Discovery and preclinical development of [^{18}F]ACI-19626, a first-in-class TDP-43 PET tracer

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Disclosures

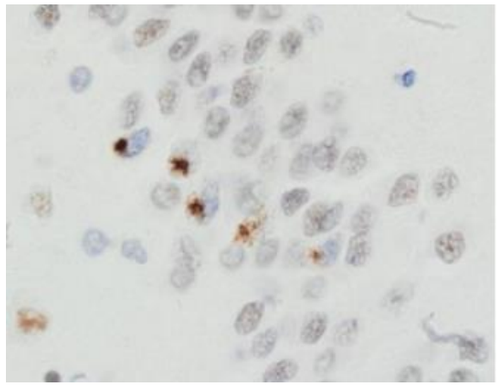
Tamara Seredenina is an employee of AC Immune

Funding

Grant from the Michael J Fox Foundation

TDP-43 PET[1] tracers can improve the diagnosis and treatment of NDD[2]

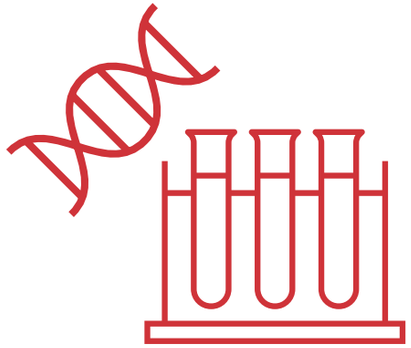
TDP-43 pathology is present in multiple neurodegenerative disorders



Neumann et al., Acta Neuropath 2023

- Primary pathology in ALS[3], FTLD-TDP[4] and LATE[5]
- Co-pathology in AD[6], PD[7], HD[8] and CTE[9]

Early diagnosis of TDP-43 proteinopathies is currently not available



- Low abundance of pathological TDP-43 species limits utility of fluid biomarkers
- Seed amplification assay holds promise*

* Audrain et al., 2023 Brain Comm

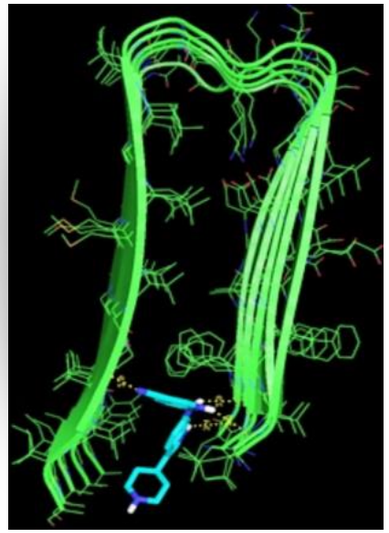
Benefits of PET tracers for imaging have been validated

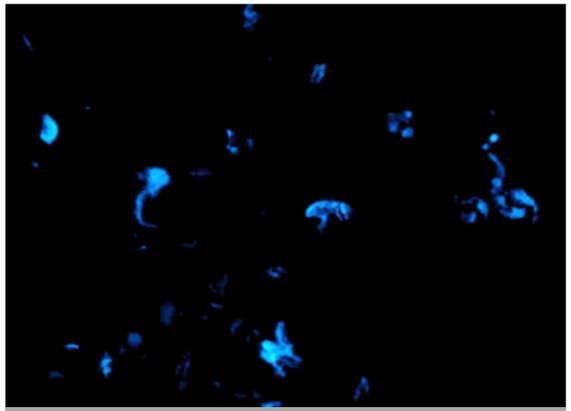
- Patient stratification, focused recruitment and monitoring for better clinical trials
- May enable combination treatment of co-pathologies

(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Amyotrophic lateral sclerosis; (4) Frontotemporal lobar degeneration with TDP-43 pathology; (5) Limbic-predominant age-related TDP-43 encephalopathy; (6) Alzheimer's disease; (7) Parkinson's disease; (8) Huntington's disease; (9) Chronic traumatic encephalopathy

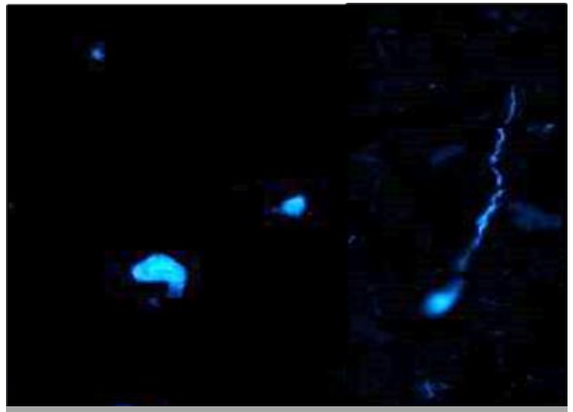
Precision medicine approach enabled by the Morphomer® platform

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

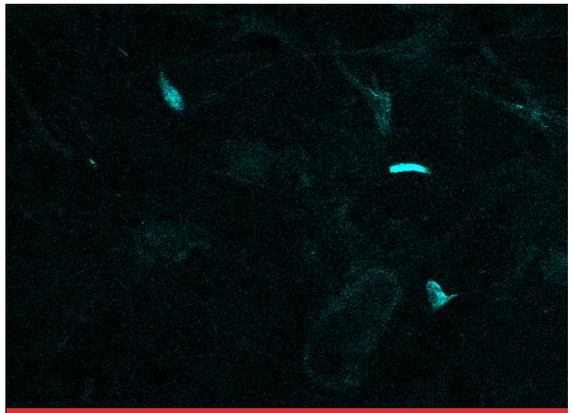




Tau NFTs[3]
PI-2620



a-syn[4] Lewy bodies
ACI-12589



TDP-43[5] inclusions

Leverage the Morphomer® small molecule platform:

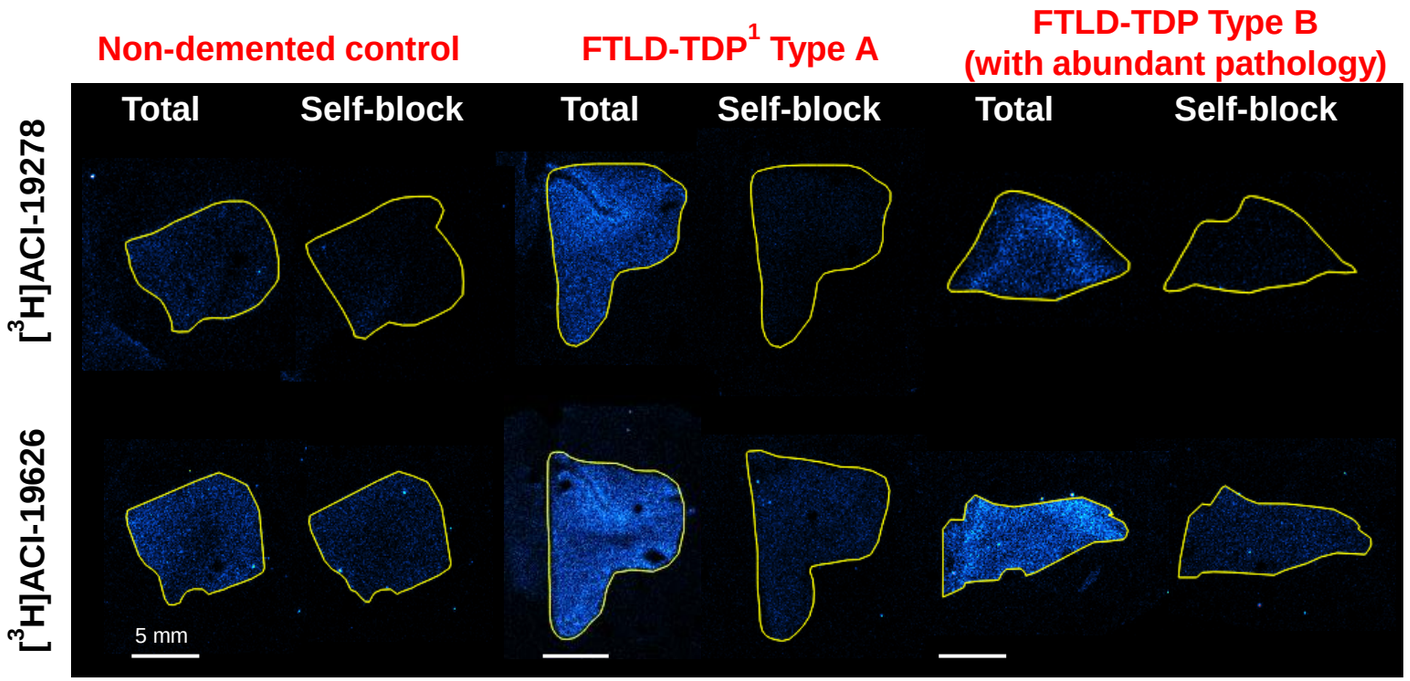
- Non-peptidic, small molecules with CNS-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, a-syn)
- Pharmacokinetics suitable for brain PET imaging

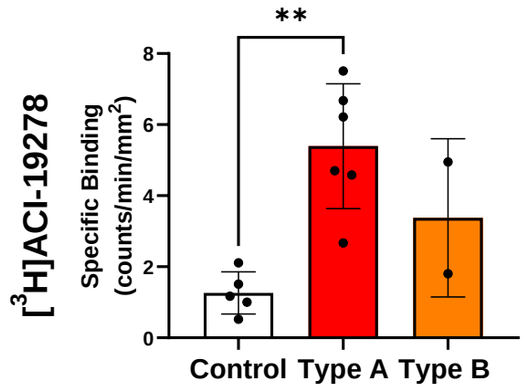
- Lead molecules, ACI-19278 and ACI-19626, display an optimal profile for CNS PET tracer development

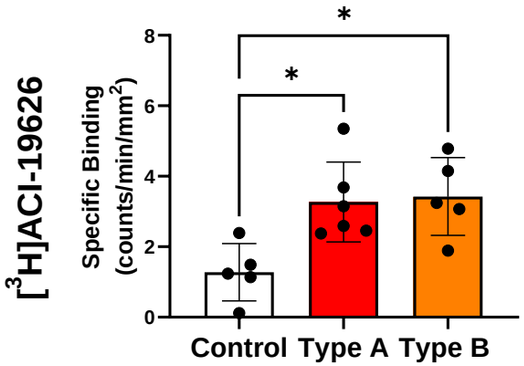
(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Neurofibrillary tangles; (4) Alpha synuclein; (5) TAR DNA binding protein-43

Target engagement

Classical autoradiography on FTLD-TDP[1] brain sections







Ref: ACI unpublished data

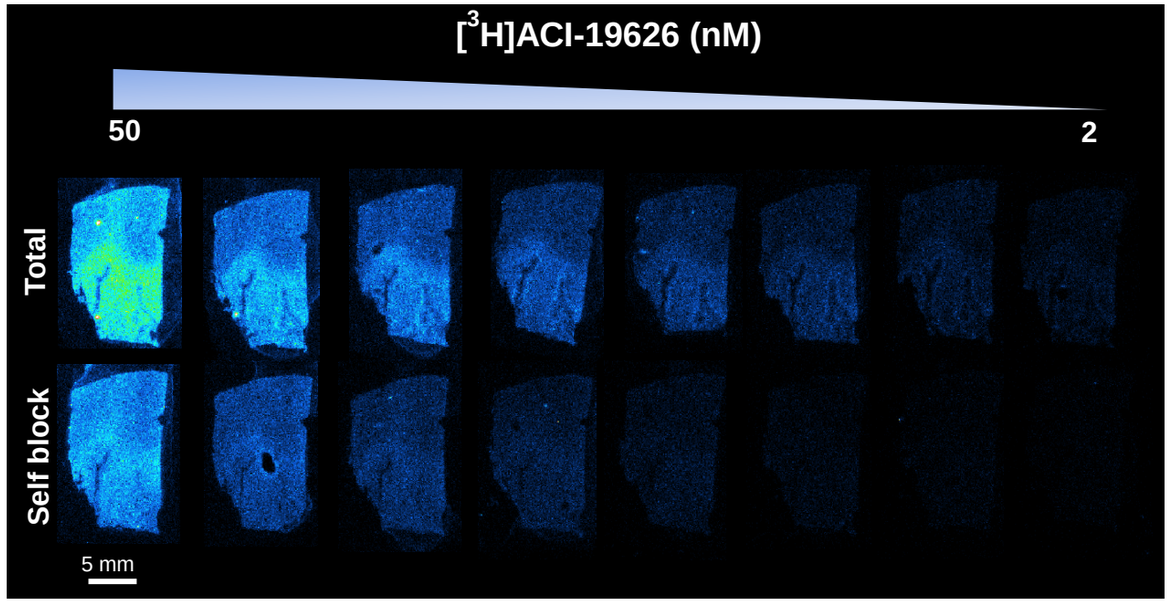
- The first proof of target engagement on brain samples with FTLD-TDP type A pathology with a method having resolution translatable to human PET
- FTLD-TDP type A pathology is commonly found in brains of FTLD-TDP GRN[2], LATE[3] and AD[4]
- FTLD-TDP type B pathology is found in most cases of FTD-MND[5] and ALS[6]

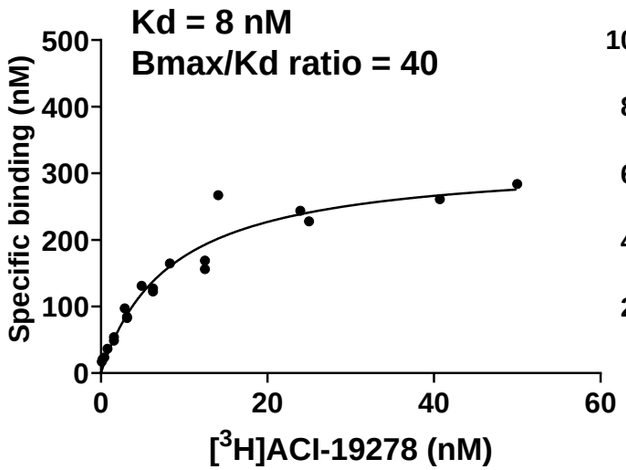
(1) Frontotemporal lobar degeneration with TDP-43 pathology; (2) mutation in progranulin gene; (3) limbic-predominant age-related TDP-43 encephalopathy; (4) Alzheimer's disease; (5) motor neuron disease; (6) Amyotrophic lateral sclerosis

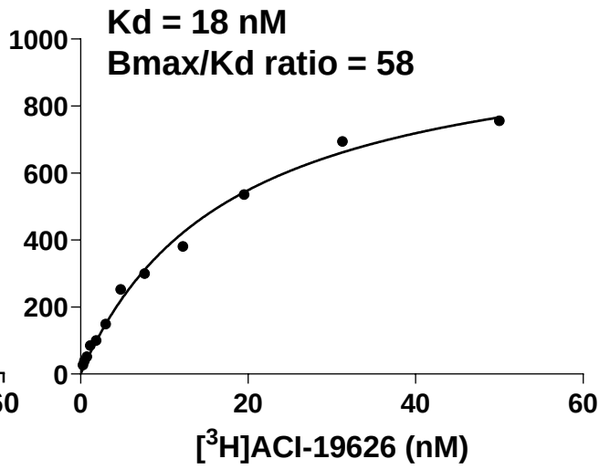
Target engagement and binding affinity

Classical autoradiography on FTLD-TDP[1] type A brain sections

FTLD-TDP[1] Type A sections







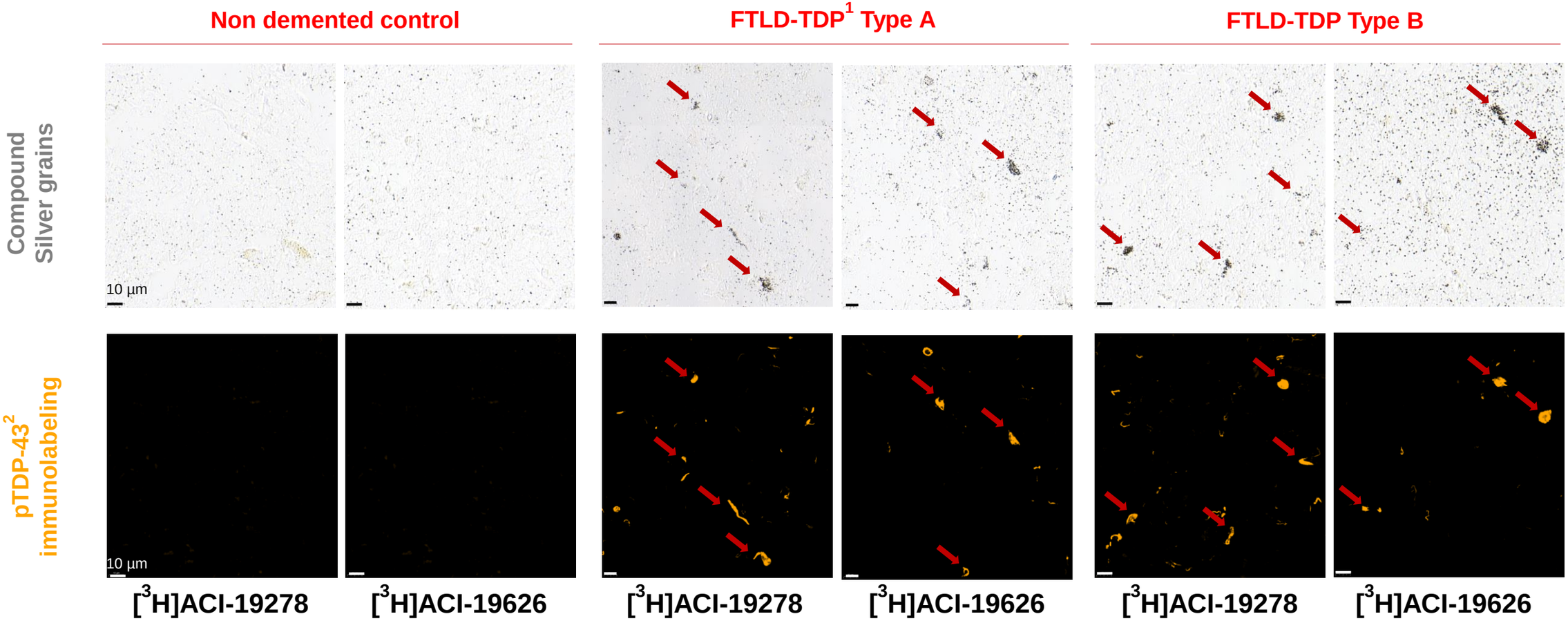
Ref: ACI unpublished data

- High affinity binding (Kd=10-20 nM) on brain sections with FTLD-TDP type A pathology by classical ARG[2]
- Optimal *in vitro* binding potential (Bmax/Kd > 40) for further development as brain PET tracer

(1) Frontotemporal lobar degeneration with TDP-43 pathology; (2) autoradiography

Characterization of target engagement

Specific binding to TDP-43 pathological aggregates by high resolution autoradiography



- ACI-19626 and ACI-19278 show strong target engagement on human brain samples with FTLD-TDP pathology, visualized by compound co-localization with pTDP-43 antibody labeling

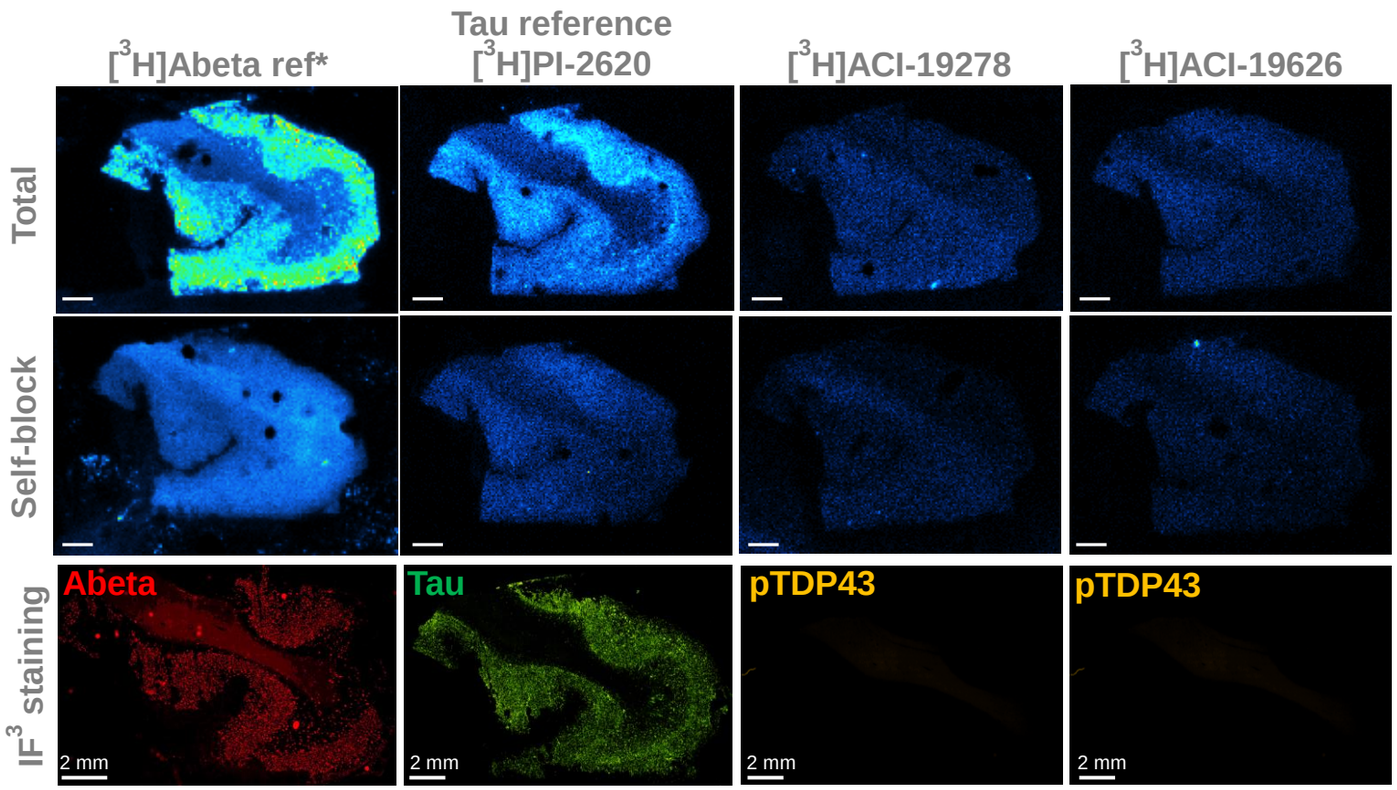
(1) Frontotemporal lobar degeneration with TDP-43-immunoreactive pathology; (2) Immunolabeling with phospho-TDP-43 pS409/410 antibody

Ref: ACI unpublished data

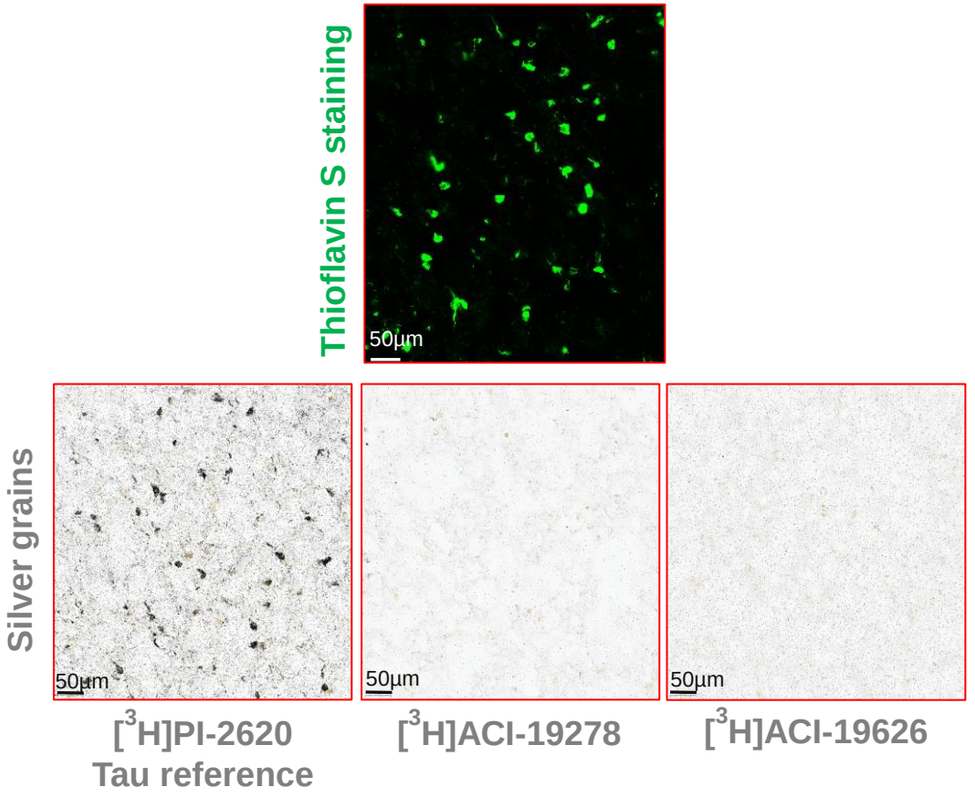
Selectivity over Abeta and pathological Tau

On sections from Alzheimer's disease brains by autoradiography

Autoradiography in AD[1] tissue sections



High-resolution ARG[2] in Tau-rich AD sections



Ref: ACI unpublished data

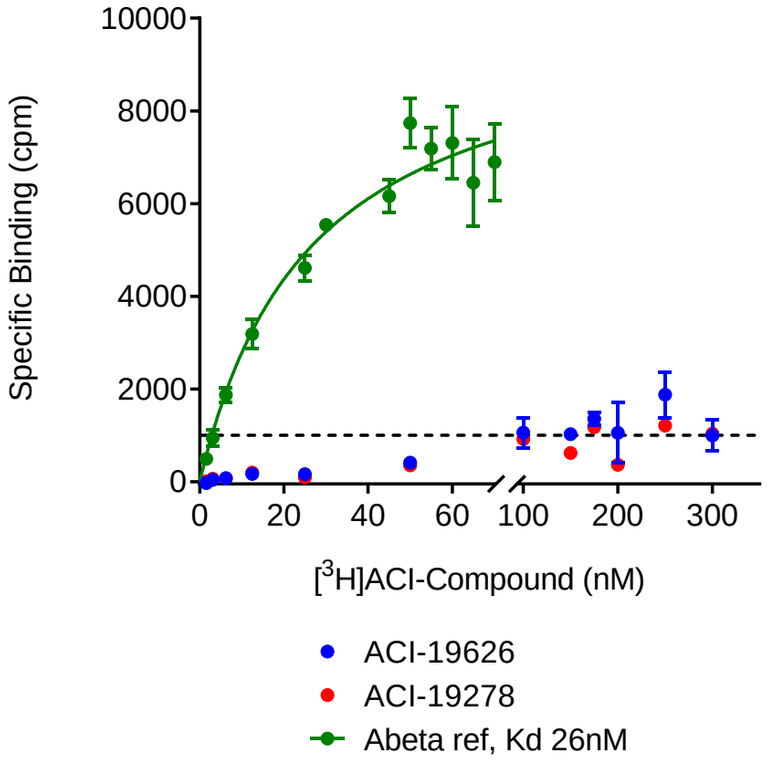
- ACI-19626 and ACI-19278 display selectivity to TDP-43 over Abeta and Tau in AD brain sections

(1) Alzheimer's disease; (2) Autoradiography; (3) Immunofluorescence; (4) neurofibrillary tangles; *visualization scale for Abeta ref was set differently from the other compounds

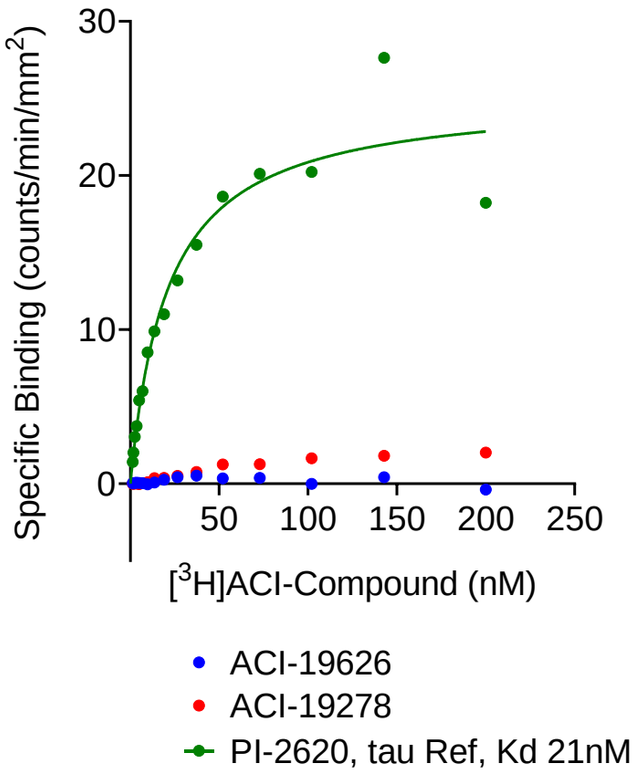
Selectivity over Abeta, pathological Tau and α-synuclein

Saturation binding experiments in AD[1] and PD[2] brain homogenates

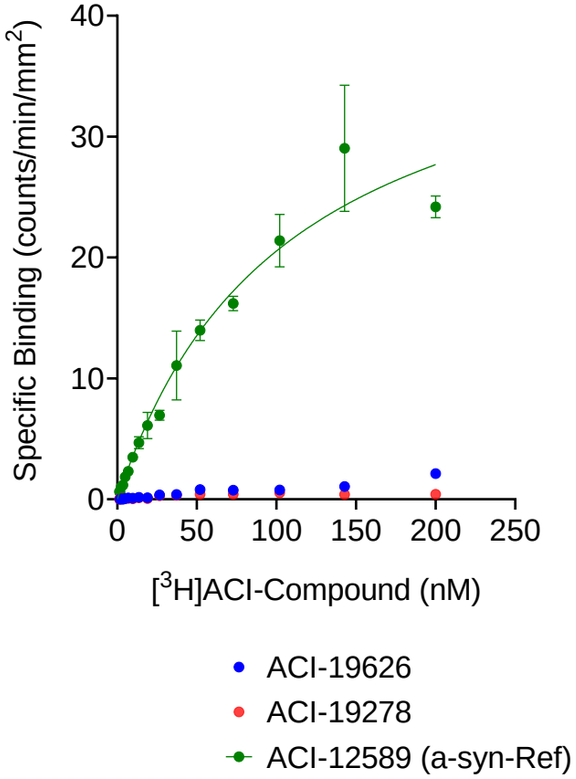
AD brain homogenates



Tau PHF



PD brain homogenates



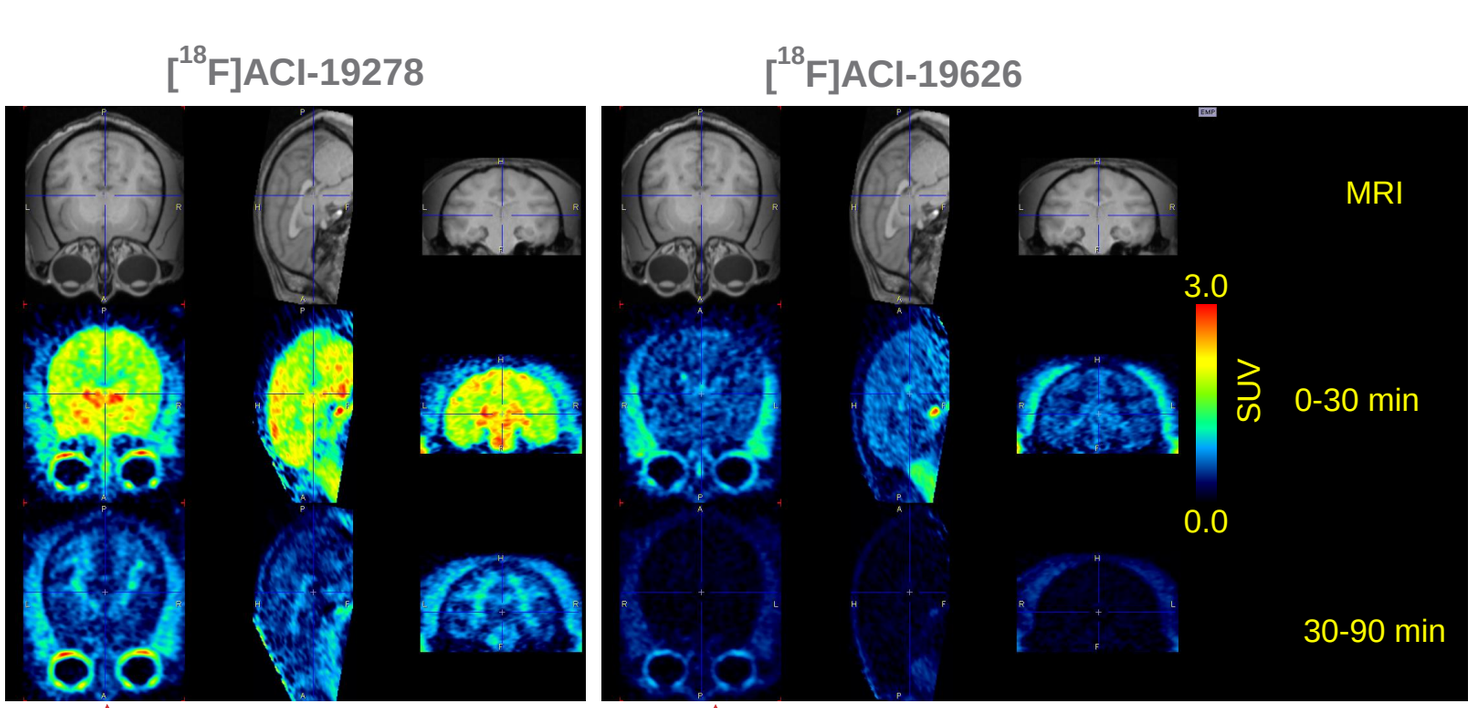
Ref: ACI unpublished data

- ACI-19278 and ACI-19626 display selectivity to TDP-43 over Abeta and Tau in AD brain homogenates, and α-synuclein in PD brain homogenates

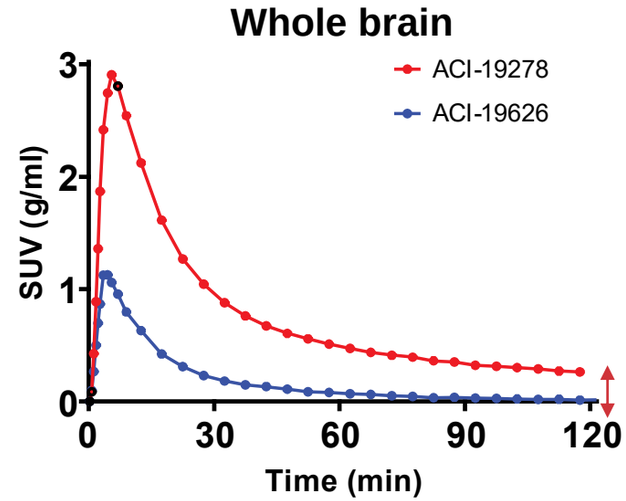
(1) Alzheimer's disease; (2) Parkinson's disease

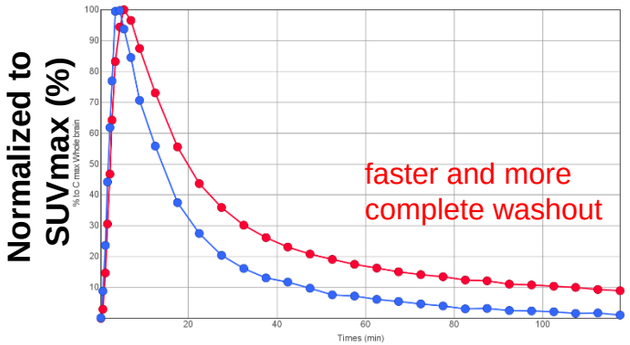
Characterization of pharmacokinetic (PK) profile

^{18}F PK profile in brain after intravenous administration in non-human primates (NHP)



Scans were performed in the same rhesus monkey





Ref: ACI unpublished data

[^{18}F]ACI-19626 has an improved PK profile in NHP compared to [18F]ACI-19278:

- Enters the brain rapidly
- Displays faster and more complete washout
- Shows a more homogenous brain distribution

AC Immune’s first-in-class TDP-43 PET tracer

First-in-class	▪ With our extensive experience in tracer development, several series with distinct chemical scaffolds identified that bind specifically to pathological TDP-43 aggregates
Product profile I	▪ Two first-in-class TDP-43 ligands, ACI-19278 and ACI-19626, that show: • Low nM Kd on FTLD-TDP brain tissue • Potential to detect TDP-43 pathology in various indications[1]
Product profile II	• Selectivity over Abeta, Tau and α-syn; clean off-target profile (e.g. MAO-A, MAO-B) • No significant metabolites detected • Rapid brain uptake and fast washout in non-human primates
Development status	▪ ACI-19626 selected for the First-in-Human study and preclinical activities ongoing ▪ First-in-Human study to commence in Q4 2024
Further optimization	▪ Medicinal chemistry optimization continues to explore SAR and enrich our TDP-43 PET tracer library with additional candidates

(1) FTLD-TDP, ALS, AD and LATE

Acknowledgements

Efthymia Vokali
Tamara Seredenina
Nicolas Dreyfus
Elodie Chevalier
Tariq Afroz
Monisha Ratnam
Tania Melly
Gabrielle Bodley
Dorian Charmey
Mathieu Clavel
Thomas Jaquier
Myriam Ravache
Christophe Delgado
Jacqueline Kocher
Andreia Serra
Heiko Kroth
Jerome Molette
Viktoria Gerasymchuk
Just Genius
Ruth Luthi-Carter
Francesca Capotosti
Johannes Streffer
Andrea Pfeifer
Nuno Mendonça
Madiha Derouazi
Marie Kosco-Vilbois

JPND research
EU Joint Programme – Neurodegenerative Disease Research

ImageTDP43

Prof. Magda Polymenidou
Prof. Emanuele Buratti
Prof. John Van Swieten
Dr. Harro Seelaar

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Grant ID: MJFF-022232

Brain banks

- **Neurodegenerative Disease Brain Bank UCSF, Prof. William Seeley** (funding support from NIH grants P01AG019724 and P50AG023501, the Consortium for Frontotemporal Dementia Research, and the Tau Consortium).
- **Netherlands Brain Bank**, Netherlands Institute for Neuroscience, Amsterdam. All Material has been collected from donors from whom a written informed consent for brain autopsy and the use of the material and clinical information for research purposes had been obtained by the NBB.
- **Queen Square Brain Bank for Neurological Disorders, UCL, Prof. Tammaryn Lashley**
- **NeuroResource,** UCL Queen Square Institute of Neurology**, Dr. Jia Newcombe**
- **Target ALS, Prof. Robert Bowser**
- **University of Kentucky, Prof. Peter Nelson**

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