging
		PSP[3] diagnostic						Life Molecular Imaging
a-synuclein (a-syn)	**a-Syn-PET tracer**	PD[4], a-synucleinopathies						
	Morphomer™ a-syn *(a-syn inhibitor)*	PD, a-synucleinopathies						Proprietary Programs
TDP-43	**TDP-43[5]-PET tracer**	TDP-43-opathies						
Neuro-inflammation	**Morphomer™ NLRP3[6]-ASC[7]**	Non-CNS[8]						
	Morphomer™ NLRP3-ASC	NeuroOrphan						

Therapeutic
Diagnostic

(1) Alzheimer's disease; (2) Positron emission tomography; (3) Progressive supranuclear palsy; (4) Parkinson's disease; (5) TAR DNA-binding protein 43; (6) (NOD)-like receptor protein 3; (7) Apoptosis-associated speck-like protein containing a CARD, also called PYCARD; (8) Central nervous system

Morphomer™: Key advantages/benefits

Innovating development with first- and best-in-class candidates

1. **CNS[1]-optimized** compounds with favorable brain penetration and pharmacokinetics
2. **Rationally designed, highly selective** candidates bind intracellular protein aggregates
3. **Focused library** of ~12,000 conformation-specific compounds reflecting years of research know-how
4. **Proprietary suite of assays** to identify and validate successful compounds
5. **Broadly applicable** for potentially disease-modifying therapeutics and precision diagnostics

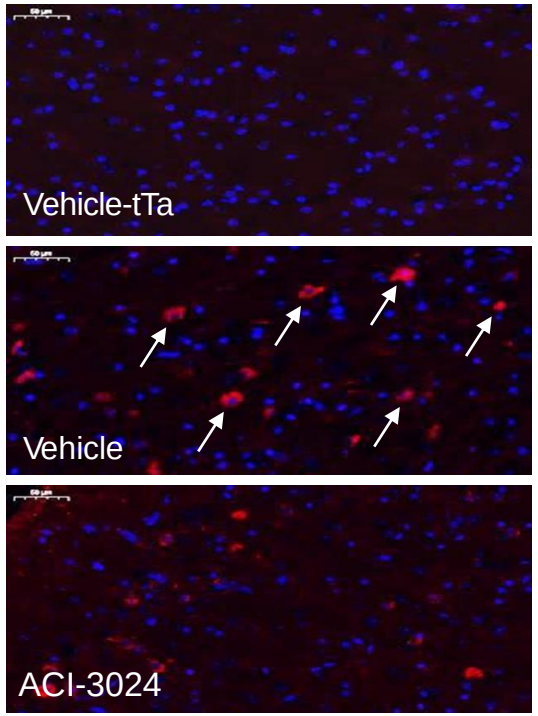
(1) Central nervous system

1

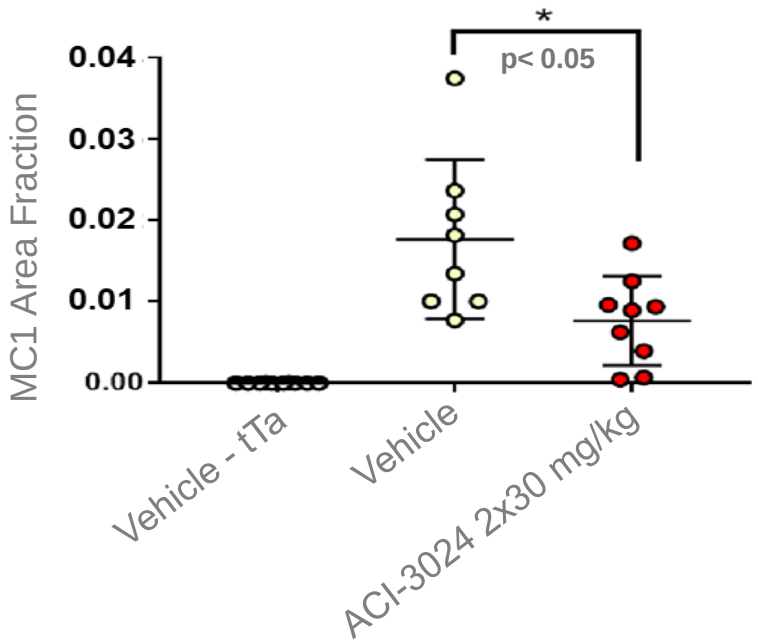
CNS[1]-optimized compounds with favorable brain penetration

Disaggregation capacity of Tau aggregation inhibitor, ACI-3024, in brains of Tg4510 mice

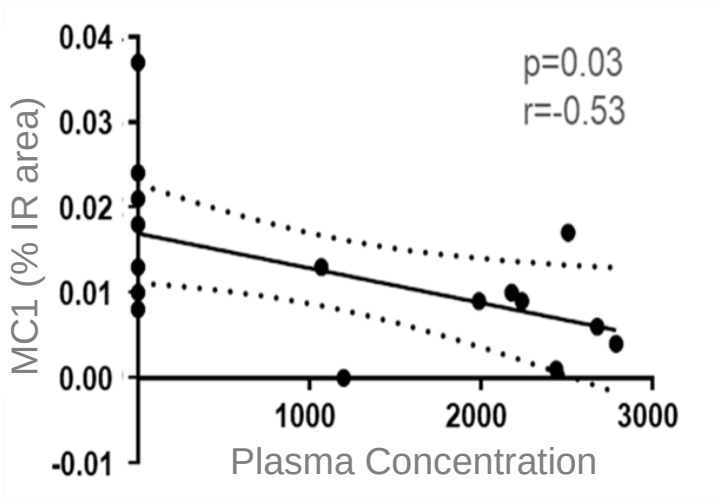
IHC[2] with MC1 in red for misfolded Tau and DAPI in blue for nuclei



Area of misfolded Tau levels in brain sections



MC1 area correlates with drug concentration



Poli S, *et al.*, CTAD 2018

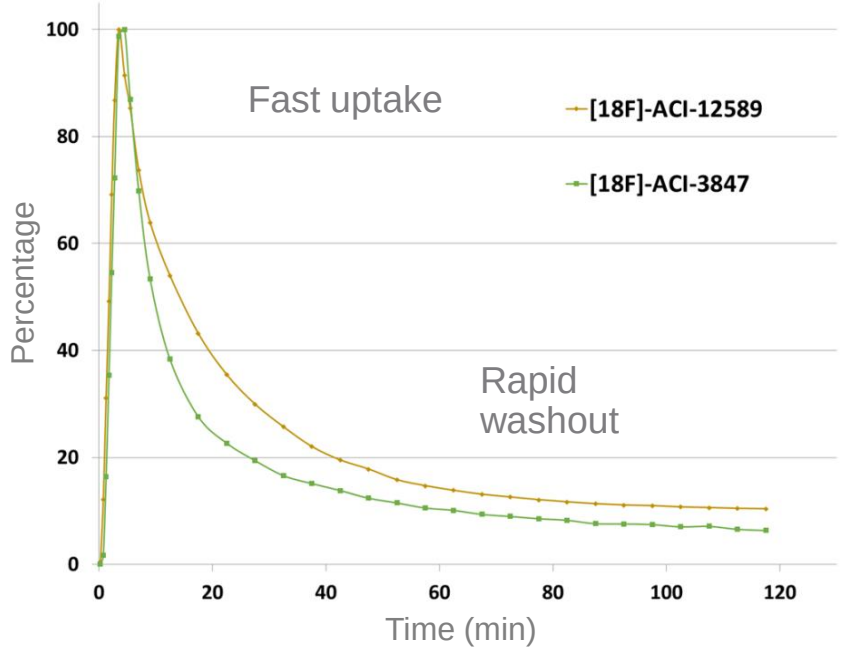
- Treatment with ACI-3024 significantly reduced misfolded Tau in the brains where the pathology is manifested
- The decrease was proportional to the plasma exposure to ACI-3024

(1) Central nervous system (2) Immunohistochemistry

1

CNS[1]-optimized compounds with favorable pharmacokinetics

Ideal pharmacokinetic profile for a-syn[2] tracers in non-human primates



	Brain uptake (min to C_{max})	Brain uptake (%ID[3]/g)	Remaining at 120 min (% of C_{max})
ACI-12589	3.5	4.3	10
ACI-3847	4.5	2.6	6

Capotosti F, *et al.*, AD/PD™ 2021

- Both candidates display a pharmacokinetic profile in non-human primates suitable for use as brain PET[4] tracers with good and fast brain uptake, homogeneous distribution as well as rapid and complete washout

(1) Central nervous system (2) Alpha-synuclein (3) Injected dose; (4) Positron emission tomography

2

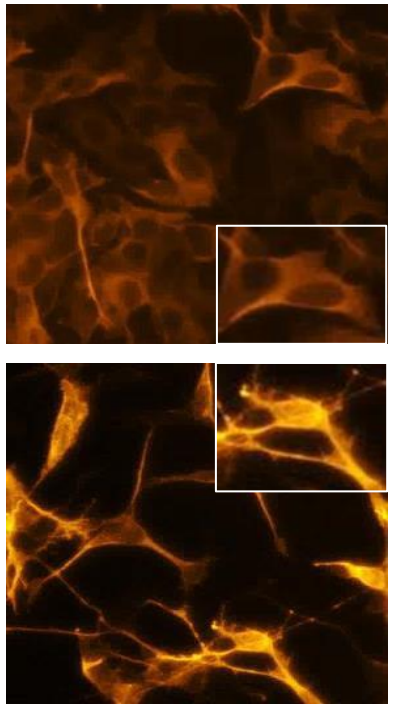
Rationally designed candidates inhibit intracellular protein aggregates

Assessing intracellular Tau misfolding *in vitro* using a human neuroblastoma cell line

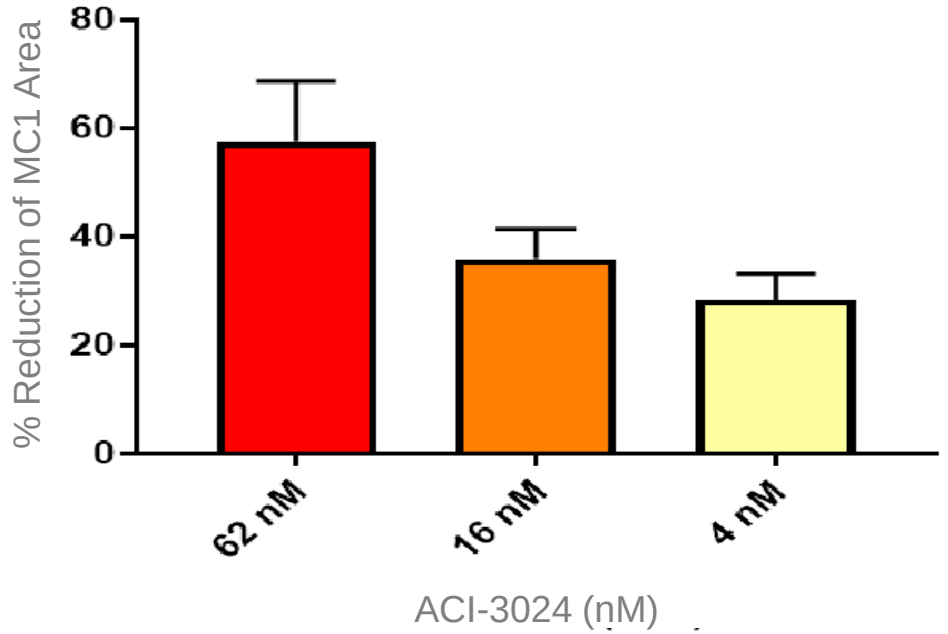
Intracellular labeling of misfolded Tau (MC1)

Undifferentiated cells

Differentiated neurons expressing Tau P301L (retinoic acid induced)



Dose-dependent reduction of misfolded Tau



Poli S, *et al.*, CTAD 2018

- Potent intracellular effect *in vitro*, demonstrating dose-dependent inhibition in the generation of pathological Tau

2 Rationally designed, highly selective candidates to differentiate NDDs[1]

Average distribution volume ratio (DVR)

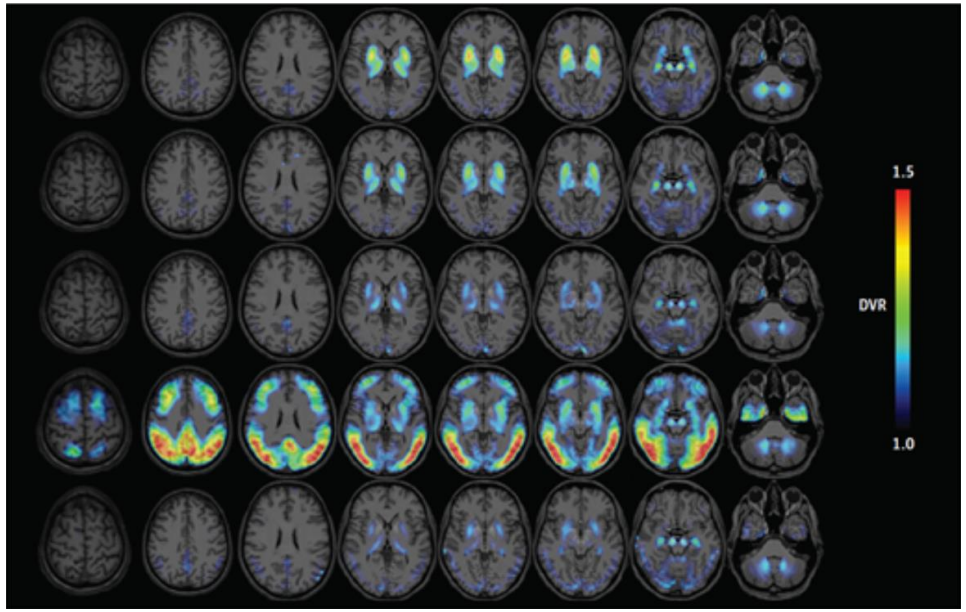
PSP[2]-RS[3]

PSP-non-RS[4]

a-syn[5]

AD[6]

Healthy control



Brendel *et al.*, JAMA Neurology 2020

JAMA Neurology | Original Investigation

July 7, 2020

Assessment of ^{18}F-PI-2620 as a Biomarker in Progressive Supranuclear Palsy

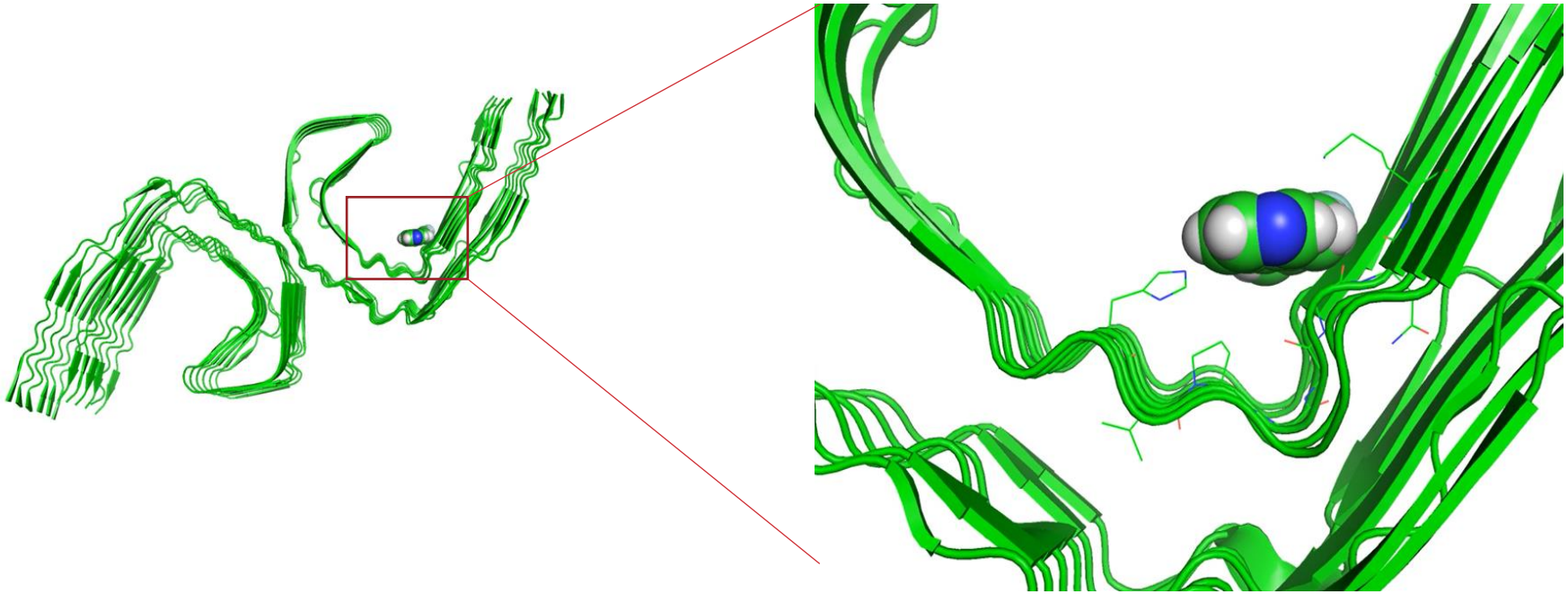
Matthias Brendel, MD, MHBA[1]; Henryk Barthel, MD, PhD[2]; Thilo van Eimeren, MD[3,4,5]; et al

- PI-2620 PET imaging can detect and assess PSP pathology in vivo to establish an earlier and more reliable diagnosis
- Differentiation at the single patient level by semi-quantitative and visual classification (sens./spec. for PSP-RS >80%)

(1) Neurodegenerative diseases; (2) Progressive supranuclear palsy; (3) Richardson syndrome; (4) PSP non-Richardson syndrome; (5) Alpha-synucleinopathies; (6) Alzheimer's disease

3 Focused library of ~12,000 conformation-specific compounds

Model illustrating the binding pocket of Morphomers™ to the beta sheets of Tau aggregates



- Library conceived to bind to beta sheets of misfolded pathological proteins
- Initially 5000 compounds, now expanded to ~12, 000
- Consistently delivers small molecules that can be used to generate therapeutic and imaging agents for Tau, a-syn and TDP-43

3 Focused library reflecting years of research know-how

7

In-house medicinal chemists

41

Outsourced chemistry FTEs[1]

115

Collective years of medicinal chemistry experience

70

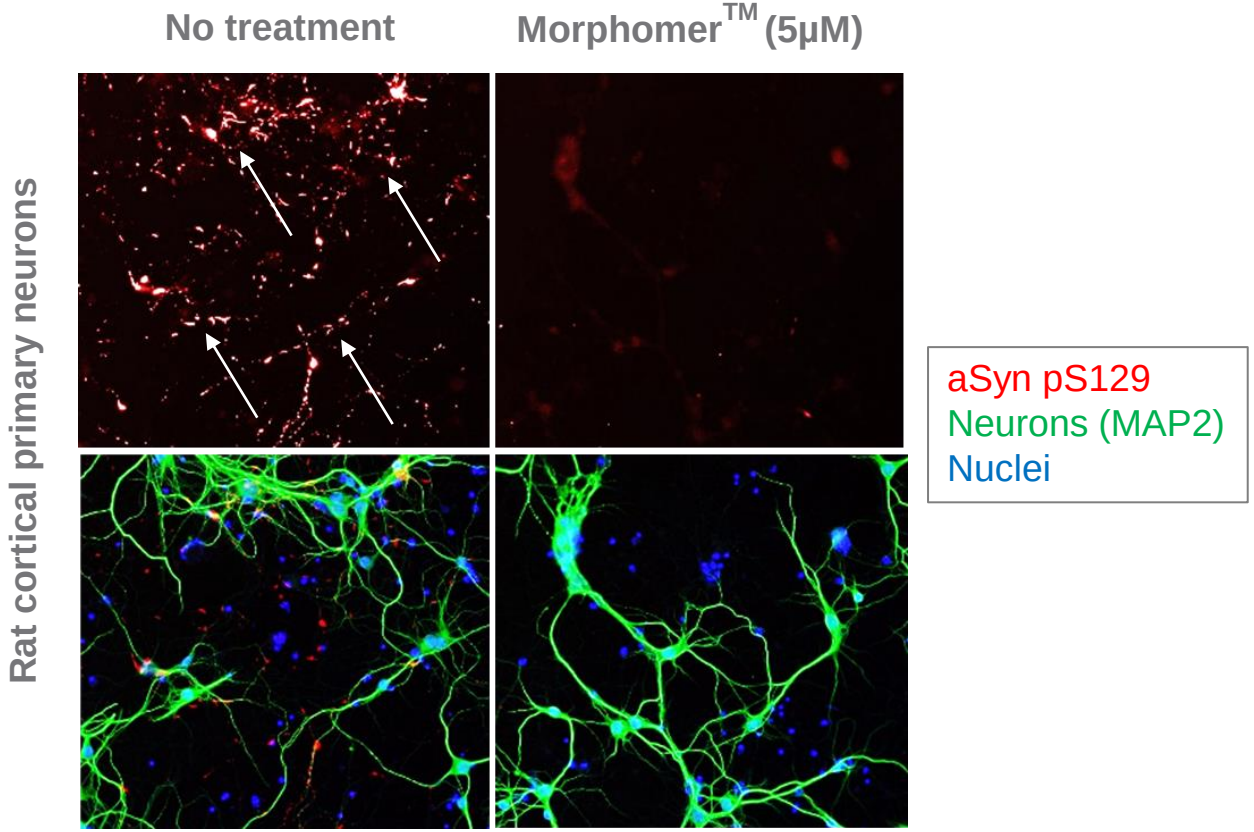
In-house biologists

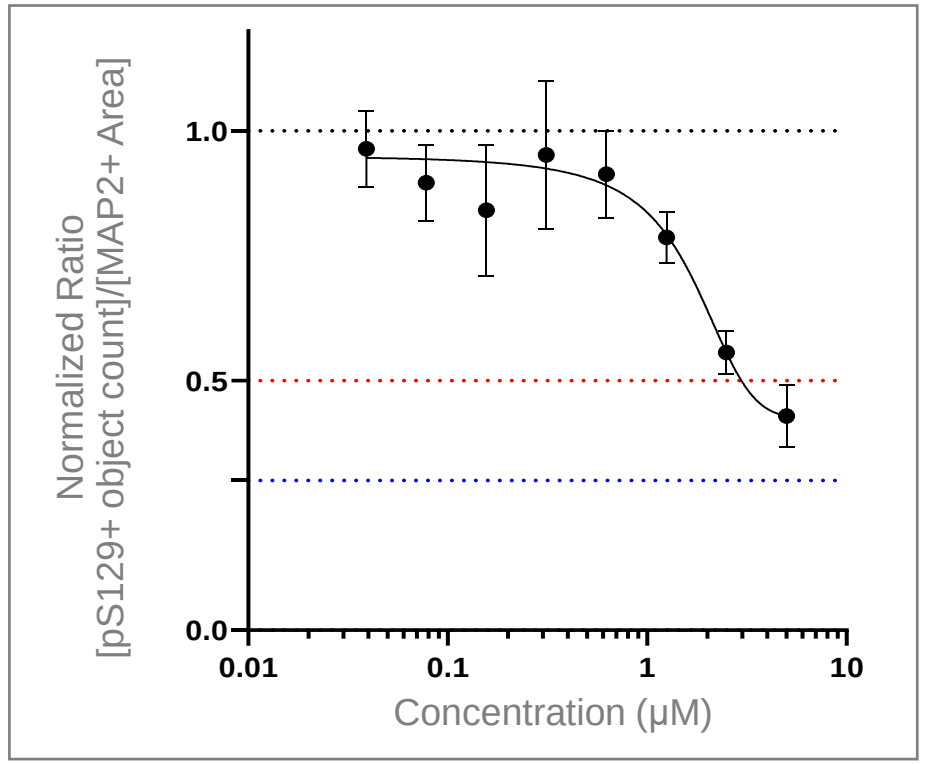
(1) Full-time equivalents

4

Proprietary suite of assays to identify and validate candidates

Screening for a-syn[1] Morphomers™ via intracellular target engagement





Ait-Bouziad N, *et al.*, AD/PD™ 2021

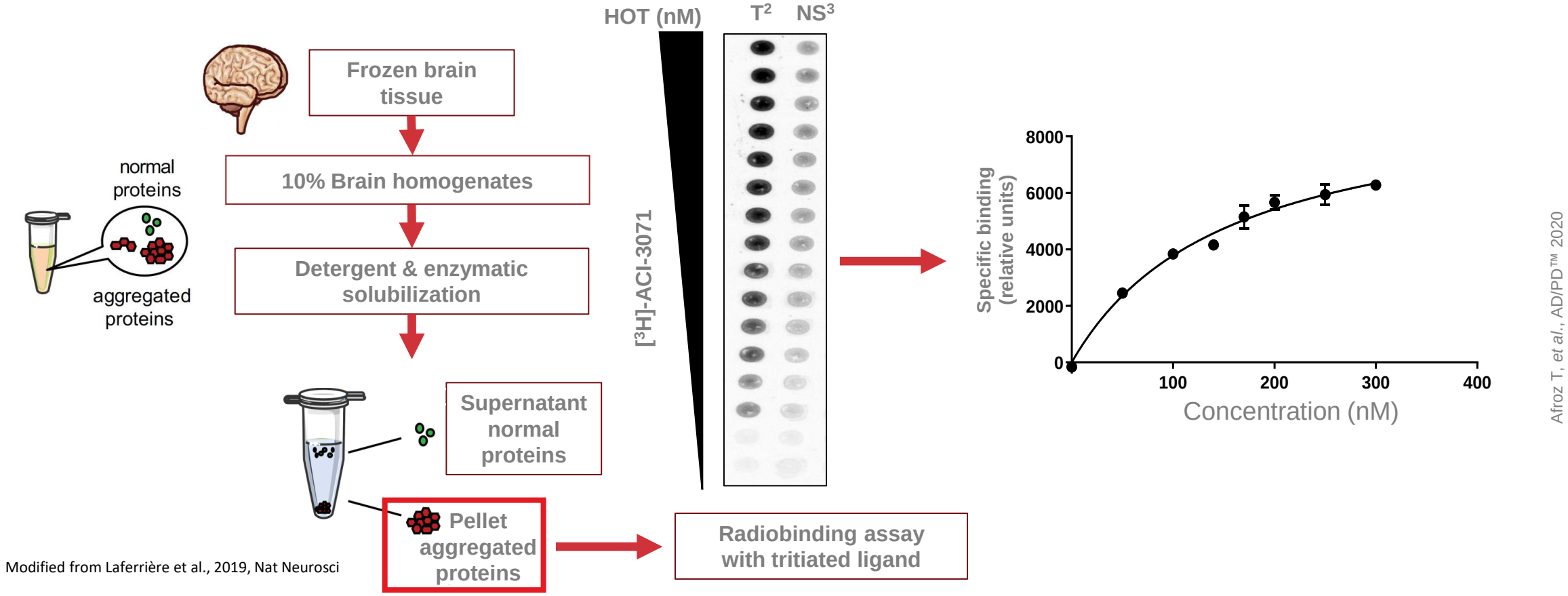
- Developed a proprietary model of a-syn aggregation using primary neurons
- Provides data to establish a candidate's capacity to prevent *de novo* aggregate formation

(1) Alpha-synuclein

4

Proprietary suite of assays to identify and validate candidates

Screening for TDP-43[1] tracers using patient-derived tissue and competitive radiobinding



Modified from Laferrière et al., 2019, Nat Neurosci

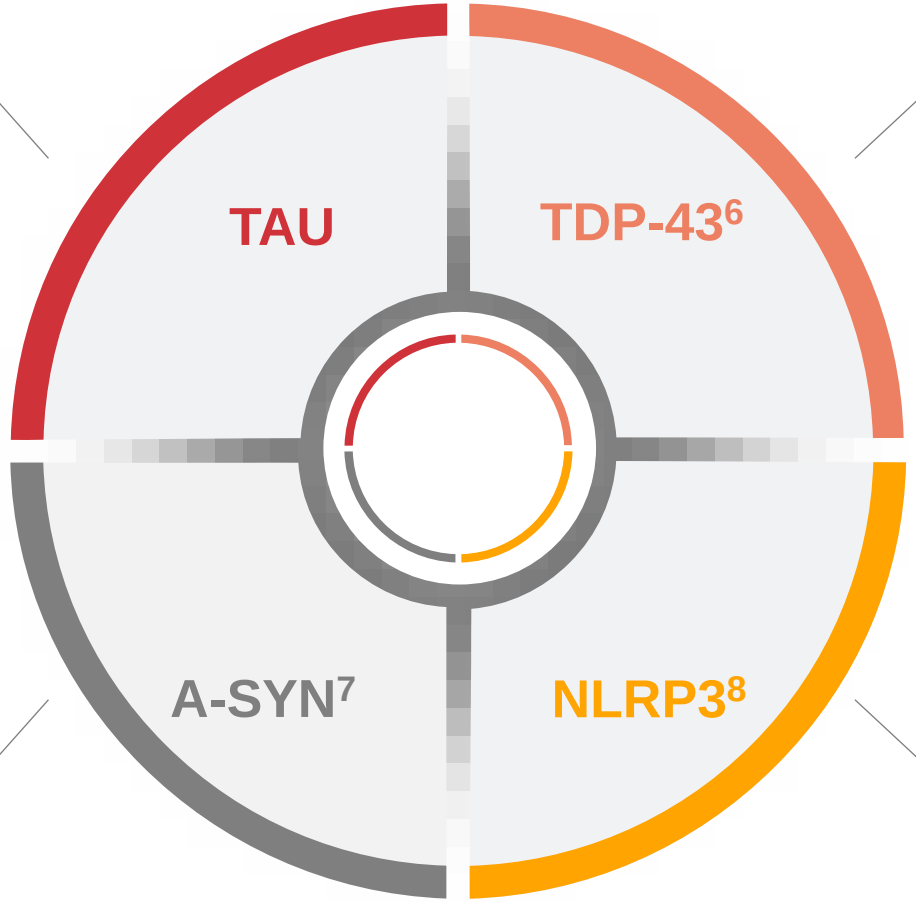
- Protocol isolates pathological TDP-43 from enriched patient-derived aggregates
- Essential to determine compound affinity for pathological aggregates in proprietary micro-radiobinding assays

(1) TAR DNA-binding protein 43; (2) Total binding; (3) Non-specific binding

5

Morphomer™ candidates address key pathologies

Only company with a suite of therapeutics and diagnostics against all major targets in NDD[1]



Alzheimer's disease

PSP,[2] other NeuroOrphan

FTLD[3], ALS[4], other NeuroOrphan

LATE[5]

Alzheimer's disease

Parkinson's disease

Alzheimer's disease

NeuroOrphan

Neuroinflammatory target

Across multiple NDD

(1) Neurodegenerative disease; (2) Progressive supranuclear palsy; (3) Frontotemporal lobar degeneration; (4) Amyotrophic lateral sclerosis; (5) Limbic-predominant age-related TDP-43 encephalopathy; (6) TAR DNA-binding protein 43; (7) Alpha-synuclein; (8) NOD-like receptor protein 3

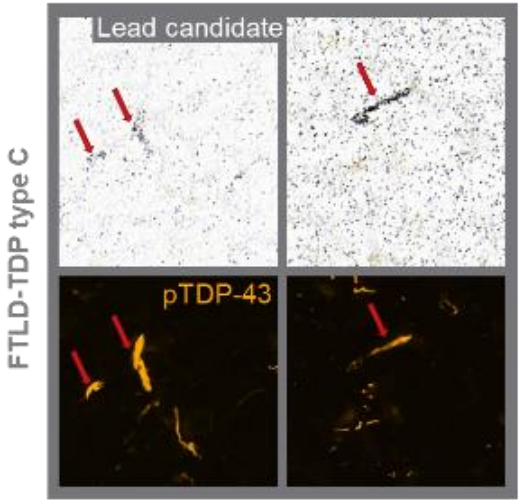
5

TDP-43[1]: growing understanding underscores need and opportunity

No diagnostic or therapeutic intervention directly targeting TDP-43 available or in clinic

- RNA/DNA-binding protein that functions as a regulator of gene transcription and RNA metabolism
- Cytoplasmic aggregation of TDP-43 is a major pathology in Alzheimer's disease and several other NDDs[2]
- Strongly related to cognitive decline[3] and episodic memory loss[4]
- LATE[5] is a recently defined and highly prevalent TDP-43 pathology that causes age-related dementia that strongly mimics Alzheimer's disease[8]

	Indication	% TDP-43
NeuroOrphan	Amyotrophic lateral sclerosis	97%[6]
	Frontotemporal lobar degeneration	45%[6]
Large Market	Alzheimer's disease	50%[7]
	LATE	100%[8]



Target engagement by TDP-43 PET tracer candidate

Afroz T, *et al.*, AD/PD™ 2021

- TDP-43 is a critical primary target and co-pathology in NeuroOrphan and large CNS indications
- ACIU's first-in-class diagnostics and therapeutics are substantial value creation opportunities

(1) TAR DNA-binding protein 43; (2) Neurodegenerative diseases; (3) Wilson et al., 2013; (4) Nag et al., 2017; (5) Limbic age-related TDP-43 encephalopathy; (6) Ling et al., 2013; (7) Josephs et al., 2014; (8) Schneider AD/PD 2020

5

Therapeutic potential in targeting microglia and NLRP3[1]-ASC[2] pathway

Reducing neuroinflammation through multiple mechanisms

Immune modulation shows great potential in NDD[3]

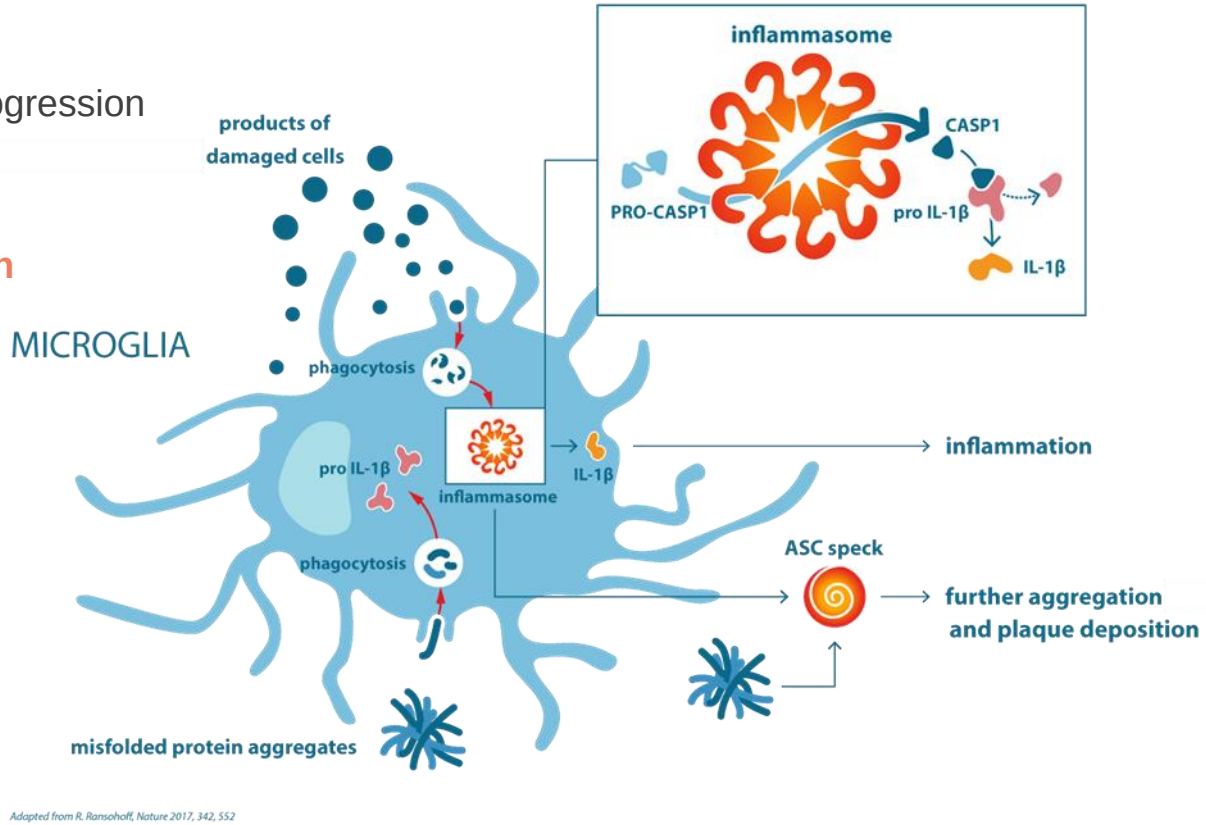
- Hyperstimulated microglia are emerging as a hallmark in NDD
- Hyperstimulation drives inflammation, neuronal death and disease progression

ACIU targets the NLRP3-ASC pathway to reduce neuroinflammation

- Maintain phagocytosis of misfolded proteins
- Decrease pro-inflammatory factors
- Do not alter diffuse mechanisms (side effects)

NLRP3-ASC pathway addressed with two approaches

- Intracellular NLRP3 activity (SMEs[4])
- Extracellular ASC specks (mAbs[5])



(1) (NOD)-like receptor protein 3; (2) Apoptosis-associated speck-like protein containing a CARD, also called PYCARD; (3) Neurodegenerative diseases; (4) Small molecule entities; (5) Monoclonal antibodies

5

Neuroinflammation exacerbates proteinopathy-driven damage

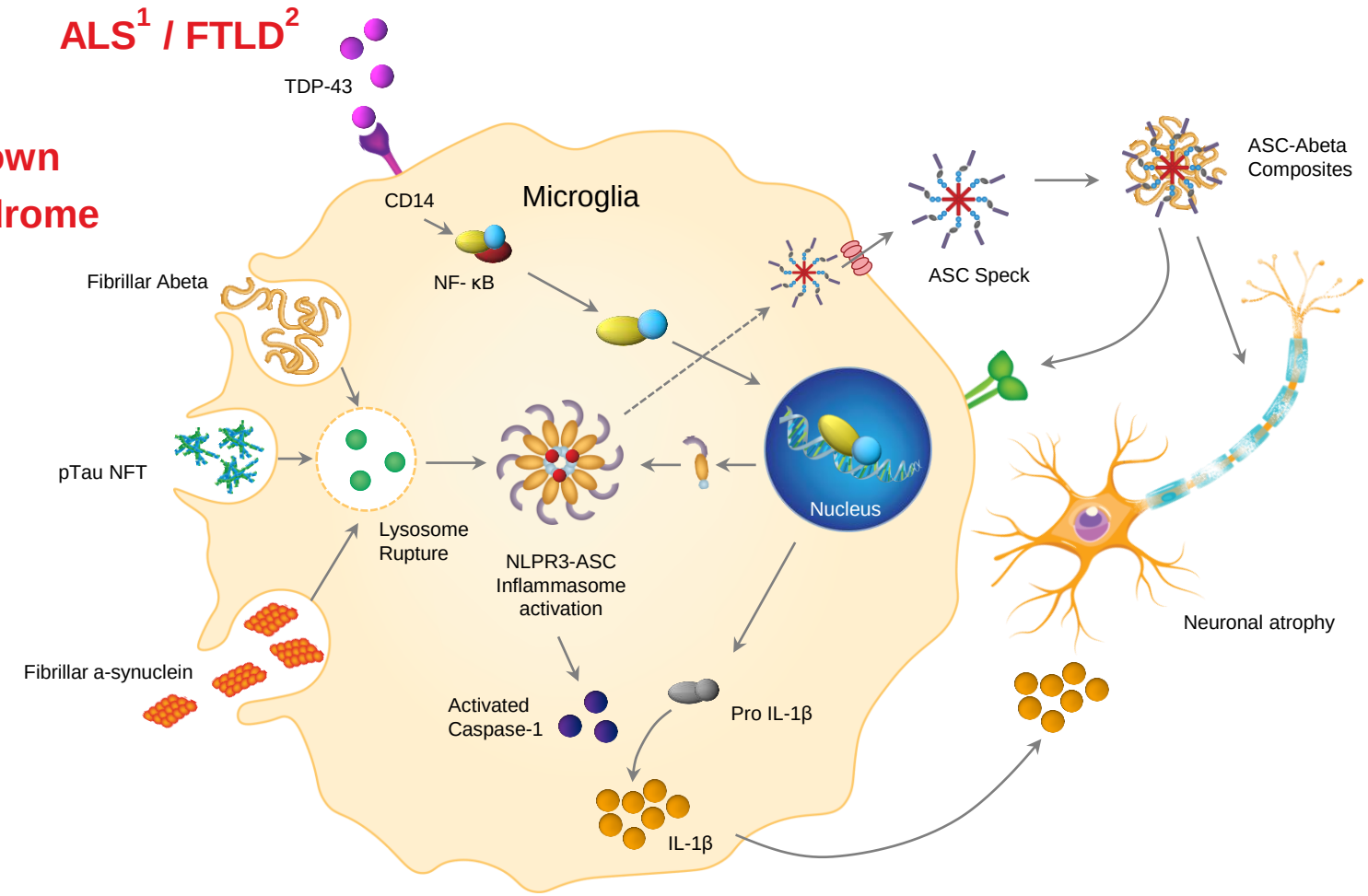
Key target for multiple neurodegenerative diseases

ALS[1] / FTLD[2]

Down syndrome

Alzheimer's disease

Parkinson's disease



(1) Amyotrophic lateral sclerosis; (2) Frontotemporal lobar dementia; (3) TAR DNA binding protein-43; (4) Apoptosis-associated speck-like protein containing a CARD, also called PYCARD; (5) neurofibrillary tangle

Morphomer™: Key advantages/benefits

Accelerating early-stage development with first-/best-in-class candidates

1 **CNS[1]-optimized** compounds with favorable brain penetration and pharmacokinetics

- Able to engage target proteins in any brain compartment

2 **Rationally designed, highly selective** candidates bind intracellular protein aggregates

- Potential for best-in-class efficacy and safety

3 **Focused library** of ~12,000 conformation-specific compounds reflecting years of research know-how

- Remarkable efficiency; library enriched for compounds that bind beta-sheet aggregates
- Rapid hit-to-lead optimization; process enables further expansion and optimization of library

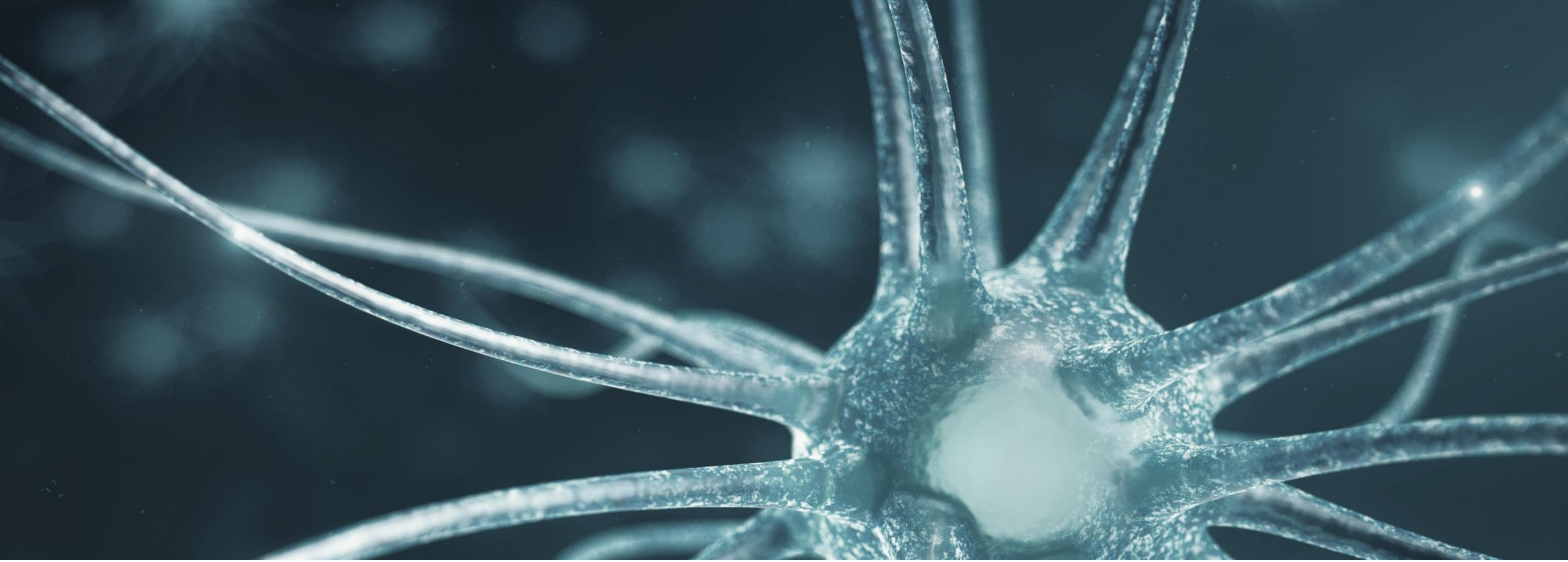
4 **Proprietary suite of assays** to identify and validate successful compounds

- State-of-the-art translational animal models evaluate intended mechanism of action

5 **Broadly applicable** for potentially disease-modifying therapeutics and precision diagnostics

- Able to engage targets intracellularly and extracellularly to disrupt key disease processes
- Able to bind targets with pharmacokinetics optimized for PET[2] imaging

(1) Central nervous system; (2) Positron emission tomography



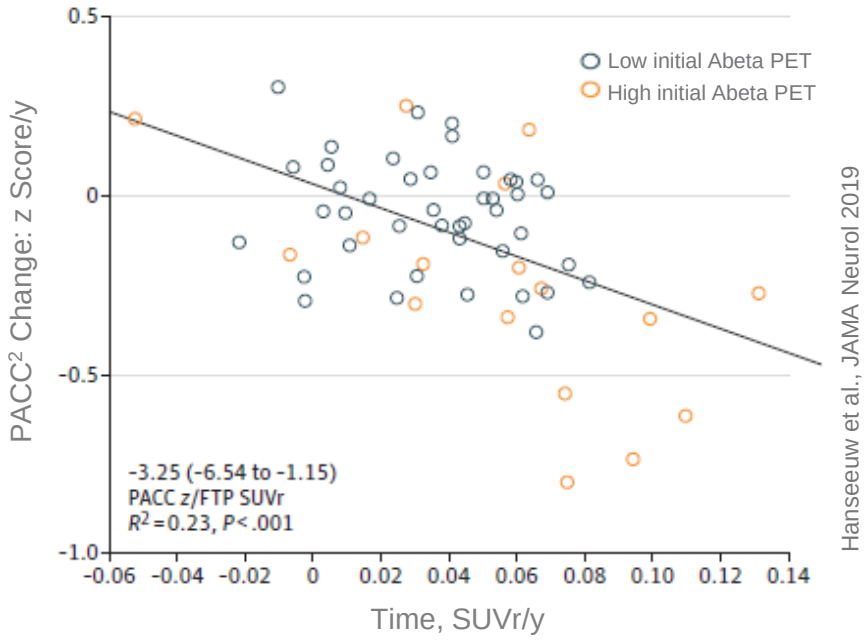
Therapeutic Morphomer™ programs

Sonia Poli, PhD, Life Cycle Leader

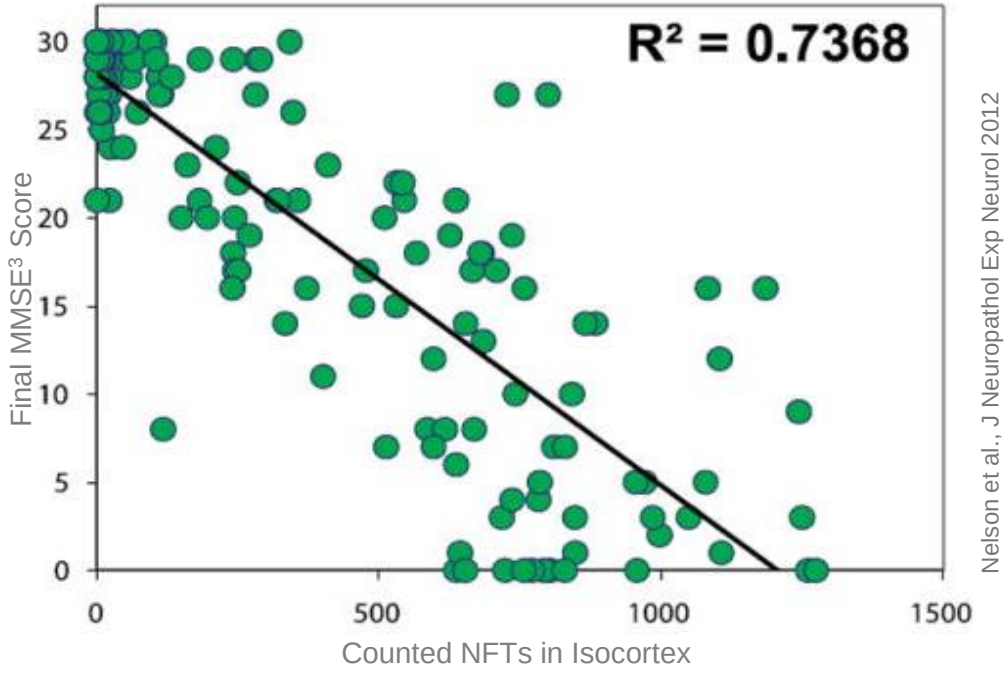
Tau Pathology: Correlation with the rate of cognitive decline

A key driver of Alzheimer's disease pathology with wide therapeutic window

Tau PET[1] changes are closely associated with the rate of cognitive decline



Density of neurofibrillary tangles (NFTs) significantly correlates with final cognitive status

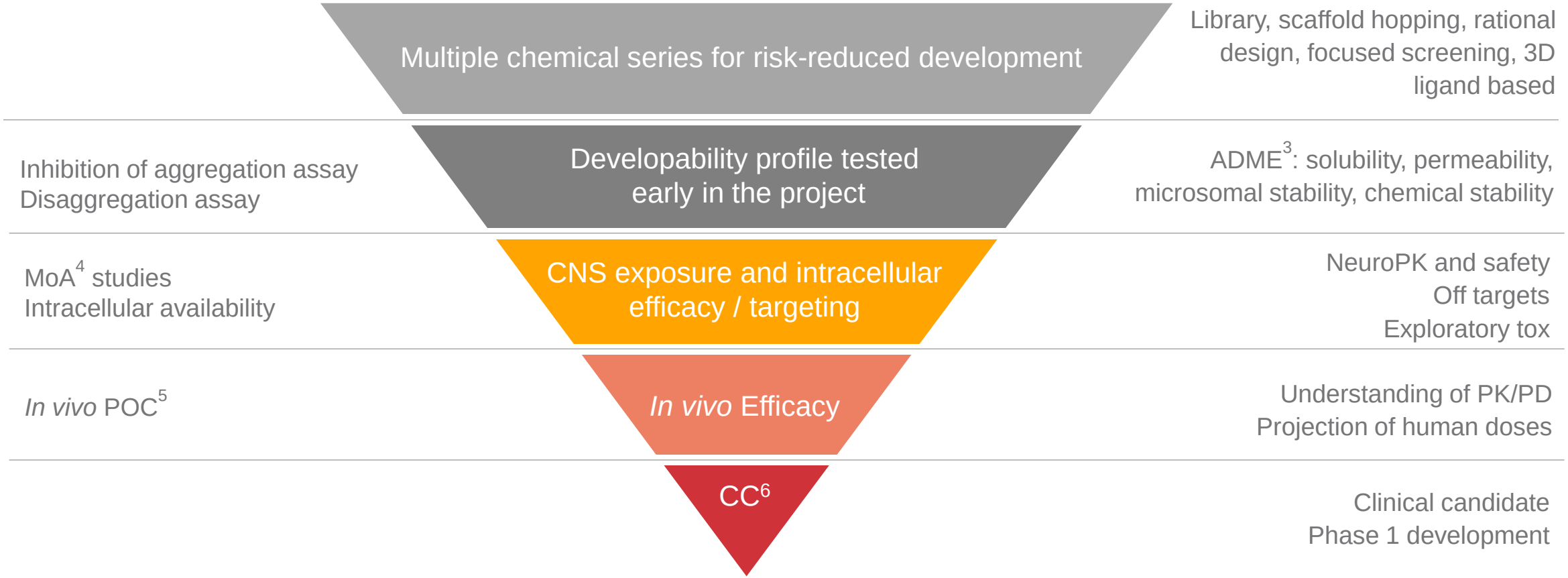


- Tau-targeted approaches may have a much broader therapeutic window to potentially disrupt, slow or prevent disease progression at both early and advanced stages

(1) Positron emission tomography; (2) Preclinical Alzheimer cognitive composite; (3) Mini-mental state examination

Comprehensive screening tailored to CNS[1]-targeted small molecules

Proprietary library and mechanistic assays, combined with BBB[2] and safety assessment



- Lead candidates selected based on proteinopathy-relevant MoA and developability profile for CNS

(1) Central nervous system; (2) Blood-brain barrier; (3) Absorption, distribution, metabolism, and excretion; (4) Mechanism of action; (5) Proof-of-concept; (6) Clinical candidate

Morphomer therapeutics: Discovery and validation of ACI-3024

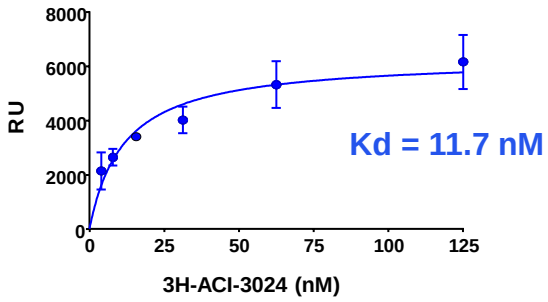
First-in-class, conformation–specific small molecule Tau aggregation inhibitor

- Proprietary library screened for the Tau therapeutic program (>1000 molecules)
- More than 1000 compounds synthesized
- Broad range of technologies employed to achieve optimization (scaffold hopping, rational design, 3D-ligand base)
- ACI-3024 qualified as clinical candidate
- Eight distinct chemical series identified

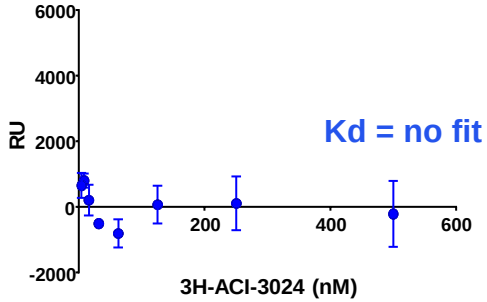
ACI-3024 is highly selective for human pathological Tau

Binding specificity across patient-derived protein aggregates

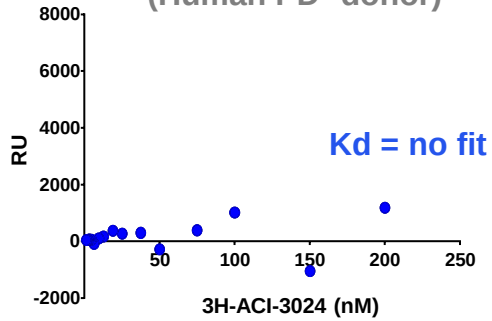
Tau-rich (human AD[1] donor)



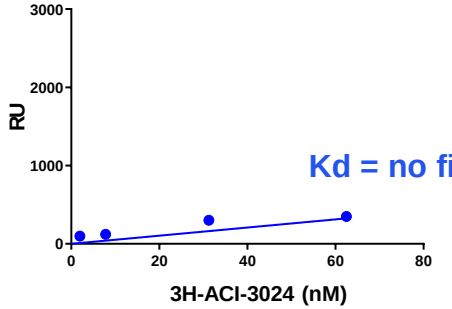
Abeta-rich (human AD donor)



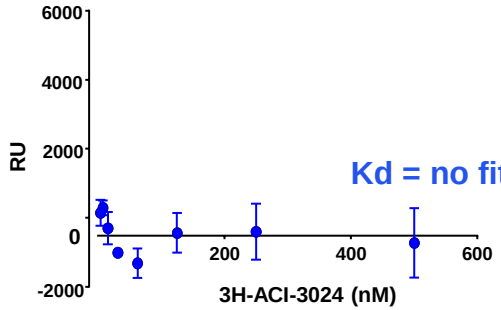
a-Synuclein-rich (Human PD[2] donor)



Tau monomer (recombinant)



Healthy donor



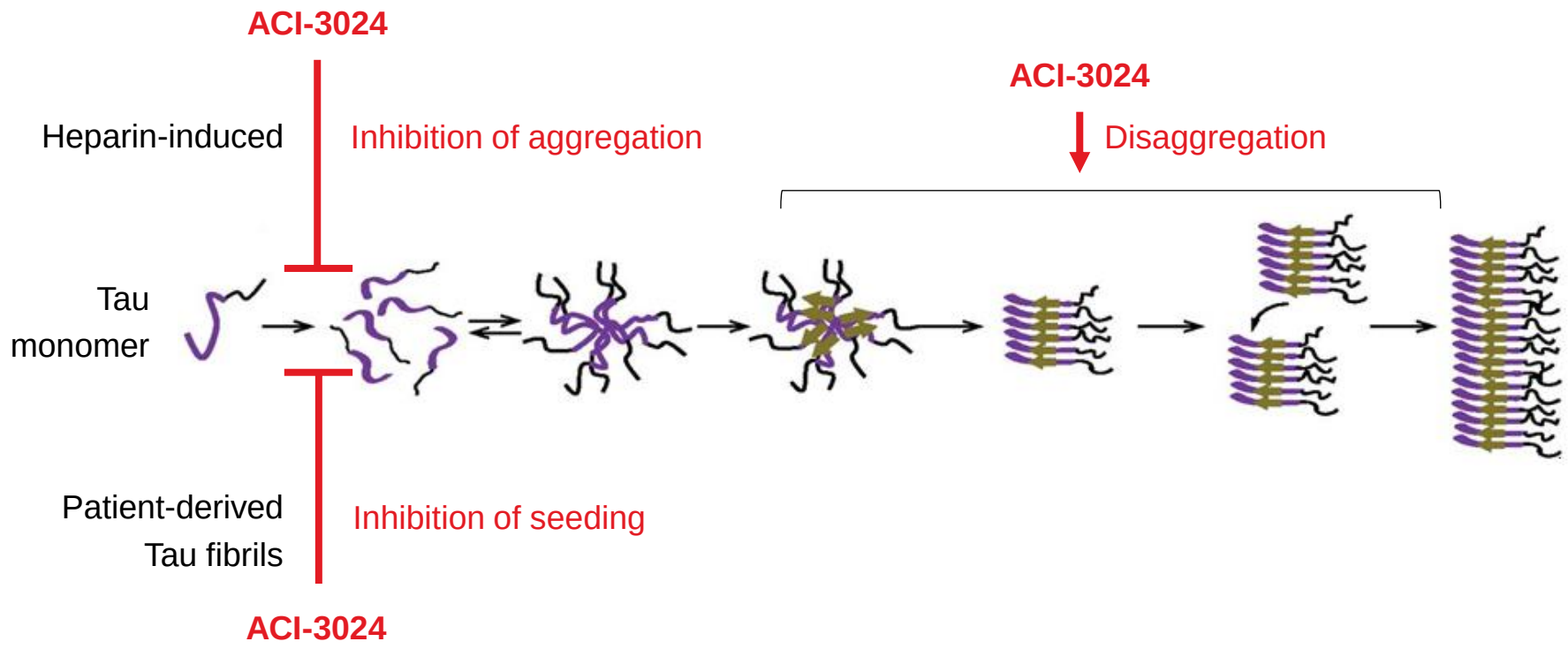
AC Immune unpublished data

- ACI-3024 is highly selective for Tau over Abeta and a-synuclein
- ACI-3024 does not bind to non-pathological Tau monomer

(1) Alzheimer's disease; (2) Parkinson's disease

Characterizing the anti-Tau mechanism of action

Proprietary Tau seeding and aggregation assay



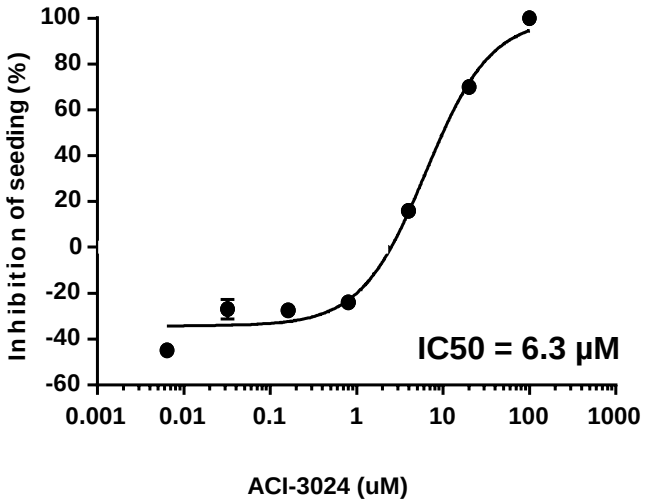
Adapted from Pavlova et al, 2016

- Successfully established series of assays to investigate Morphomer™ Tau aggregation inhibitor *in vitro* efficacy

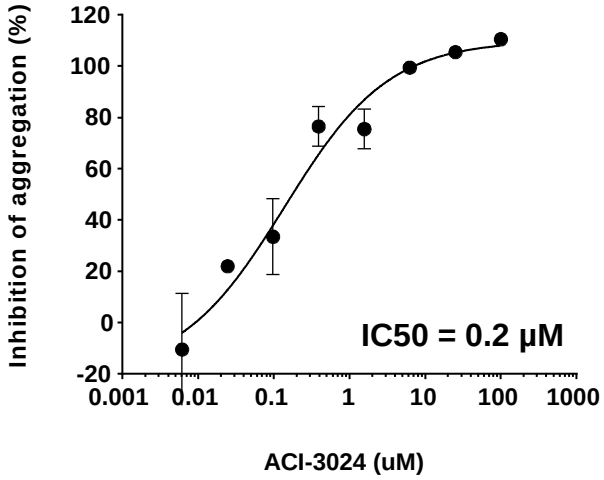
ACI-3024 shows broad *in vitro* activity against Tau aggregation

Multiple points of intervention

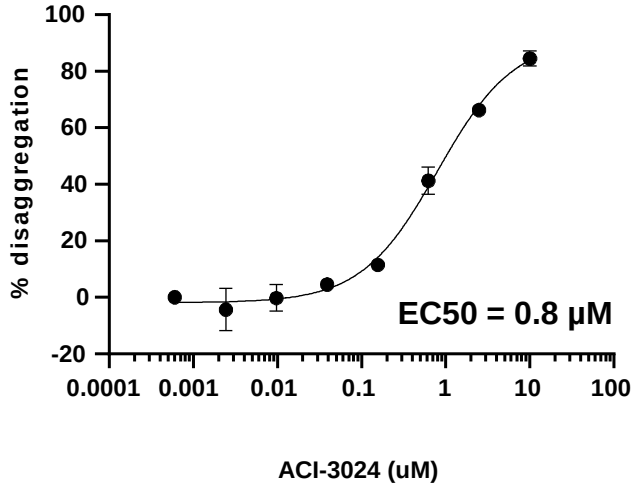
Inhibition of seeding



Inhibition of aggregation



Tau disaggregation



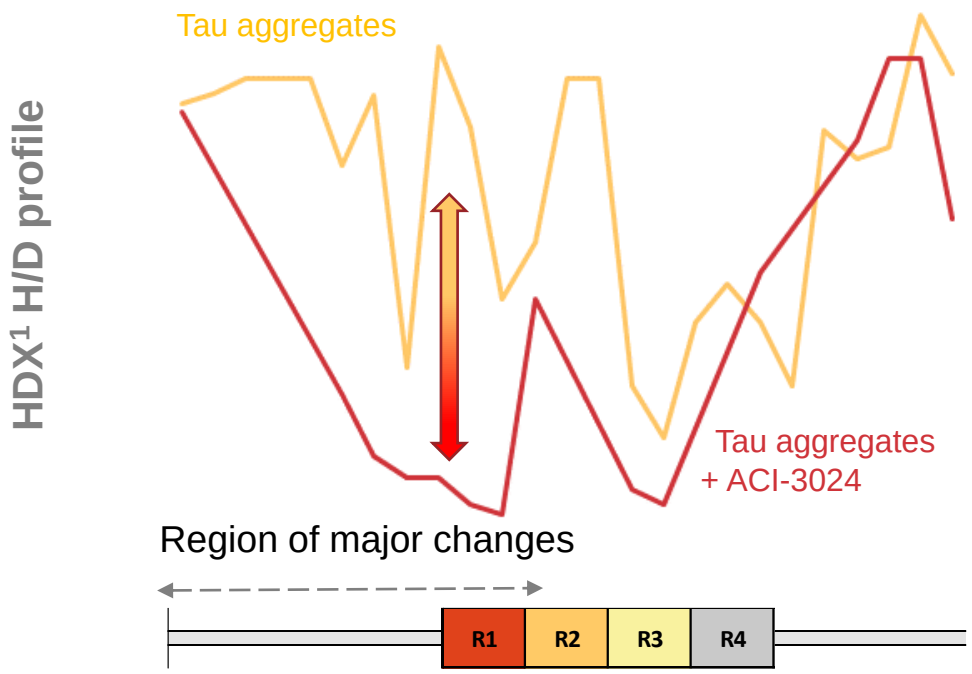
AC Immune unpublished data

- ACI-3024 inhibits Tau seeding, Tau aggregation, and promotes Tau disaggregation

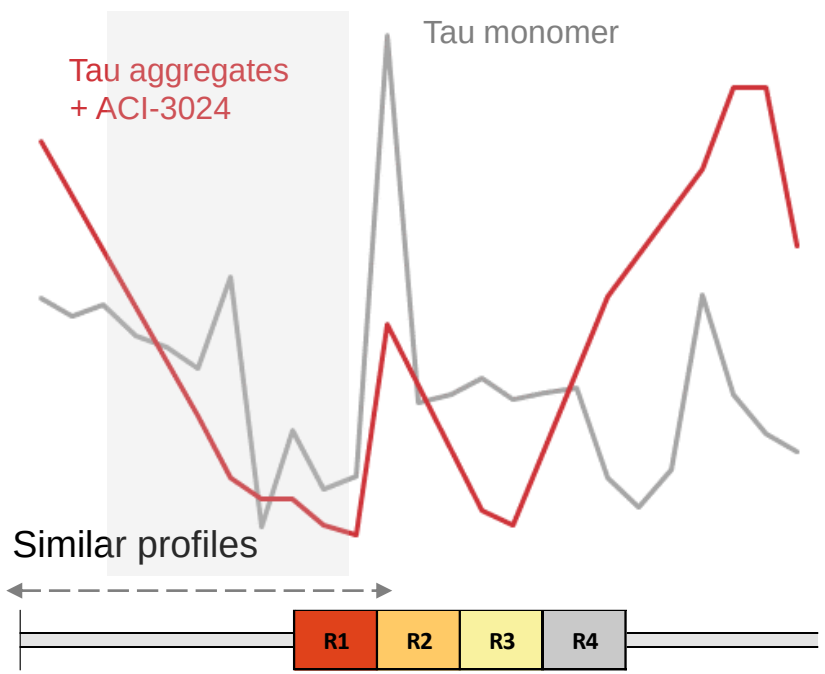
Binding induces conformational change in Tau

Tau aggregates treated with ACI-3024 return to monomer-like conformation

Tau aggregates +/- ACI-3024



ACI-3024 induced changes vs. monomer

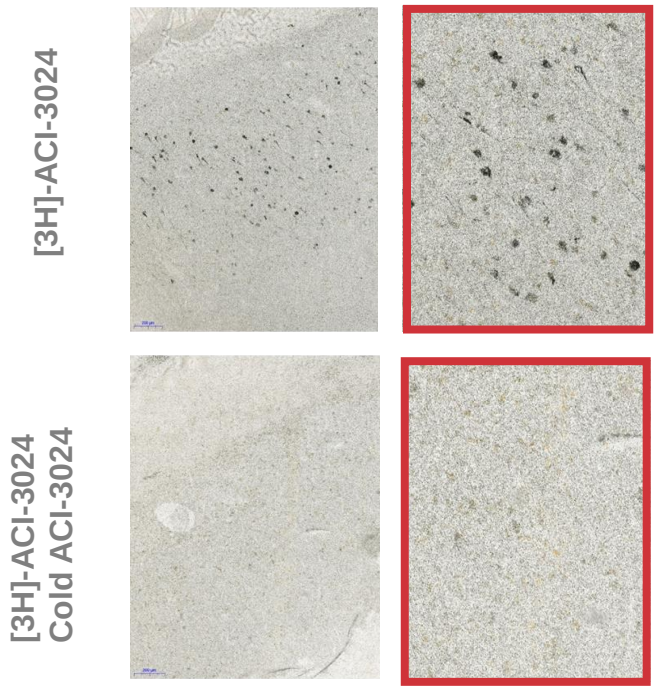


- ACI-3024 induces profound changes within the microtubule binding domain
- Tau aggregates exposed to ACI-3024 change conformation from pathological to monomer like

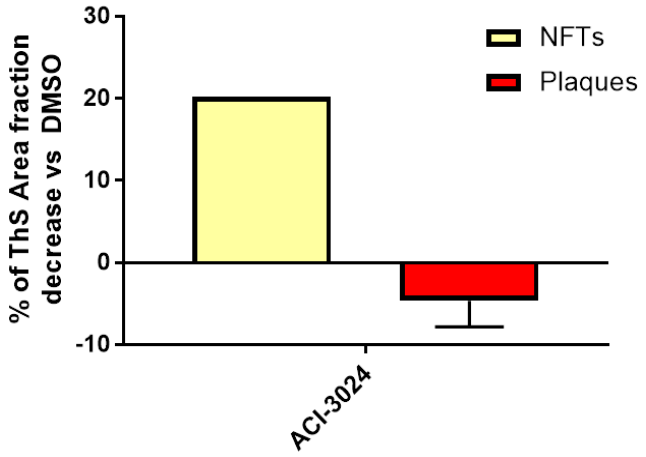
(1) Hydrogen/deuterium exchange

Physiological target engagement and activity in AD[1]-derived samples

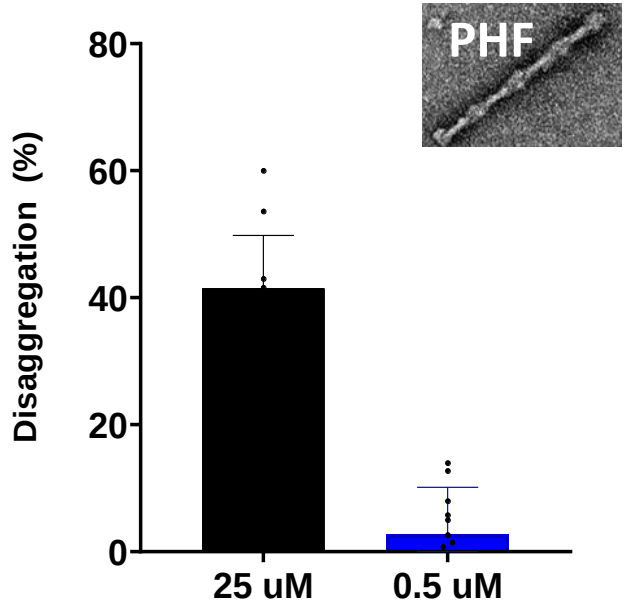
Target engagement by high resolution autoradiography



***Ex vivo* disaggregation of Tau NFT[2] on human AD brain sections**



Disaggregation of human AD brain- derived PHF[3]

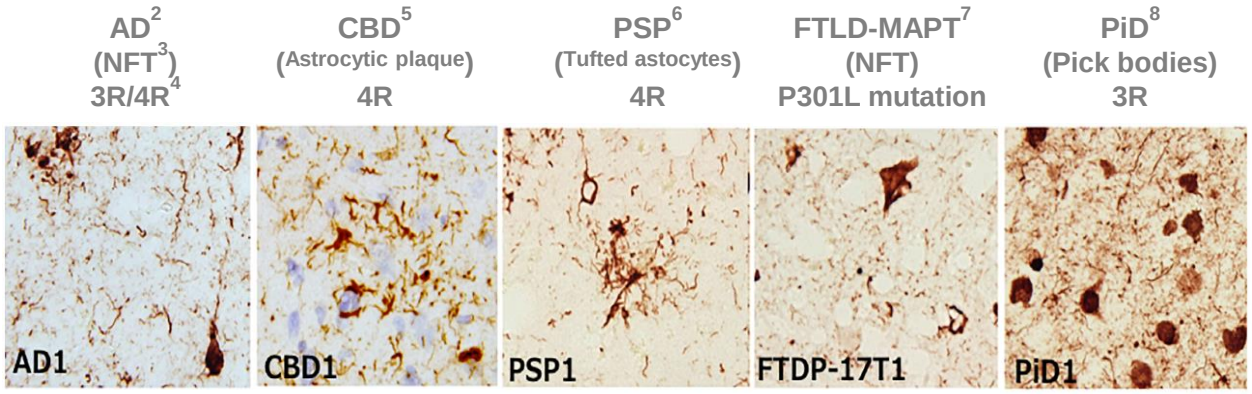


- ACI-3024 specifically binds and disaggregates Tau NFTs from human AD brains, even in the presence of Abeta
- ACI-3024 disaggregates human AD brain-derived PHF

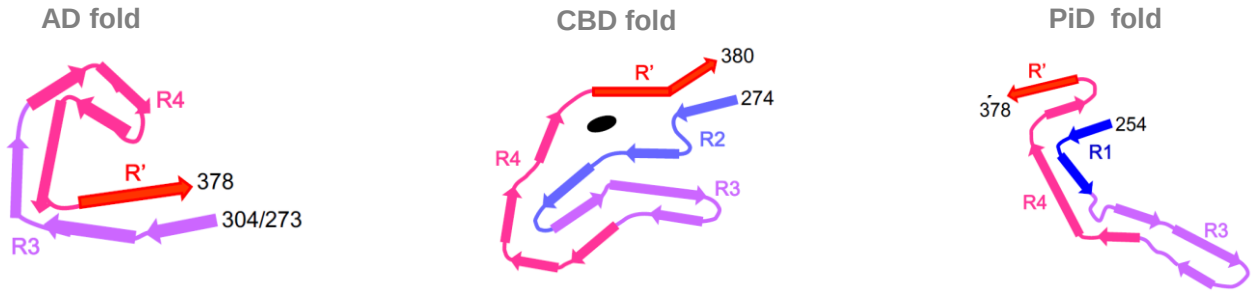
(1) Alzheimer's disease; (2) Neurofibrillary tangles; (3) Paired helical filament Tau

Future potential as therapeutic agents across Tauopathies

In vitro evaluation of Tau morphomer MoA[1] to support further development in rare Tauopathies



Adapted from Kametani - Frontiers in Neurosci (2020)



Adapted from Zeng, Y, Cellular and Molecular Lifesciences (2020)

Disaggregation of Tau isoforms and mutants by ACI-3024

Tau isoforms	EC_{50} (µM)
4R2N	2.6
4R1N	3.3
4R0N	2.6
3R2N	1.9
3R1N	3.1
3R0N	3.5

Tau mutants	EC_{50} (µM)
V248L	2.5
G272V	5.9
P301L	4.2
R406W	10.7

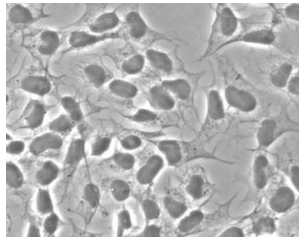
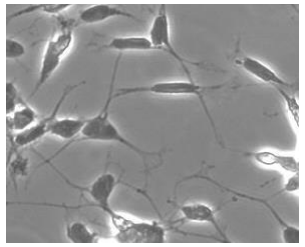
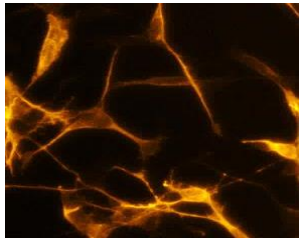
- Different Tauopathies present different Tau aggregates
- ACI-3024 can equally disaggregate 3R and 4R Tau isoforms as well as Tau mutants relevant for rare Tauopathies

(1) Mechanism of action; (2) Alzheimer's disease; (3) Neurofibrillary tangles; (4) 3-repeat / 4-repeat; (5) Corticobasal degeneration; (6) Progressive supranuclear palsy; (7) Frontotemporal lobar degeneration caused by a MAPT gene mutation; (8) Pick's disease

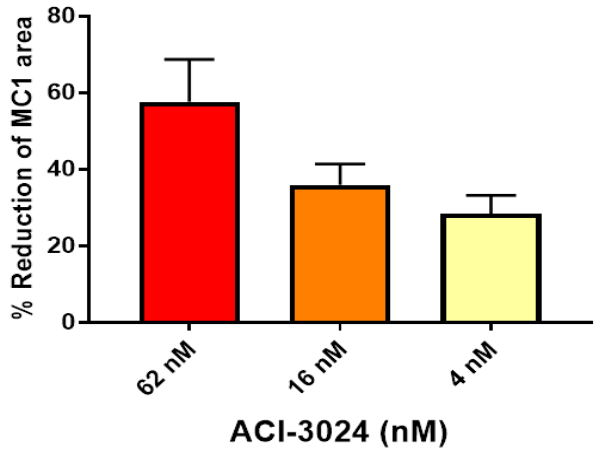
Highly potent reduction of intracellular pathological Tau

Dose-dependent reduction of misfolded Tau in FLTD-Tau[1] brain cells

Reduction of intracellular Tau pathology

	Bright field	Misfolded Tau (MC-1)
Undifferentiated cells		
Retinoic acid differentiated cells		

Dose-dependent reduction of pathological Tau



Mean + SEM

- *In vitro* treatment with ACI-3024 led to a dose-dependent decrease of misfolded Tau at low nM concentrations

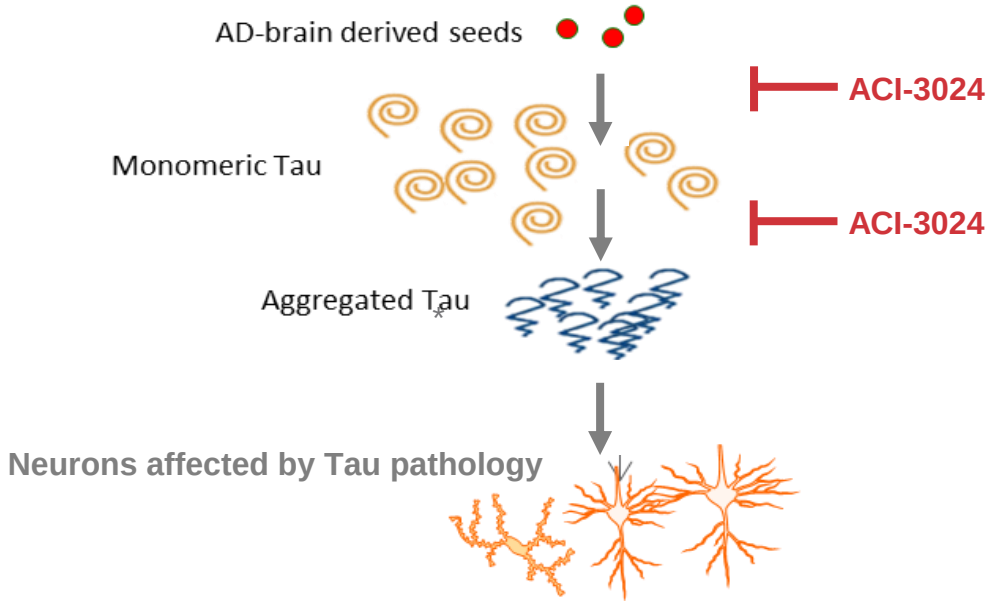
(1) Brain cells overexpressing Tau with P301L mutation

ACI-3024 has positive effect on Tau-induced neurodegeneration

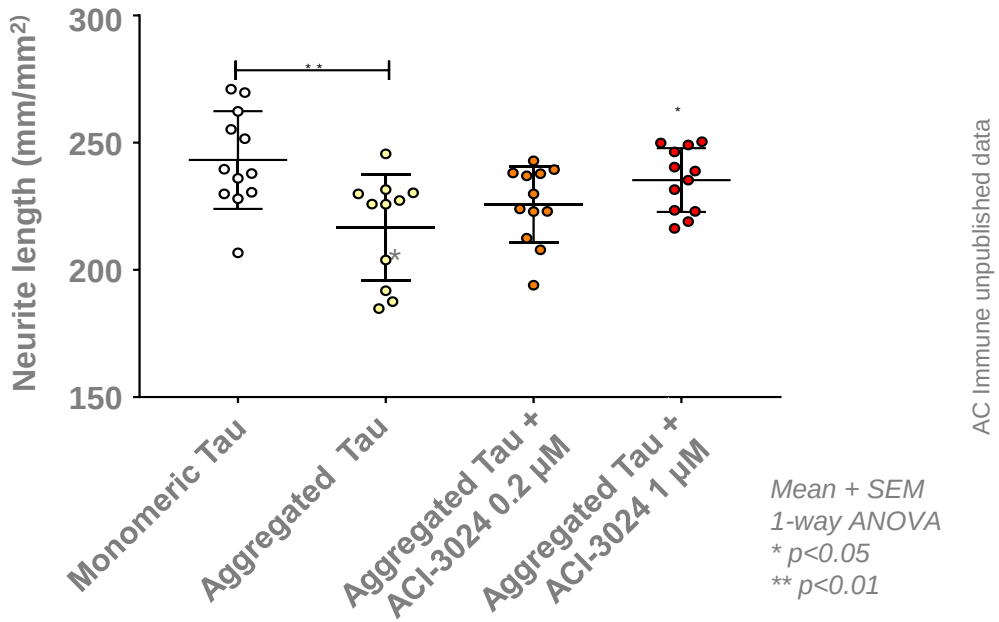
Detoxification of Tau promotes neuronal health *in vitro*

Reduced Tau-induced neurodegeneration after seeding with human AD-brain derived Tau

Experimental design[1]



Neurodegeneration assessed by neurite length
Rat primary neuron microglia co-cultures



- Detoxification of Tau aggregates with ACI-3024 significantly decreased Tau-induced neurodegeneration

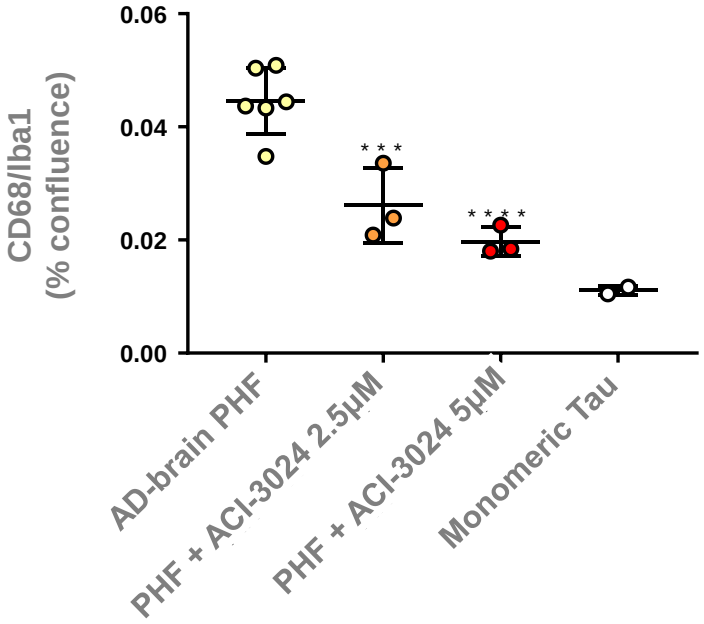
(1) Full-length Tau aggregated with 1/200 PHF seeds for 3 days; pre-incubated in presence of compounds for 1h and then incubated with cells for 3 days

ACI-3024 significantly reduces Tau-induced neuroinflammation

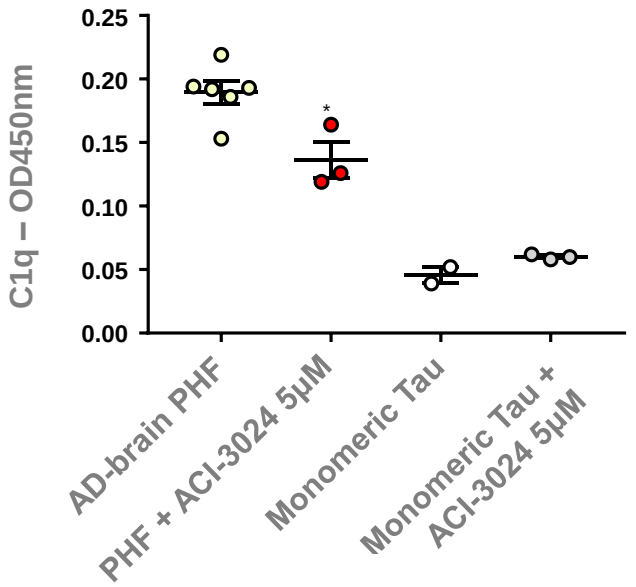
Decreased microglial activation *in vitro*

Human AD[1]-brain derived Tau activation of rat primary microglial cells

CD68+ microglia cells



C1q release from microglia



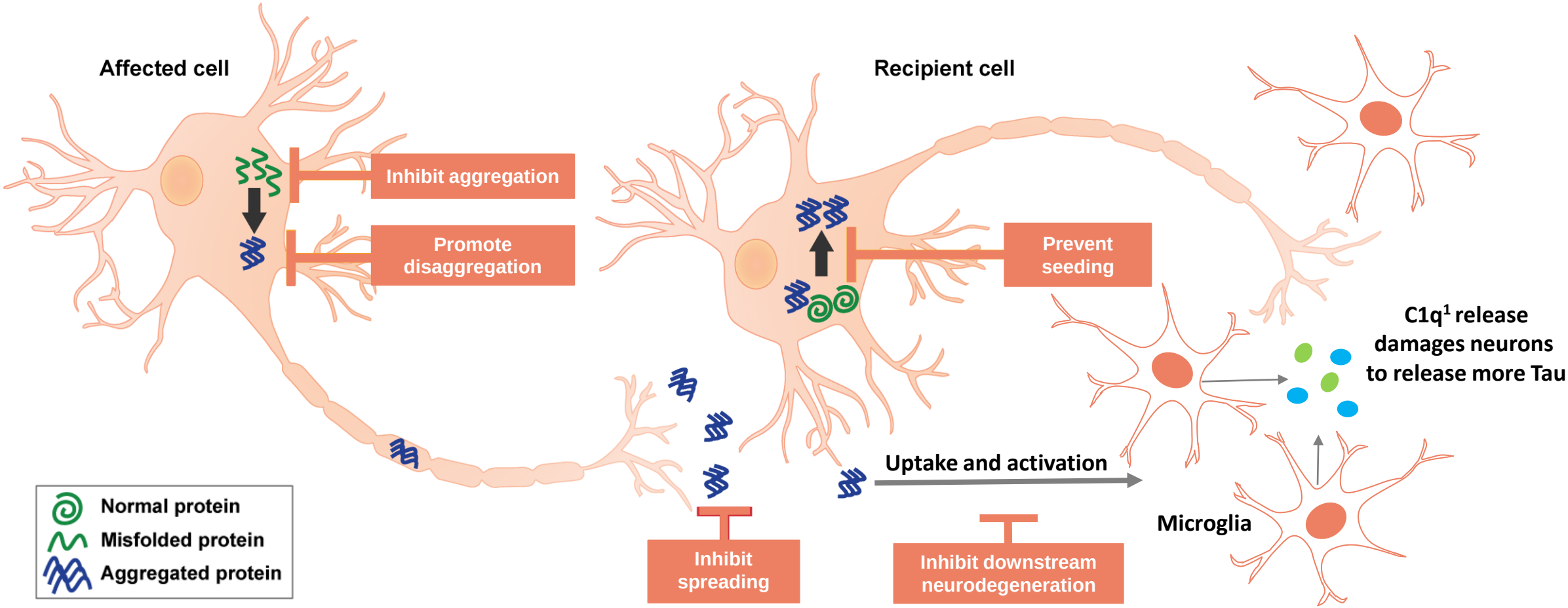
AC Immune unpublished data

Mean + SEM
1-way ANOVA
* p< 0.05
*** p< 0.005
**** p< 0.001

- Detoxification of Tau aggregates significantly decreases pathological Tau induced-microglial activation

(1) Alzheimer's disease

ACI-3024: proposed mode of action



- Targeting both intracellular seeds and extracellular spreading for full control of the disease pathology
- Tau detoxification may reduce downstream neuroinflammation, further preventing neuronal damage

(1) Complement component 1q

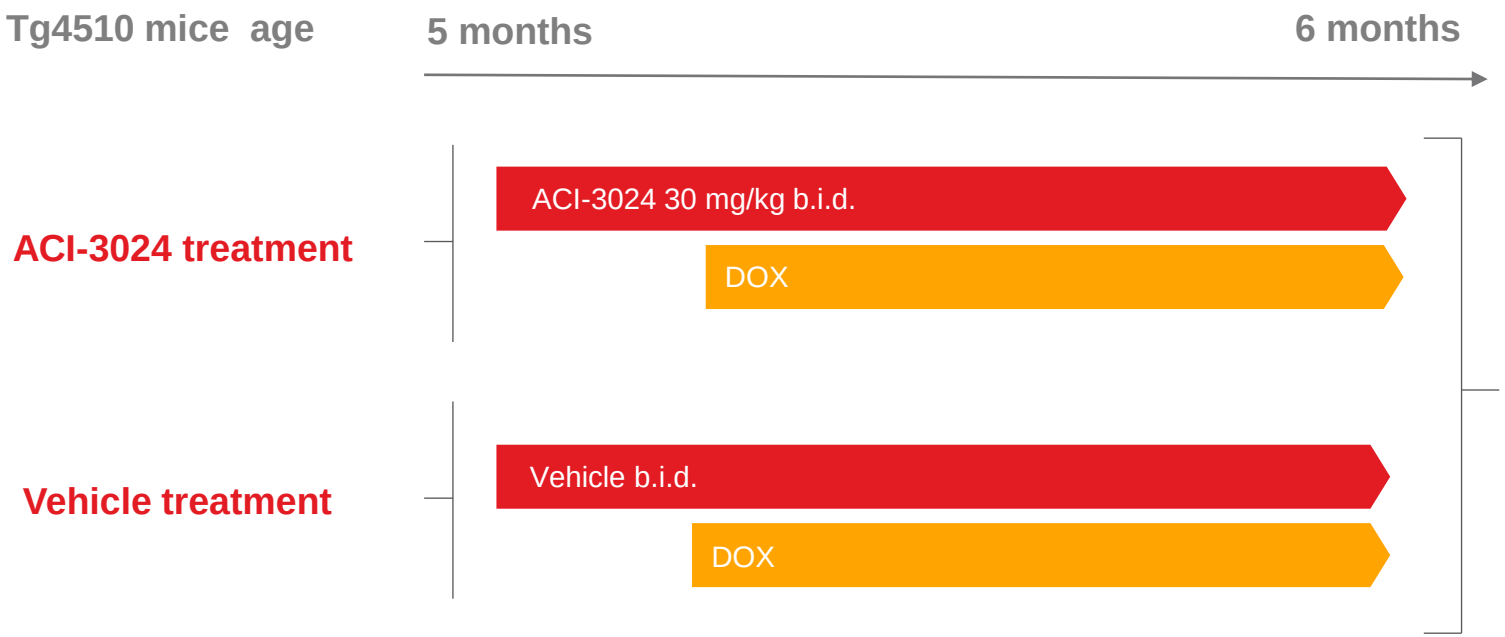
ACI-3024: summary of *in vitro* characteristics

MoA[1] on Tau aggregates	▪ Inhibition of Tau aggregation and Tau seeding ▪ Ability to disaggregate pathological Tau ▪ Effect independent of Tau and FTLD-MAPT[2] isoform and mutants
Selectivity for aggregated Tau	▪ Selective binding to AD[3] brain-derived pathological Tau (Kd 11.7 nM) ▪ No binding to monomeric forms of Tau or to healthy control tissue ▪ No binding to Abeta from AD human brain ▪ No binding to alpha-synuclein from PD[4] human brain
Intracellular activity on Tau misfolding	▪ Dose-dependent decrease of intracellular misfolded Tau at low nM concentrations in a cellular assay
Inhibition of ND[5] and NI[6]	▪ Significantly reduces Tau induced neurodegeneration ▪ Significantly decreases pathological Tau induced-microglial activation

(1) Mechanism of action; (2) Frontotemporal lobar degeneration caused by a MAPT gene mutation; (3) Alzheimer's disease; (4) Parkinson's disease; (5) Neurodegeneration; (6) Neuroinflammation

In vivo evaluation of ACI-3024 after oral administration

Tauopathy model: transgenic mice expressing human FTLD-MAPT[1] Tau mutation (P301L)[2]



End-Points

- Biochemistry:
  - Total, aggregated, and hyper-phosphorylated brain Tau
  - Total CSF Tau
- Immuno-histochemistry:
  - Misfolded Tau
- Neuroinflammation:
  - Microglial analysis
- Plasma concentrations of ACI-3024

- An independent dose response experiment performed at 10, 30 or 100 mg/kg BID

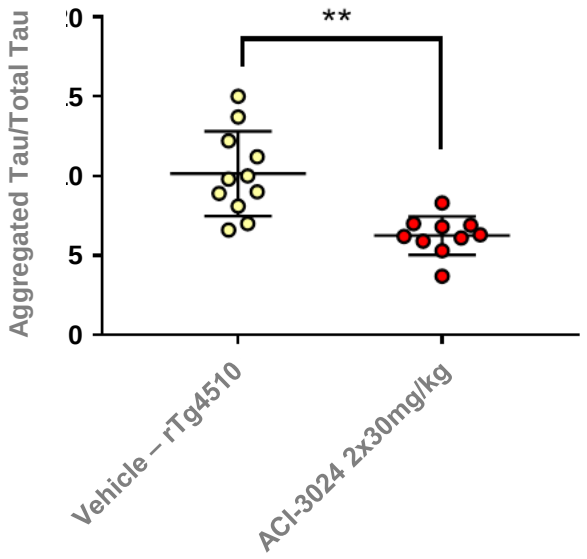
- *In vitro* cellular assays combined with preclinical brain pharmacokinetics led to the *in vivo* dose and dosing regimen
- Dose selection driven by ability to maintain target ACI-3024 CSF[3] concentration over 24-hour period

(1) Frontotemporal lobar degeneration caused by a MAPT gene mutation; (2) rTg4510 mice express repressible (Tet promotor Tau on/off) human 4R0N Tau carrying the P301L mutation (SantaCruz, 2005); (3) Cerebrospinal fluid

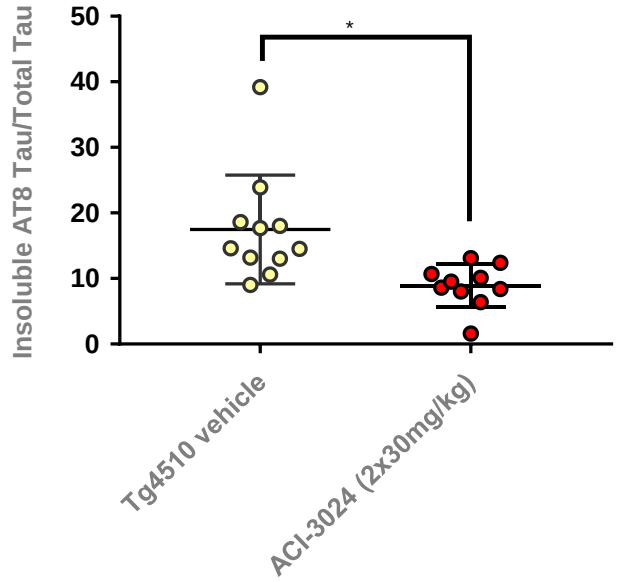
ACI-3024 significantly reduces phosphorylated pathological Tau *in vivo*

Biochemistry: Analysis of pathological Tau in Tau ON/OFF rTg4510 mice

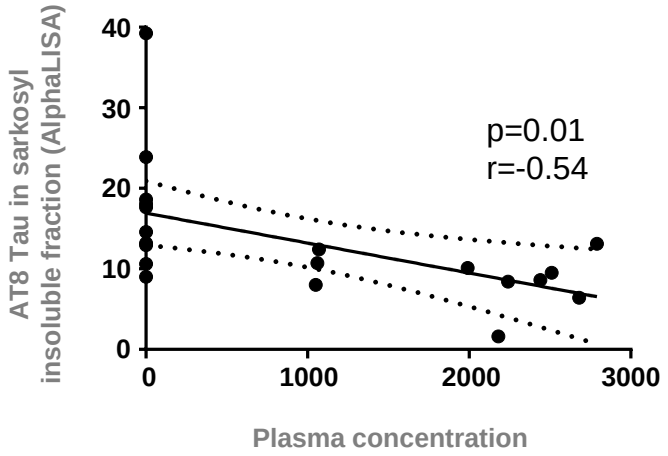
Aggregated Tau[1] normalized to total Tau[2]



Insoluble hyper-phosphorylated Tau[3] normalized to total Tau[2]



Dose-proportional reduction of Tau aggregates



Mean + SEM
1-way ANOVA
*** p< 0.001; * p< 0.05

Poli S, et al., CTAD 2018

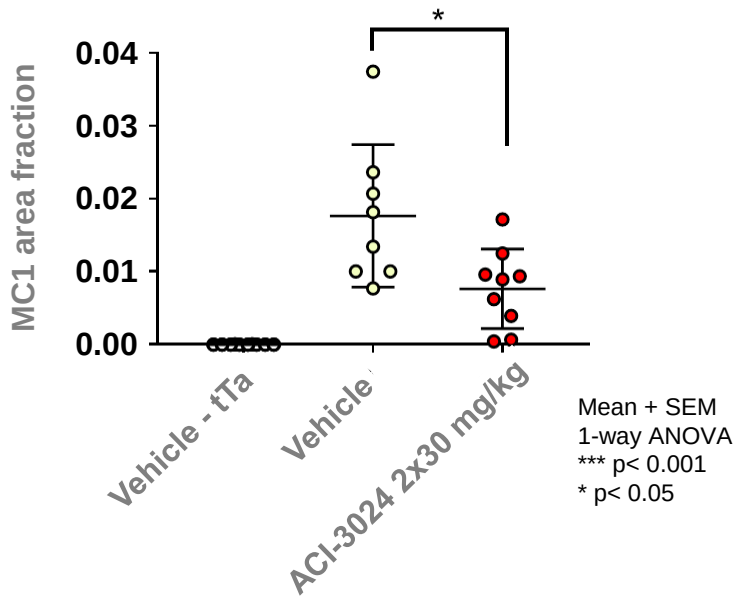
- Significantly reduced aggregated, insoluble pS202/pT205 hyper-phosphorylated Tau in cortical homogenates
- The decrease was proportional to the plasma exposure of ACI-3024

(1) HT7xHT7; (2) HT7xTau13; (3) AT8xHT7

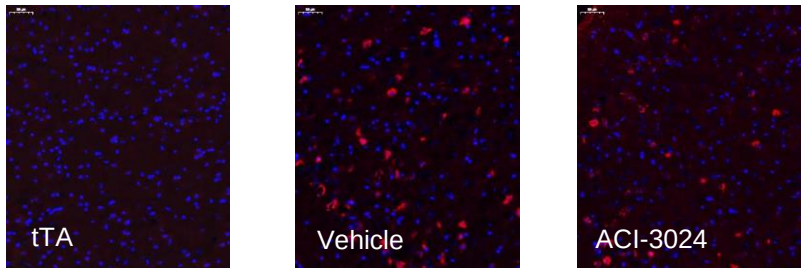
Dose-dependent reduction in Tau misfolding *in vivo*

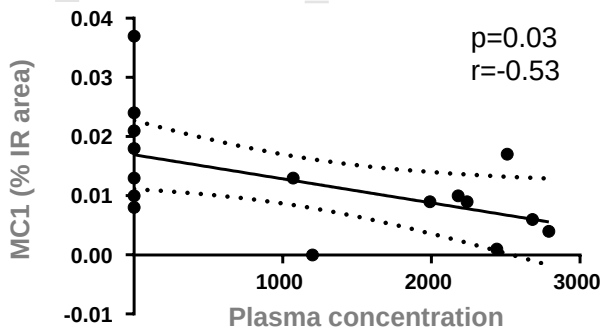
Immunohistochemistry: Analysis of misfolded Tau (MC1) in rTg4510 brain section

MC1 in brain sections



Representative staining (MC1 in red, DAPI: blue)



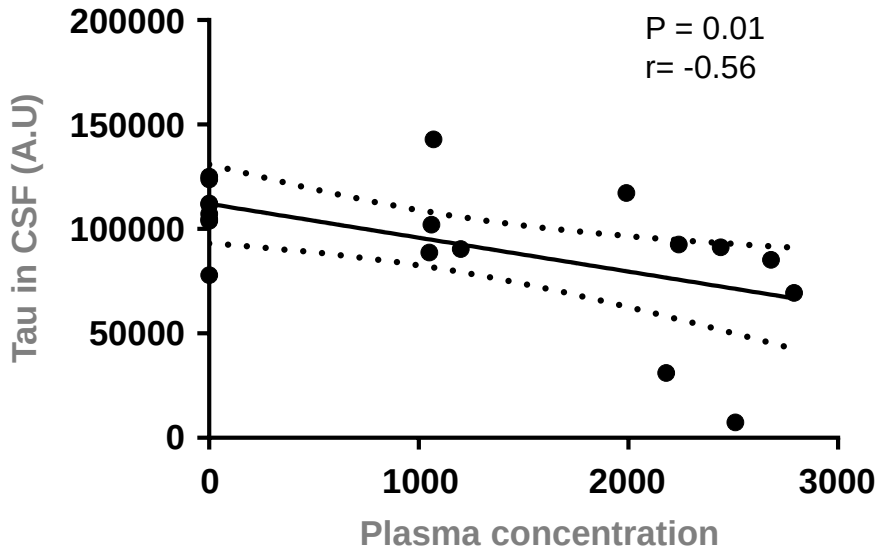


- Treatment with ACI-3024 significantly reduced misfolded Tau
- The decrease is correlated with the ACI-3024 plasma exposure

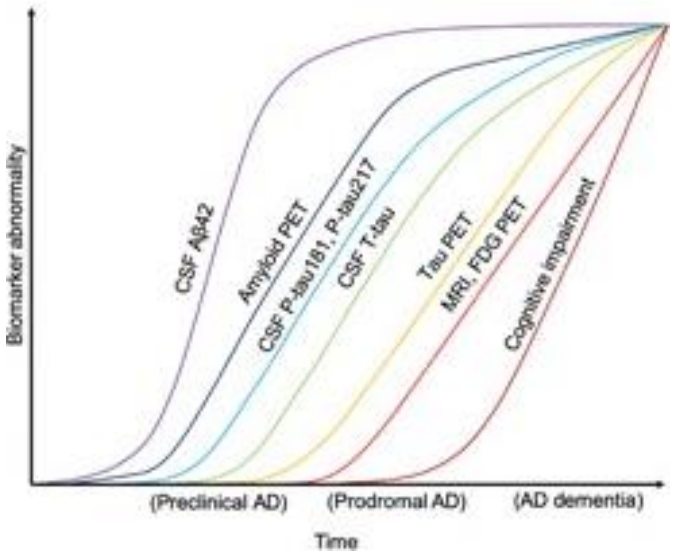
Dose-dependent reduction of Tau in CSF[1] may indicate brain clearance

Potential as a biomarker for efficacy

Dose-dependent reduction of total Tau in CSF



Relationship between CSF and PET[2] biomarkers



Mattsson-Carlgren et al Sci Adv 2020

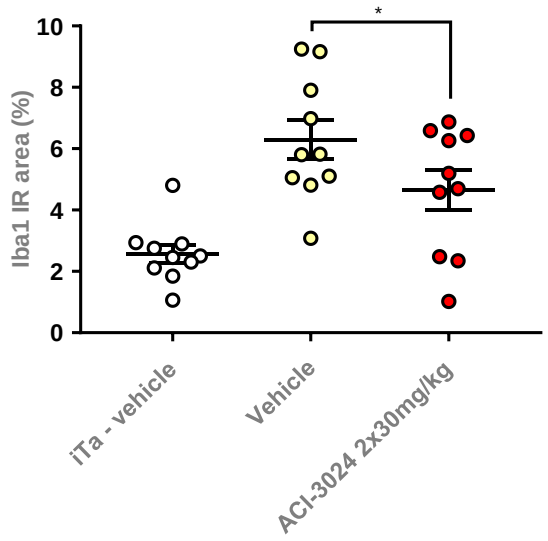
- The significant inverse correlation between CSF Tau and ACI-3024 exposure in plasma might indicate an increase of Tau clearance from the brain
- CSF Tau concentrations may be explored as a biomarker for efficacy in clinical development

(1) Cerebrospinal fluid; (2) Positron emission tomography

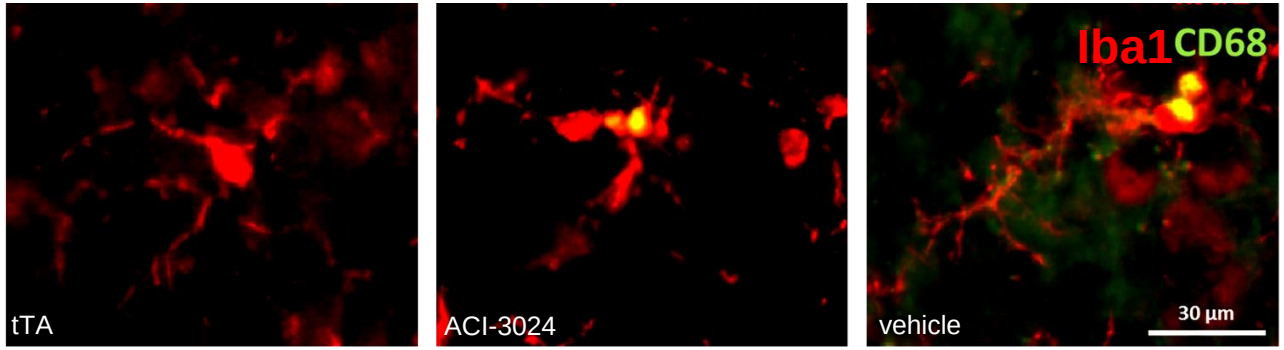
Positive effect on Tau-induced neuroinflammation *in vivo*

ACI-3024 treatment led to significant decrease in microglial activation

Total Microglia in frontal cortex



Representative microglia labelling



- Treatment with ACI-3024 reduced microgliosis
- Detoxification of Tau aggregates significantly decreases pathological Tau induced-microglial activation

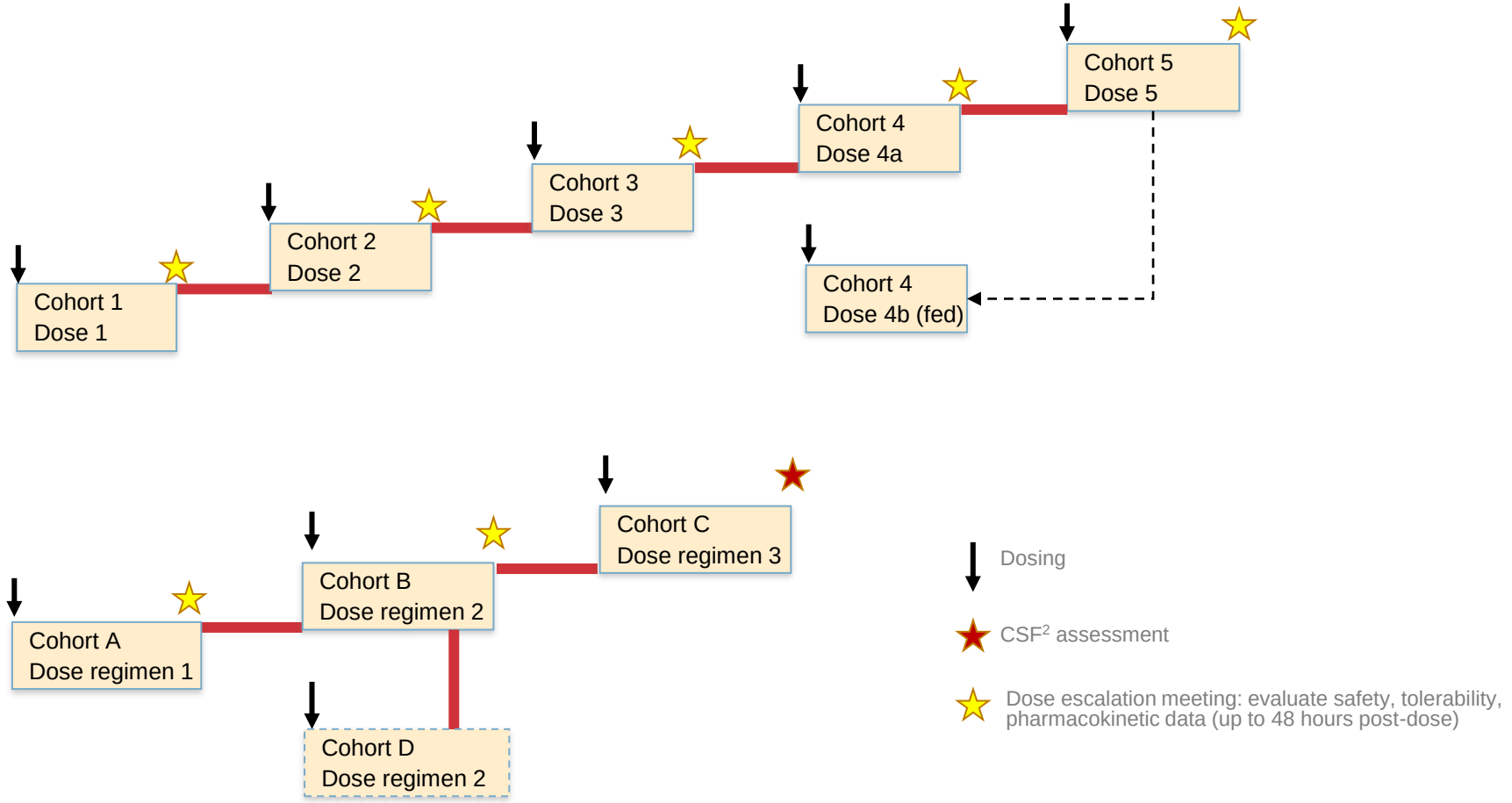
Phase 1 – SAD/MAD[1] healthy subject study

Dose escalation scheme

SAD

MAD

Study results to be shared via scientific communication at a later date



(1) Single ascending dose/multiple ascending dose; (2) Cerebrospinal fluid

Morphomer™ Tau therapeutic program

Generated first brain-penetrant Tau small molecule aggregation inhibitor

Phase 1	▪ ACI-3024 single and multiple ascending dose study completed as planned in healthy young, elderly, and Japanese subjects ▪ All cohorts completed dosing
Pharmacokinetics	▪ Dose-dependent plasma exposure ▪ Half-life of 47.5 to 101 h with steady-state reached after 12-13 days ▪ Low renal clearance ▪ Absorption increased by food
Brain exposure	▪ Exceeded ACI-3024 therapeutic target concentration in CSF[1] after multiple dose administration
Development status	▪ Multiple Tau Morphomers have demonstrated *in vitro* disaggregation of pathological Tau ▪ Novel optimized Tau Morphomer should be advanced into development for AD[2] in 2021 ▪ ACI-3024 assessment ongoing for rare NeuroOrphan indications

(1) Cerebrospinal fluid; (2) Alzheimer's disease

Morphomer™ Tau therapeutic program: summary and outlook

Generated first brain-penetrant Tau small molecule aggregation inhibitor

Selectivity and *in vivo* efficacy

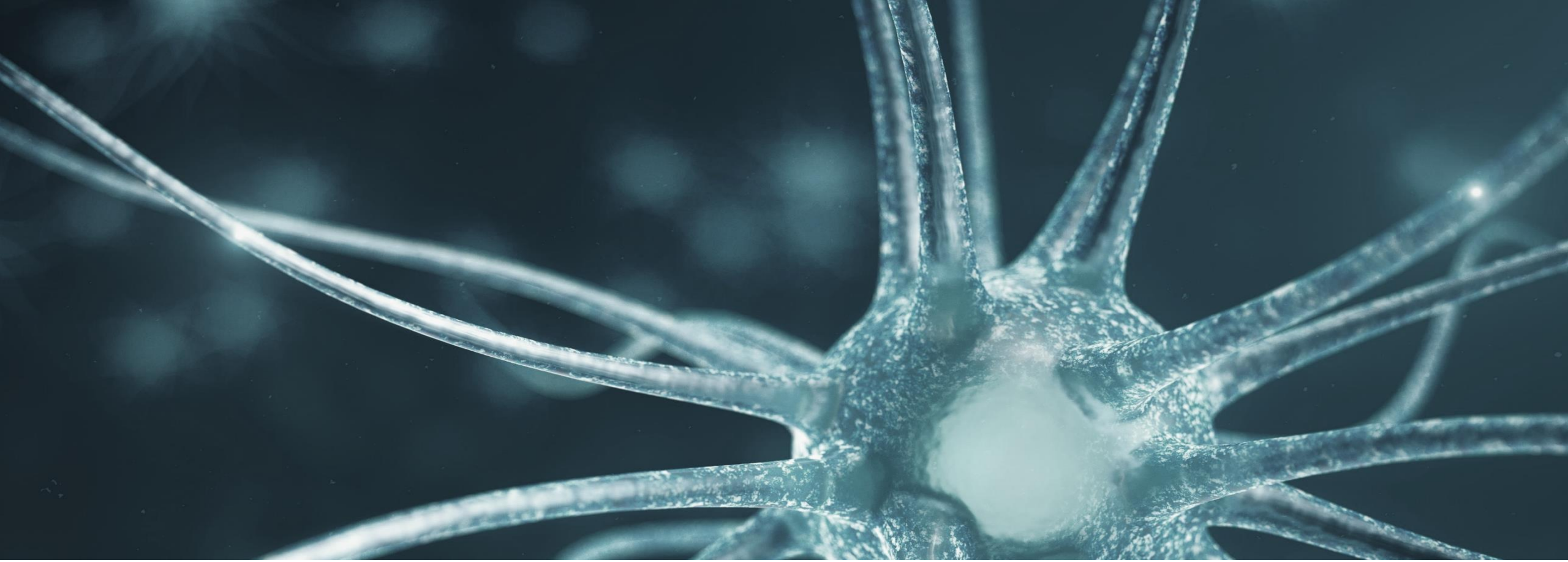
- High target specificity
- Demonstrated MoA[1] *in vitro* and *in vivo*
  - Selective inhibition of Tau seeding and aggregation
  - Promotion of disaggregation
  - Significant reduction of pathological Tau in transgenic mouse model (Tg4510)
- Consequential decrease in neuroinflammation and neurodegeneration

Brain uptake in healthy subjects

- Completed single and multiple ascending dose Phase 1 study
- Achieved therapeutic target concentration in CSF[2]

- Tau Morphomers™ have the potential to treat AD[3] and rare diseases caused by Tau misfolding and aggregation

(1) Mechanism of action; (2) Cerebrospinal fluid; (3) Alzheimer's disease



Diagnostic PET imaging agents targeting Tau, a-syn and TDP-43

Francesca Capotosti, PhD, Group leader *in vivo* pharmacology and non-clinical safety

Brain PET[1] imaging is key for precision medicine

PET imaging in neurodegenerative diseases

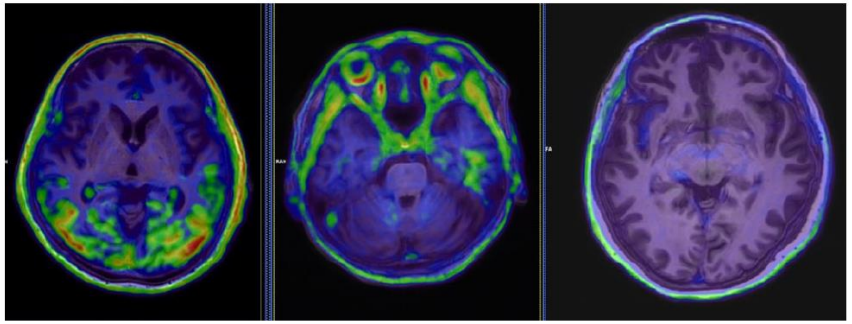
1. The vast majority of neurodegenerative diseases are sporadic; diagnosis cannot be only based on genetic testing
2. So far clinically relevant fluid markers have been identified only for few NDDs and their correlation with brain pathology remains often poorly understood
3. In AD[2], the availability of Abeta PET tracers has allowed better stratification of patient populations and target engagement of anti-Abeta immunotherapies to be proven
4. In AD and other Tauopathies, Tau tracers have the potential to provide differential diagnosis. Such tracers also have potential as prognostic and/or predictive biomarkers in clinical trials
5. There is a clear unmeet clinical need for new PET tracers for other targets in neurodegeneration such as a-syn[3] and TDP-43[4]

(1) Positron emission tomography; (2) Alzheimer's disease; (3) Alpha-synuclein; (4) TAR DNA-binding protein 43

Tau-PET[1] tracer PI-2620: A tool to assess early AD[2] and neuronal injury

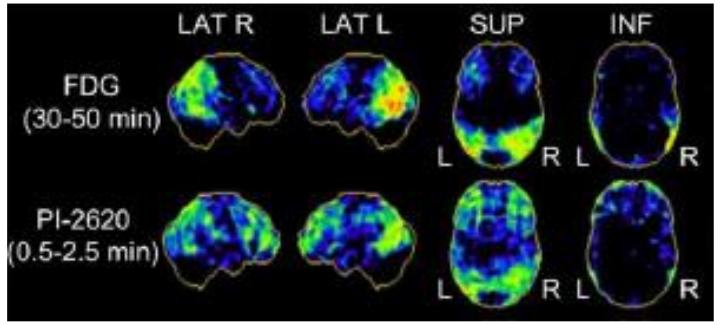
Target	Misfolded Tau (3R/4R, 3R and 4R)
Key results	▪ High specificity for pathological forms of human Tau in AD (3R/4R) and PSP[3] (4R) ▪ Outstanding PET tracer profile: excellent brain uptake, fast wash-out and low off-target binding, allowing early-stage disease imaging ▪ Good reproducibility of PET scans in test-retest studies

Phase 1 clinical study results
PI-2620 Tau PET in different disease stage



AD | Mild-cognitive impairment | Cognitively normal

Phase 1 clinical study results[4]
PI-2620 Tau PET as surrogate marker of neuronal injury in **AD**



FDG and PI-2620 early phase PET scans

Chotipanich *et al.*, Molecular Imaging 2020

Key differentiation	▪ 3R/4R Tau detection in AD; reproducible 4R Tau detection in PSP; promising 4R Tau detection in CBD[5] ▪ Potential for earlier and more reliable diagnosis: PI-2620 PET imaging can detect and assess PSP pathology *in vivo* ▪ PI-2620 PET imaging can serve as surrogate biomarker for neuronal injury and allow differential diagnosis
Development status	Phase 2 longitudinal study in AD and Phase 1 study in PSP (test-retest) nearing completion

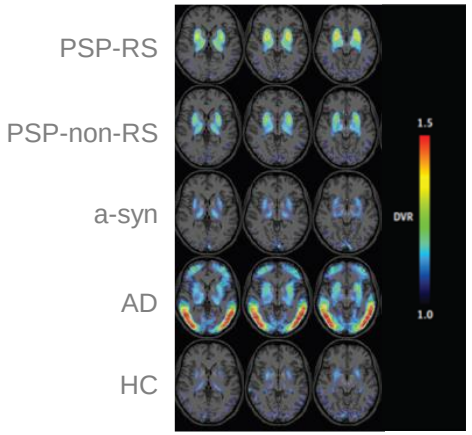
(1) Positron emission tomography; (2) Alzheimer's disease; (3) Progressive supranuclear palsy; (4) Fluorodeoxyglucose; R, right; L, left; LAT, lateral; SUP, superior; INF, inferior; (5) Corticobasal degeneration

PI-2620 is the only PET[1] tracer that can reliably detect 4-repeat (4R) Tau

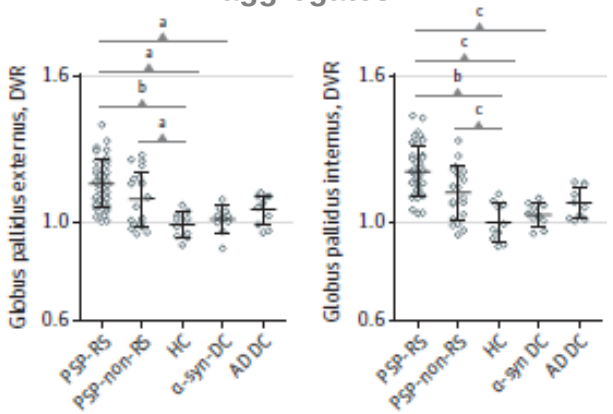
4R Tau detection may enable precision medicine approaches in PSP[2] and other Tauopathies

Study Rationale	▪ Multicenter study enrolled patients with PSP-RS[3], PSP-non-RS[4], a-synucleinopathies (MSA[5], PD[6]), AD[7], and HC[8] ▪ Strong overlap of clinical symptoms; clinical assessments lack sensitivity in early disease and specificity for pathological Tau ▪ No available biomarker currently fulfills the criteria to ensure differential diagnosis in PSP
Key results	▪ Results show clear differentiation of PSP from non-PSP patients: ▪ High specificity for pathological forms of Tau in PSP (4R) with specific autoradiography signal in PSP tissue ▪ Statistically significant signal in PSP target regions compared to healthy controls (HC) and disease controls (a-syn[9], AD) ▪ Clear target engagement (binding to 4R Tau aggregates) in autoradiography on postmortem PSP tissue

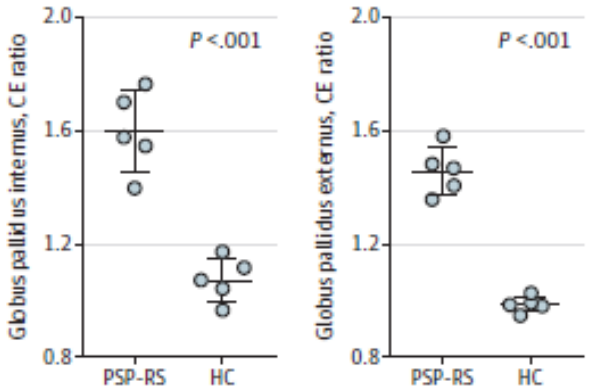
Average DVR[10]



Quantitative DVR of Tau aggregates[11]



Increased binding in postmortem PSP tissue vs. HC by ARG[12]



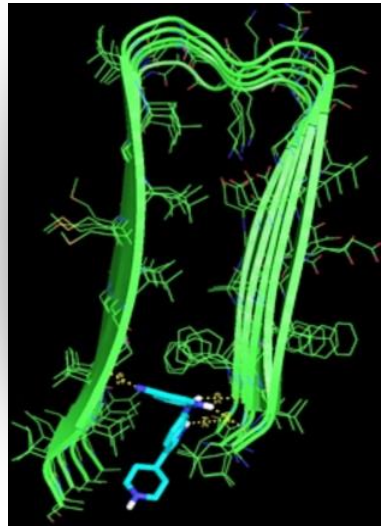
Brendel et al., JAMA Neurology 2020

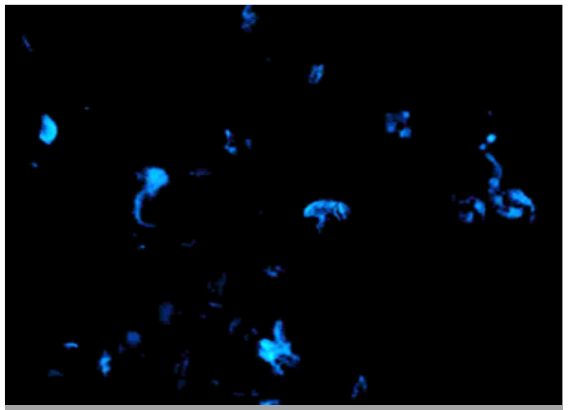
Key differentiation	▪ Reproducible 4R Tau detection in PSP; promising 4R Tau detection in CBD[13]

(1) Positron emission tomography; (2) Progressive supranuclear palsy; (3) PSP-Richardson syndrome; (4) PSP-non-Richardson syndrome; (5) Multiple system atrophy; (6) Parkinson's disease; (7) Alzheimer's disease; (8) Healthy control; (9) a-synucleinopathies; (10) Distribution volume ratio; (11) Statistics derive from multivariant analysis including center, age and sex; (12) Autoradiography; (13) Corticobasal degeneration

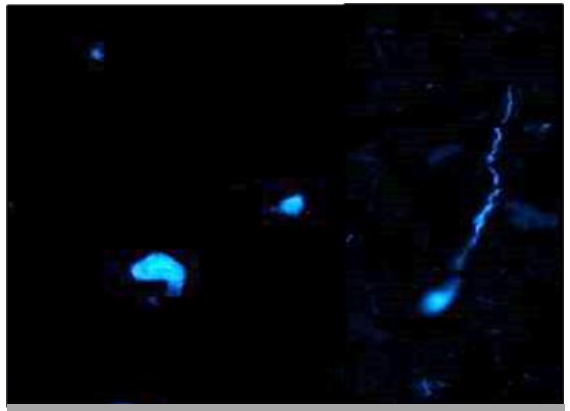
Developing a suite of PET[1] tracers against emerging targets in NDD[2]

Precision medicine approach enabled by the Morphomer™ platform

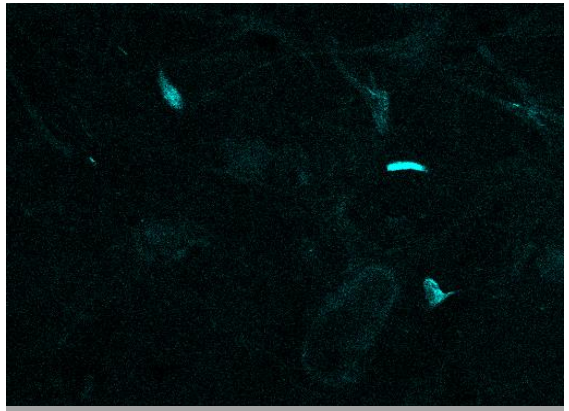




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

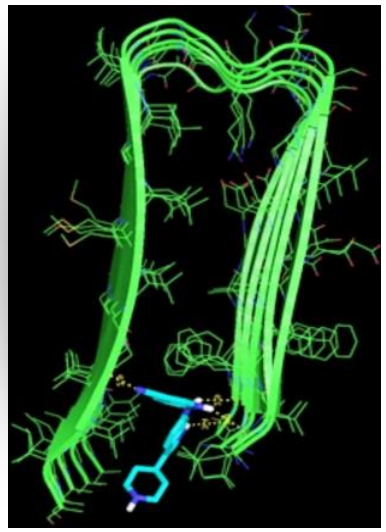
The development pathway:

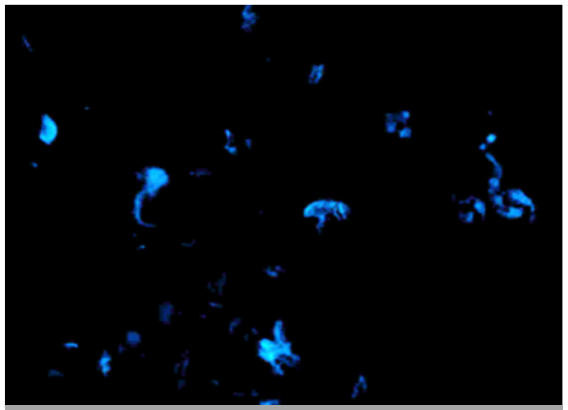
- Rely only on patient-derived brain samples for target engagement
- Minimize off-target binding to optimize signal-to-noise ratio
- Optimize selectivity against other potential co-pathologies (Abeta, Tau, TDP-43)
- Optimize brain penetration and washout

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

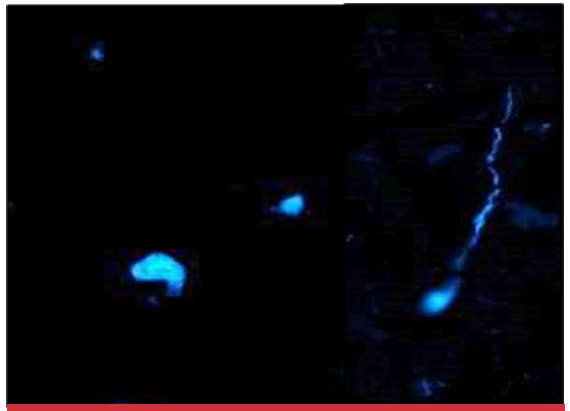
Developing a suite of PET[1] tracers against emerging targets in NDD[2]

Precision medicine approach enabled by the Morphomer™ platform

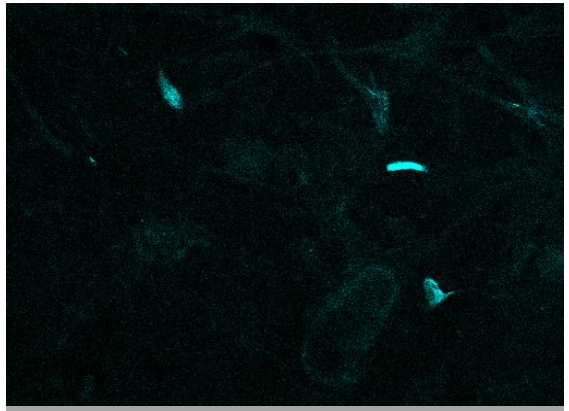




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

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- Minimize off-target binding to optimize signal-to-noise ratio
- Optimize selectivity against other potential co-pathologies (Abeta, Tau, TDP-43)
- Optimize brain penetration and washout
- >2000 Morphomers™ have been designed, synthesized and screened to date for AC Immune's PET programs

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

Early treatment of PD[1] with a pathological a-syn[2] PET[3] tracer

Diagnosing PD before onset of clinical symptoms offers improved treatment paradigms

- >90% of PD cases are sporadic; diagnosis cannot be based on genetic testing[4]
- Dopaminergic imaging has a poor correlation with clinical severity[5,6]
- a-Synuclein inclusions (Lewy bodies and Lewy neurites) appear before dopaminergic changes, i.e., premotor stage of PD[7]
- Development of fluid biomarkers limited by low abundance of pathological a-syn in biofluids
- Pathological aggregates of a-syn are intracellular, not as abundant as Abeta and Tau pathology in Alzheimer's disease and often present as part of co-pathologies[8]
- Clinical trials targeting a-syn have a higher chance of success when utilizing an a-syn tracer for recruiting a more homogeneous population as well as longitudinal surveillance
- Thus, our aim is to develop a first-in-class high affinity, selective a-syn tracer

(1) Parkinson's disease; (2) Alpha-synuclein; (3) Positron emission tomography; (4) Shah *et al*., 2014 Journal of Nuclear Medicine; (5) Fahn *et al.*, 2004. N Engl J Med; (6) Brooks *et al.*, 2003 Exp Neurol.; (7) Eberling *et al.*, 2013 J Parkinsons Dis; (8) Robinson *et al.*, 2018 Brain

ACI-3847 is a potentially first-in-class a-synuclein diagnostic

Clinical evaluation of 2nd generation PET[1] tracer supported by strong preclinical data

Target engagement and binding affinity	▪ Significantly higher specific signal in different PD[2] cases with confirmed a-syn[3] pathology as compared to non-demented control subjects ▪ Autoradiography signal directly proportional to the pathological a-syn load
Selectivity	▪ [3H]ACI-3847 displays no binding to AD[4] brain homogenates containing pathological Abeta and Tau ▪ No significant off-target binding to a panel of >130 receptors and enzymes
18F-labeling and pharmacokinetic profile	▪ Radiolabeling achieved at last synthetic step with good purity and yield ▪ Good, homogeneous brain uptake as well as a fast and complete washout in non-human primates

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

ACI-3847 first-in-human evaluation: Study objectives and demographics

Study objective: Assess brain uptake and pharmacokinetics of ACI-3847 as a PET[1] imaging marker for a-syn[2] pathology in individuals with probable PD[3] versus HV[4]

Study Subject ID	Gender	Cohort	Age	MDS-UPDRS part 3 score OFF/ON	Hoehn & Yahr score	MoCA score	Affected side: DaTscan
PD_01	Male	PD	60	49/26	2	26	Left
PD_05	Female	PD	49	52/51	2	27	Left
PD_07	Male	PD	73	52/46	2	22	Left
PD_09	Male	PD	77	46/39	2.5	23	Left
PD_11	Male	PD	65	26/21	2	28	Right
HV_04	Male	HV	30	NA	NA	30	NA
HV_06	Female	HV	71	NA	NA	30	NA
HC_08	Female	HV	50	NA	NA	30	NA
HV_10	Female	HV	77	NA	NA	28	NA
HV_12	Female	HV	64	NA	NA	28	NA

invicro

- ACI-3847 was evaluated in 5 healthy volunteers, 4 probable mild idiopathic PD cases and one relatively young *SNCA* gene duplication carrier
- 4/5 PD cases show an asymmetrical dopaminergic loss that is more pronounced in the left substantia nigra

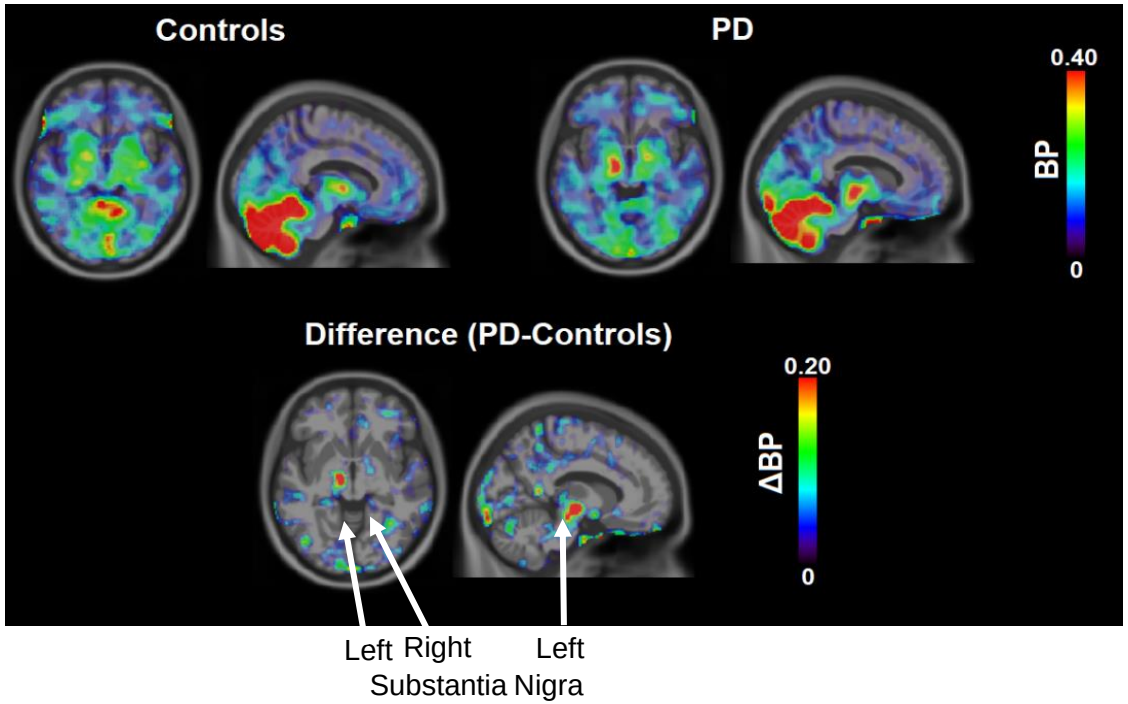
(1) Positron emission tomography; (2) Alpha synuclein; (3) Parkinson's disease; (4) Healthy volunteers

Kinetic modeling shows clear signal elevation in substantia nigra

Higher tracer uptake in idiopathic PD[1] cases compared to healthy controls

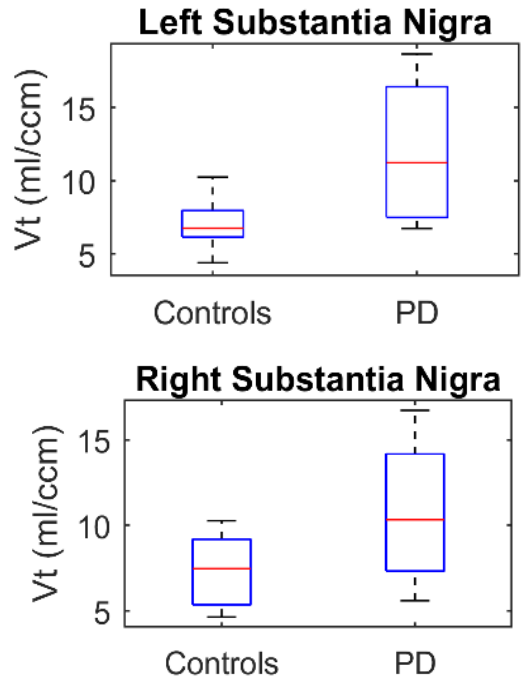
Binding potential maps

Logan reference tissue model (ref. region: middle frontal lobe)



Blood-based Vt[3]

(Logan model with blood input function)

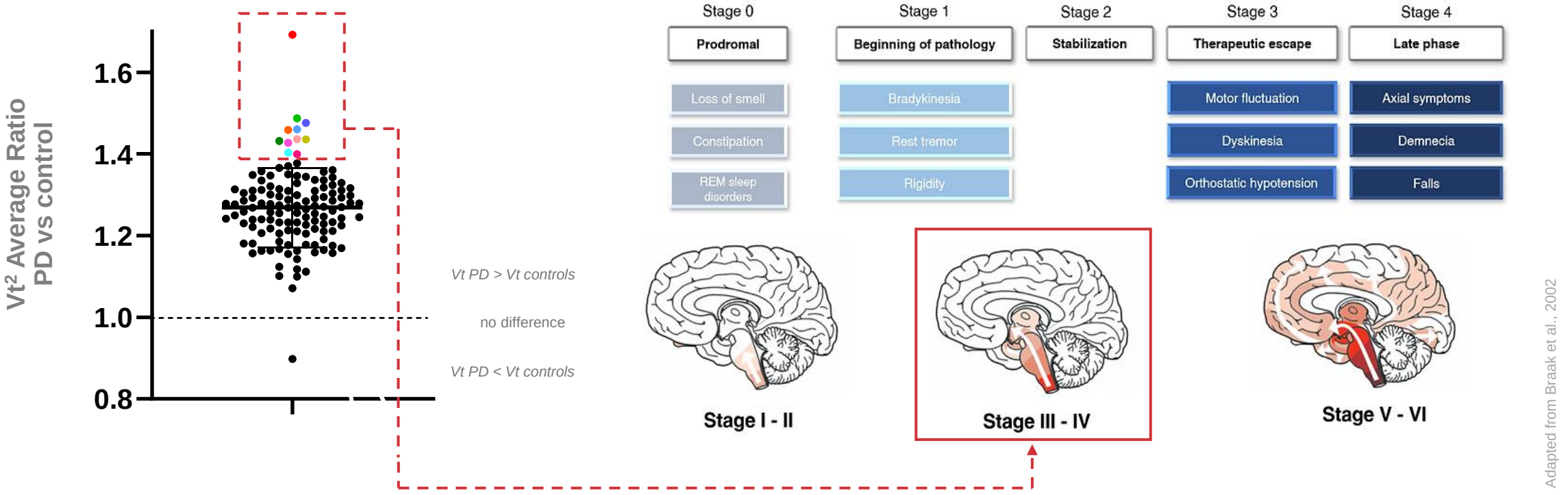


In collaboration with Prof. O. Hanssosn, Skane University Hospital

- PD subjects show slightly higher tracer uptake in brain regions that accumulate a-synuclein, including substantia nigra, despite overlapping signal between PD cases and healthy controls

(1) Parkinson's disease; (2) Alpha synuclein; (3) Volume of distribution

Signal elevation more pronounced in regions associated with early PD[1]



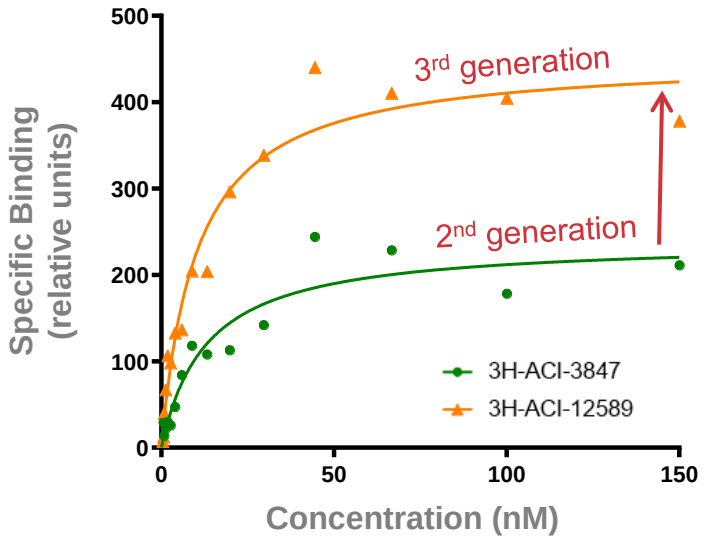
- ACI-3847 differentiates brain regions associated with early PD; good correlation with patient profile of FiH[3] study
- Initiated follow up clinical study in indications with expected higher levels of a-synuclein pathology

(1) Parkinson's disease; (2) Volume of distribution; (3) First-in-human

3rd generation a-syn[1] tracers have improved properties

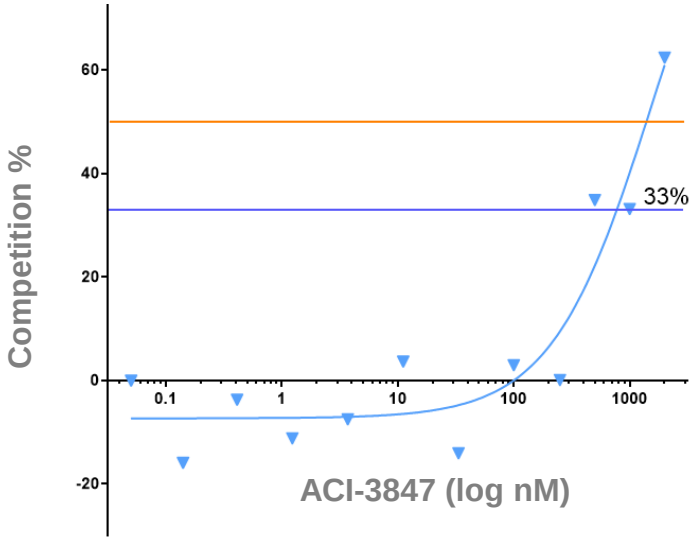
Candidates with increased target occupancy and different binding sites

Saturation binding on tissue homogenates from idiopathic PD[2] cases



Increased target occupancy

Limited displacement of newly identified ligands by ACI-3847



Indicates distinct a-syn binding pockets

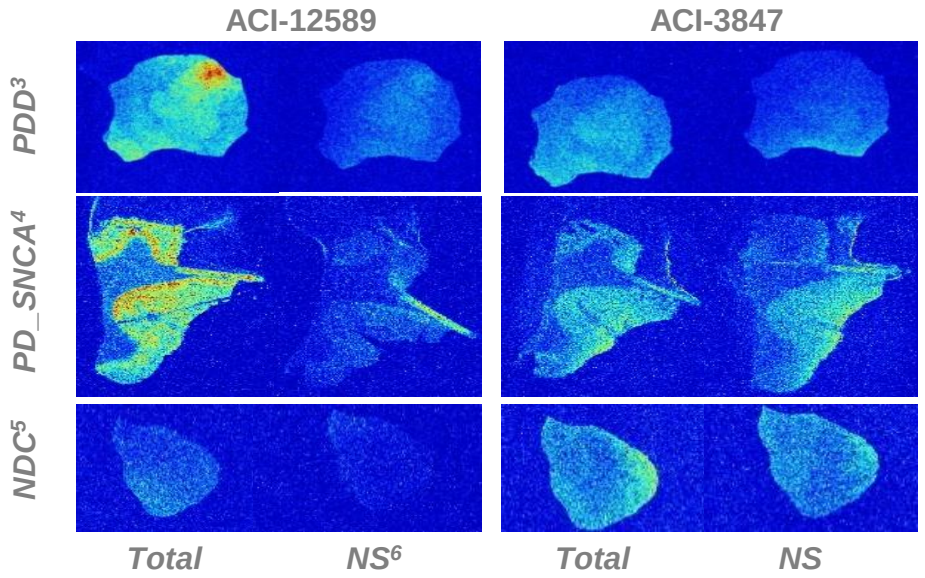
- Newly identified compounds are highly promising with up to 10-fold increased target occupancy
- Potential for enhanced differentiation between diseased and healthy subjects based on recognition of a different and more abundant a-syn binding pocket

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

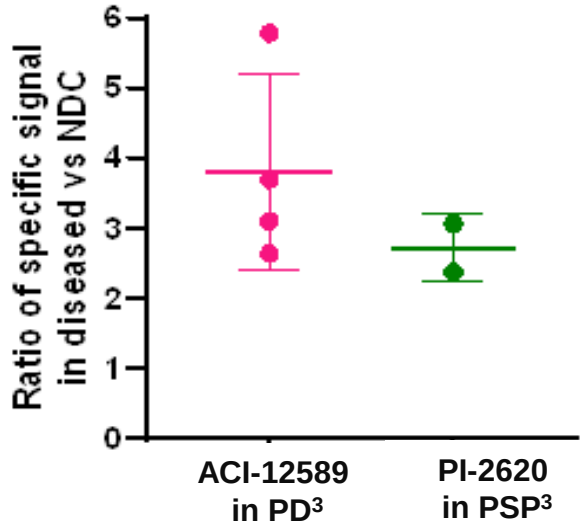
ACI-12589 is a potentially best-in-class a-synuclein PET[1] tracer

Ex vivo characterization of 3rd generation tracer

Comparison of 2nd and 3rd generation a-syn[2] PET tracers



Comparison of 3rd generation a-syn PET tracer and PI-2620 (Tau PET tracer)

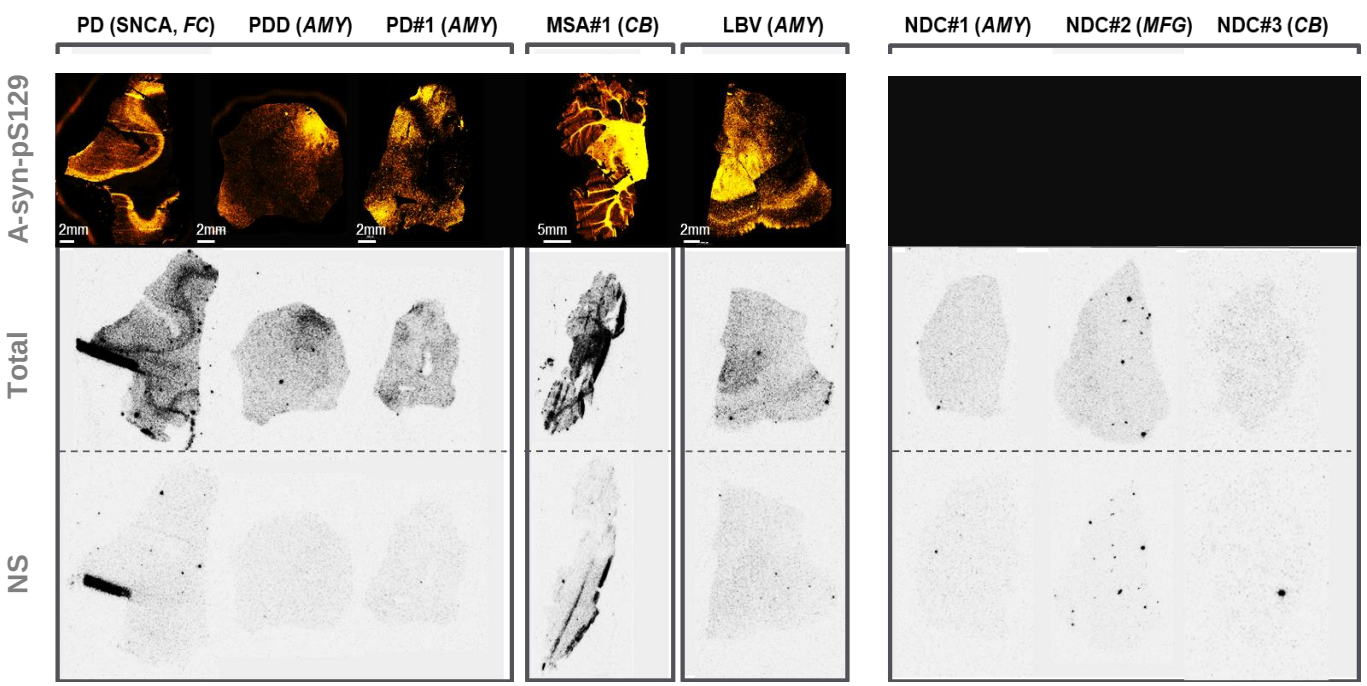


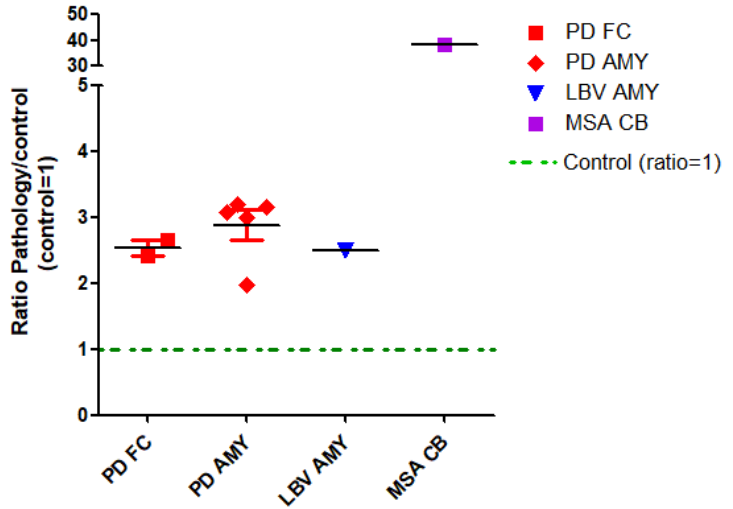
- Compared to ACI-3847, ACI-12589 provides:
  - Stronger, more specific signal in tissue from different PD[7] patients, even tissue with limited a-syn pathology
  - Better differentiation between disease and non-disease controls
- *Ex vivo*, ACI-12589 showed a similar signal elevation in PD *vs* control cases as PI-2620 in PSP

(1) Positron emission tomography; (2) Alpha synuclein; (3) Parkinson's disease (PD) with dementia; (4) PD with SNCA G51D mutation; (5) Non-diseased control; (6) Non-specific (7) Parkinson's disease

ACI-12589: A potentially broadly applicable diagnostic agent

Potential to diagnose a range of alpha-synucleinopathies





Total = Total binding (1.7nM)
NS = Non-specific binding (1µM)

In collaboration with Prof. A. Varrone, Karoliska Institute

Karolinska Institutet

PD_SNCA: PD with SNCA G51D mutation
PDD: Parkinson's disease with dementia

PD: idiopathic PD
LBV: Lewy body variant

MSA: multiple system atrophy
NDC: non-diseased control

FC: Frontal cortex
AMY: Amygdala

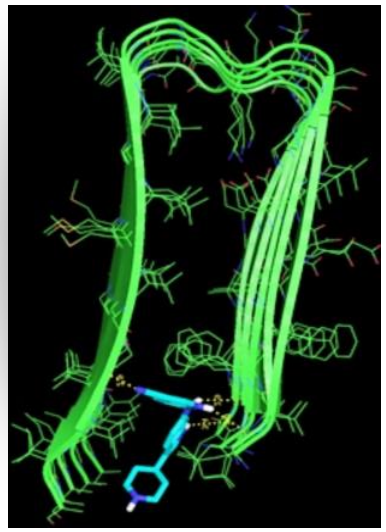
CB: Cerebellum
MFG: Middle frontal gyrus

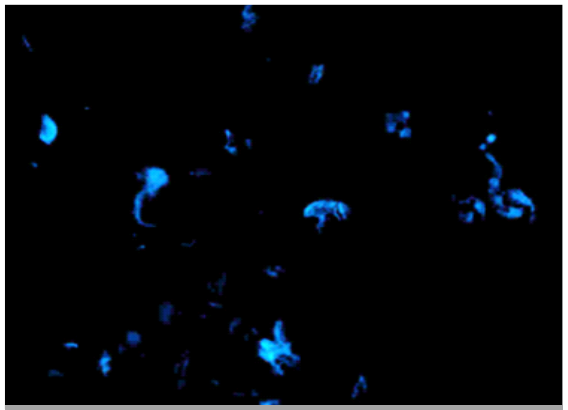
- Target engagement across the full spectrum of synucleinopathies, despite differences in morphology and brain localization of a-synuclein aggregates
- Recently initiated first-in-human clinical study – results expected in Q3 2021

AC Immune

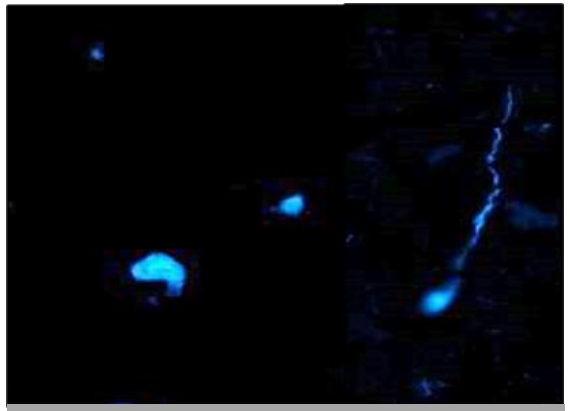
Developing a suite of PET[1] tracers against emerging targets in NDD[2]

Precision medicine approach enabled by the Morphomer™ platform

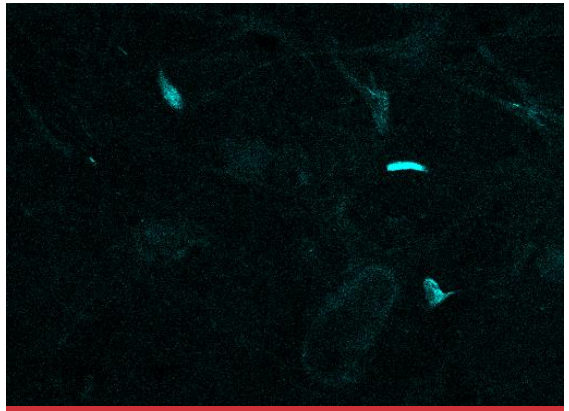




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

The development pathway:

- Rely only on patient-derived brain samples for target engagement
- Minimize off-target binding to optimize signal-to-noise ratio
- Optimize selectivity against other potential co-pathologies (Abeta, Tau, TDP-43)
- Optimize brain penetration and washout
- >600 Morphomers™ have been designed, synthesized and screened to date for AC Immune's TDP-43 PET program

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

First-in-class TDP-43[1] PET[2] imaging tracer

Designed to facilitate clinical development and enable precision medicine

Target	Aggregated TDP-43
Key results	▪ Identified reference compound (Compound A) with binding to pathological TDP-43 aggregates ▪ Target engagement confirmed by micro-autoradiography on a subset of FTLD-TDP[3] Type C pathology ▪ PK[4] study in mice confirmed good, rapid brain uptake (4.11%)

Binding affinity on FTLD-TDP brain-derived TDP-43 aggregates

Type A

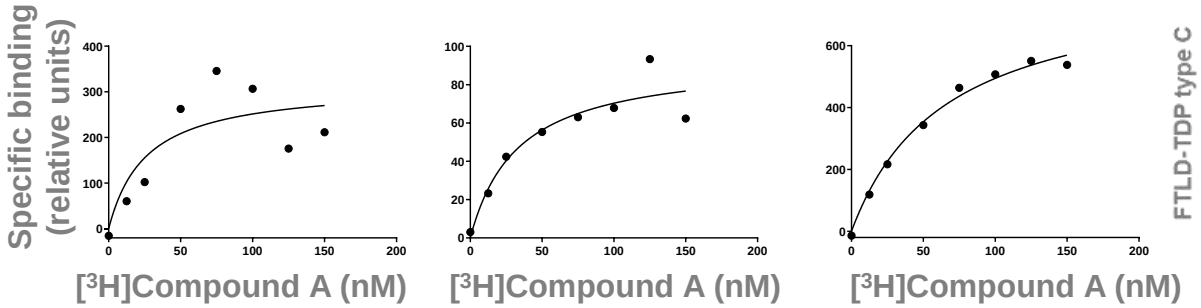
Kd = 26 nM

Type B

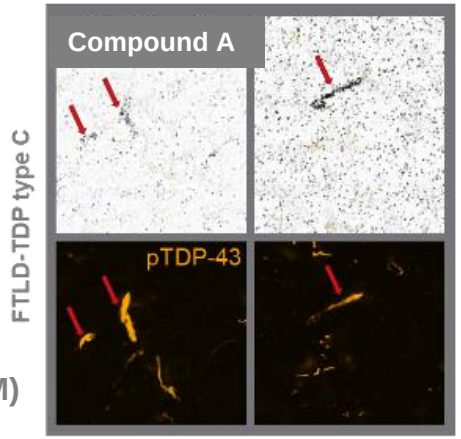
Kd = 33 nM

Type C

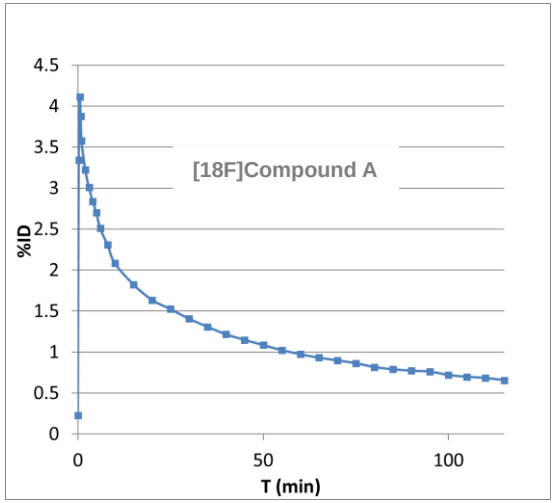
Kd = 65.37 nM



Target engagement by micro-autoradiography



Brain PK profile



Ref: AC Immune unpublished data

Key differentiation	▪ First-in-class PET tracer for TDP-43
Next steps	▪ Identify lead compound and initiate IND-enabling studies

(1) TAR DNA binding protein-43; (2) Positron emission tomography; (3) Frontotemporal lobar degeneration with TDP-43 pathology; (4) Pharmacokinetic

Delivering first- and best-in-class PET[1] tracers for NDD[2]

Tau-PET program

Life Molecular Imaging

PI-2620, a next-generation Tau PET tracer:

- Showed reduced off-target binding compared with first-generation Tau PET tracers; potential for earlier diagnosis
- Successfully completed Phase 1 in AD[3]; currently being evaluated in a Phase 2 longitudinal AD trial and Phase 1 in PSP[4]

a-syn[5]-PET program

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

2nd generation tracer ACI-3847:

- Completed first-in-human trial in idiopathic PD[6]; showed a small signal elevation in relevant brain regions
- Currently evaluated in different synucleinopathies with expected higher a-synuclein pathology

3rd generation tracer ACI-12589:

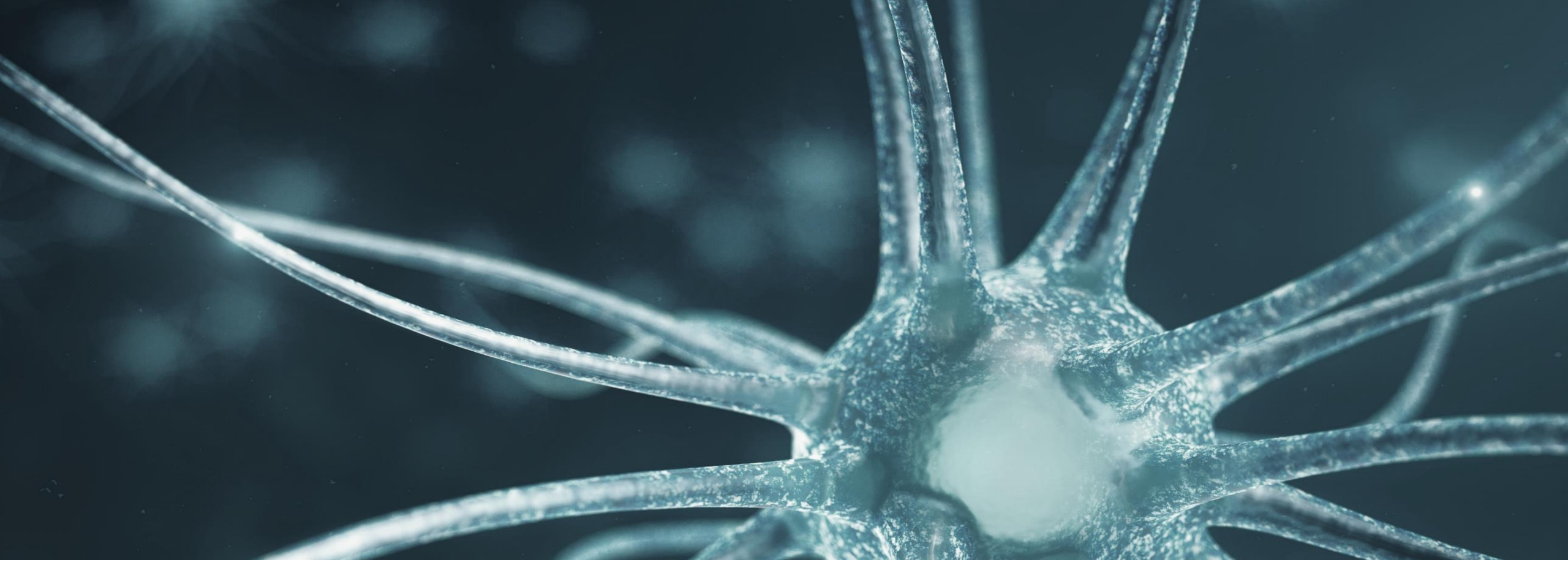
- Showed superior *ex vivo* properties
- Recently initated first-in-human evaluation with results expected Q3 2021

TDP-43[7]-PET program

JPND research

- Established state-of-the-art screening assays based on patient-derived tissue with expected high translational value
- Identified candidates showing nanomolar affinities on tissues from patients with TDP-43 proteinopathies
- Affinity and selectivity will be further optimized to deliver a potential first-in-class PET tracer for TDP-43

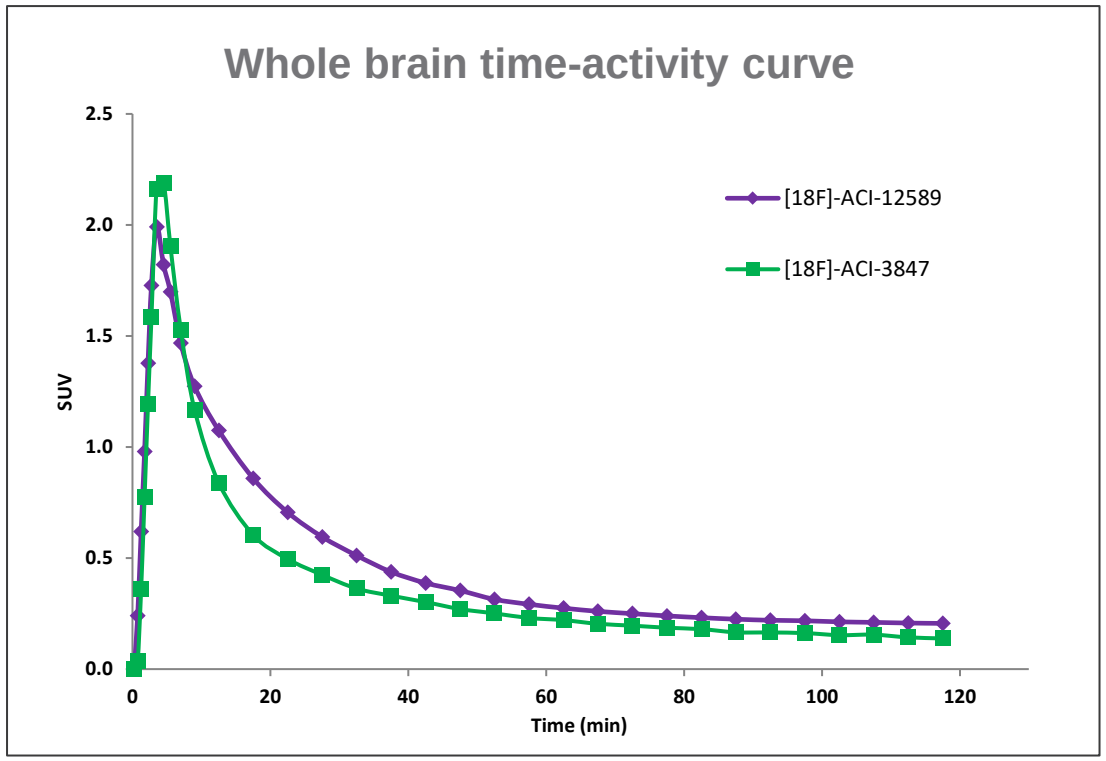
(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Alzheimer's disease; (4) Progressive supranuclear palsy; (5) Alpha-synuclein; (6) Parkinson's disease; (7) TAR DNA binding protein -43



Backup slides

ACI-12589 has a favorable PK[1] profile in non-human primates

ACI-12589 may have potential as a PET[2] tracer

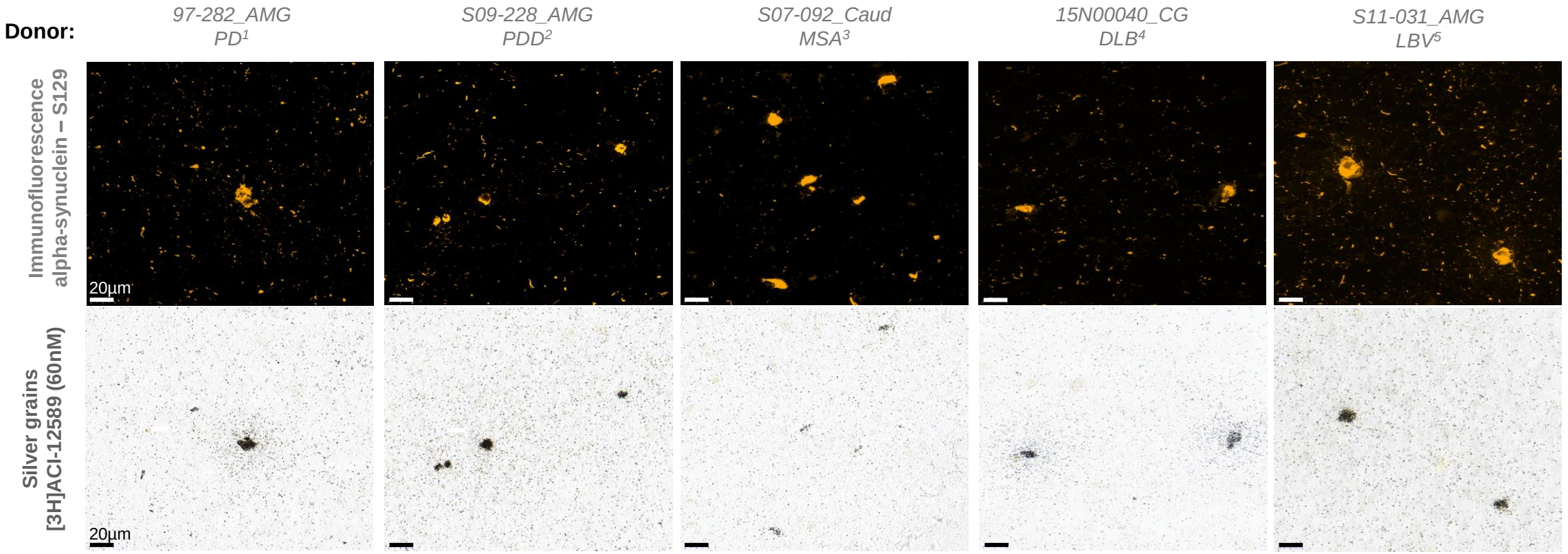


NHP ID	Brain Uptake (min to C_{max})	Brain Uptake (% ID/g)	Peak(half peak (min)	Remaining at 120 min (% of C_{max})
Target	< 10	>3	<30	<10
ACI-12589	3.5	4.3	14	10
ACI-3847	4.5	3-5	9	6

- [18F]ACI-12589 displays a PK in non-human primates suitable for its use as brain PET tracer with good and fast brain uptake, homogeneous distribution as well as rapid and complete washout

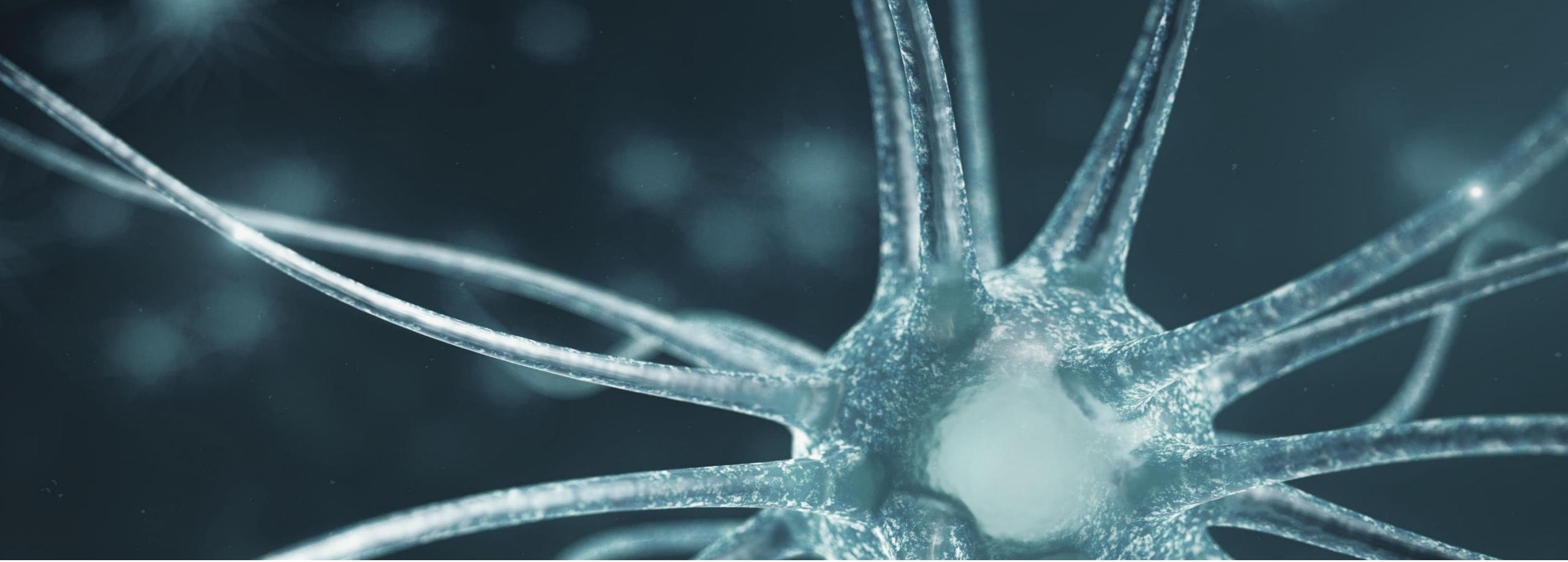
(1) Pharmacokinetic (2) Positron emission tomography

ACI-12589 shows target engagement across alpha-synucleinopathies



- ACI-12589 displays strong target engagement on Lewy bodies and Lewy neurites, as well as alpha-synuclein aggregates of very small size, in PD and other alpha-synucleinopathies, including multiple system atrophy, dementia with Lewy bodies and Lewy body variant

(1) Parkinson's disease; (2) Parkinson's disease with dementia; (3) Multiple system atrophy; (4) Dementia with Lewy bodies; (5) Lewy body variant



Conclusion

Andrea Pfeifer, PhD, Chief Executive Officer

AC Immune value drivers

PRECISION MEDICINE

Novel Therapeutics and Diagnostics

- Key differentiation
- Diagnose and treat specific pathologies
- Potential for tailored combination therapies

PLATFORMS

SupraAntigen™ and Morphomer™

- Generate best-in-class candidates to diagnose and target neurodegenerative diseases
- Clinically validated across multiple programs

PIPELINE

Broad – Diverse – Late-Stage

- Addressing several key pathologies in NDD[1]
- Validating partnerships fund late-stage development
- Early-stage programs generate future value

(1) Neurodegenerative disease

Multiple catalysts to drive value in 2021

Opportunities for further value creation

Biologic
Small Molecule
Diagnostic

Q1

ACI-35.030 ✓
Phase 1b/2a interim analysis (second highest dose)[1]

ACI-24 ✓
- Phase 1b top line study reporting in DS
- Phase 2 interim analysis (12-month)[6] in AD

a-Syn[2] PET tracer[3] ✓
First patient in FiH[4] study

Q2

Semorinemab
Phase 2 primary completion[5]

ACI-24 in AD
Phase 2 interim analysis (18-month)[6]

pTau vaccine (JACI-35.054[7])
Phase 1b/2a interim analysis[8]

ACI-3024
Select NeuroOrphan indication

Q3

a-Syn PET tracer[3]
FiH study readout

Morphomer a-syn
Start *in vivo* PoC studies

TDP-43[9] PET tracer
Initiate IND[10]-enabling studies

Q4

ACI-35.030
Phase 1b/2a interim analysis (highest dose)[11]

ACI-24 in DS[12]
Submit IND for optimized formulation

Morphomer NLRP3[13]-ASC[14]
- Report *in vivo* PoC in non-CNS[15] disease model
- Start *in vivo* PoC studies (CNS) with validated candidate

Anti-NLRP3-ASC antibody
Start *in vivo* PoC

Anti-TDP-43 antibody
Initiate IND-enabling toxicology studies

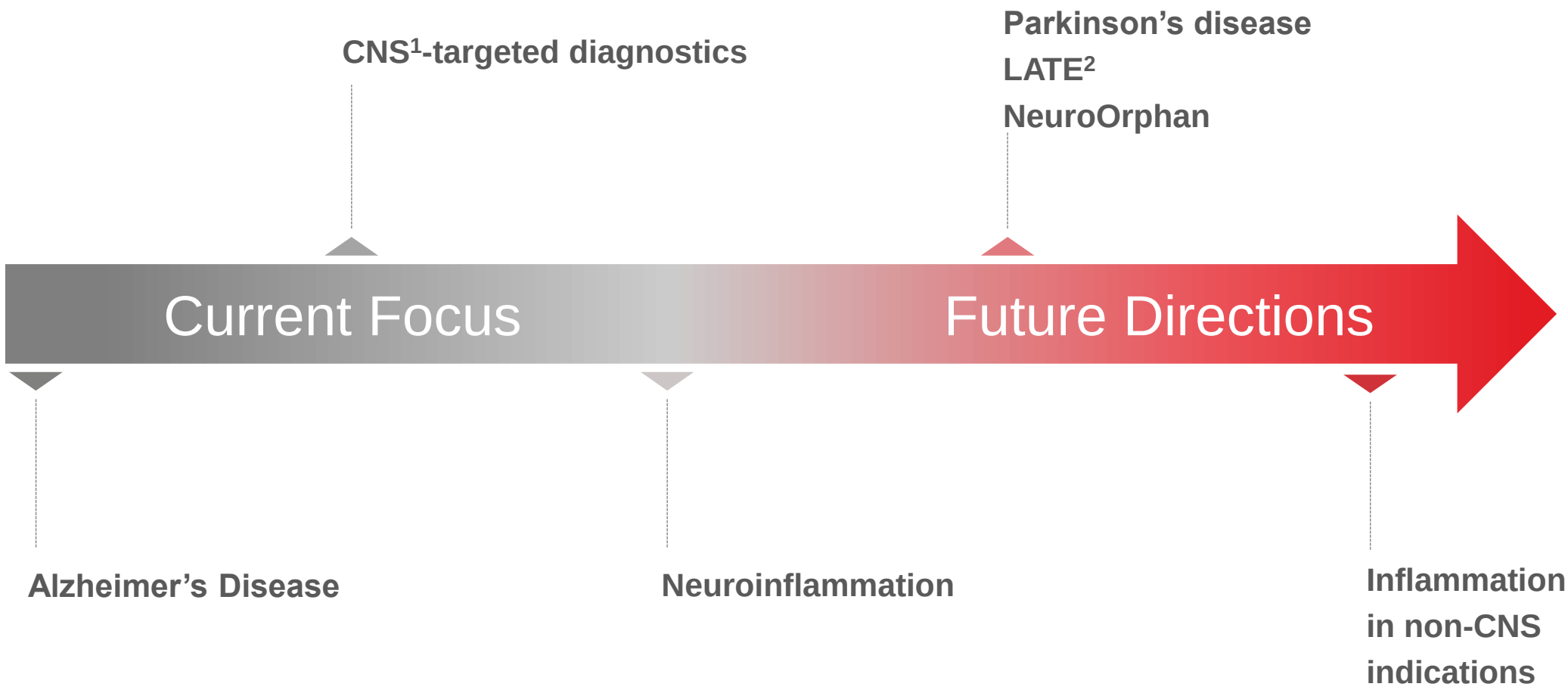
TDP-43 biofluid diagnostic
Establish validation-ready assay

(1) Cohort 1.2: safety/tolerability and immunogenicity; (2) Alpha synuclein; (3) 3rd-generation compound; (4) First-in-human clinical study; (5) Lauriet study in moderate Alzheimer's disease; estimated last patient, last visit; (6) Safety/tolerability and immunogenicity; (7) Alternative pTau vaccine; (8) JACI-35.054: safety/tolerability and immunogenicity; (9) TAR DNA-binding protein 43; (10) Investigational new drug; (11) Cohort 1.3: safety/tolerability and immunogenicity; (12) Down syndrome-related Alzheimer's disease; (13) (NOD)-like receptor protein 3; (14) Apoptosis-associated speck-like protein containing a CARD, also called PYCARD; (15) Central nervous system

AC Immune

AC Immune future directions

Expanding our capabilities and building a fully-integrated company



(1) Central nervous system; (2) Limbic-predominant age-related TDP-43 encephalopathy

AC Immune

We continue to shape the future of neurodegeneration by discovering and developing breakthrough therapies through pioneering science and precision medicine

Q&A