Discovery and optimization of the first-in-class TDP-43 PET tracer

Tamara Seredenina, PhD | AAIC 2023 | July 17th

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Disclosures

Tamara Seredenina is an employee of AC Immune entitled to stock options

Funding

Grant from the Michael J Fox Foundation

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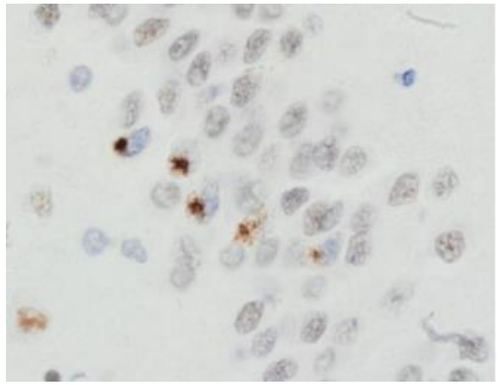
TDP-43 PET[1] tracers can improve the diagnosis and treatment of NDD[2]

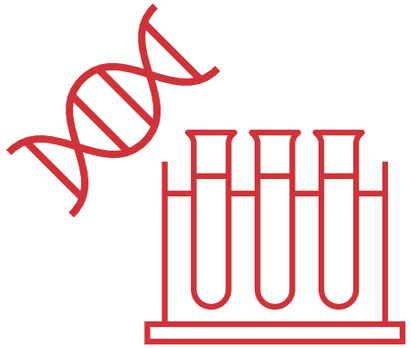
TDP-43 pathology is present in multiple neurodegenerative disorders



Neumann et al., Acta Neuropath 2023

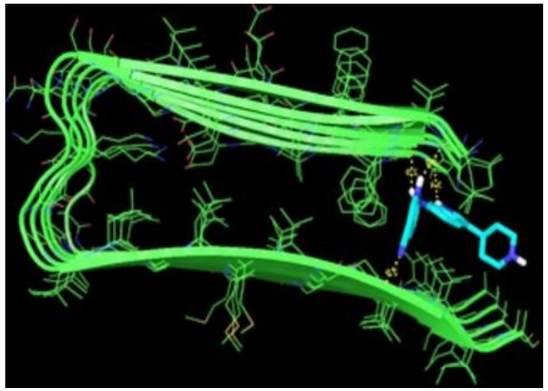
- Primary pathology in ALS[3], FTLD-TDP[4] and LATE[5]
- Co-pathology in AD[6], PD[7], HD[8] and CTE[9]

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

AC Immune's Morphomer® platform enables precision medicine approach



- Non-peptidic, small molecules with CNS-drug properties binding to misfolded proteins
- Delivered Tau tracer PI-2620 and a-syn tracer ACI-12589

- ACI-19278, first-in-class TDP-43 PET tracer, identified using ACI Morphomer® platform

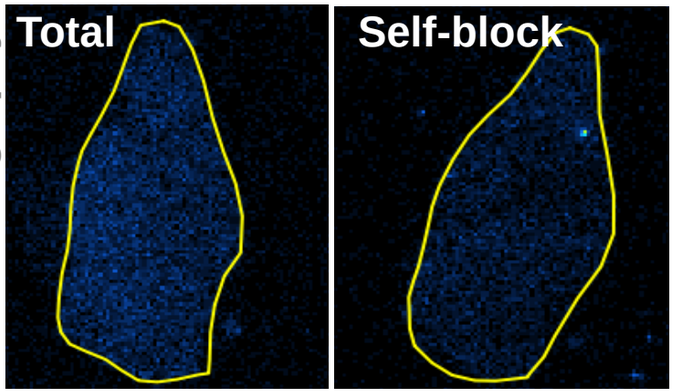
(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Amyotrophic lateral sclerosis; (4) Frontotemporal lobar degeneration with TDP-43 pathology; (5) Limbic-predominant age-related TDP-43 encephalopathy; (6) Alzheimer's disease; (7) Parkinson's disease; (8) Huntington's disease; (9) Chronic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

[3H]ACI-19278 target engagement and binding affinity

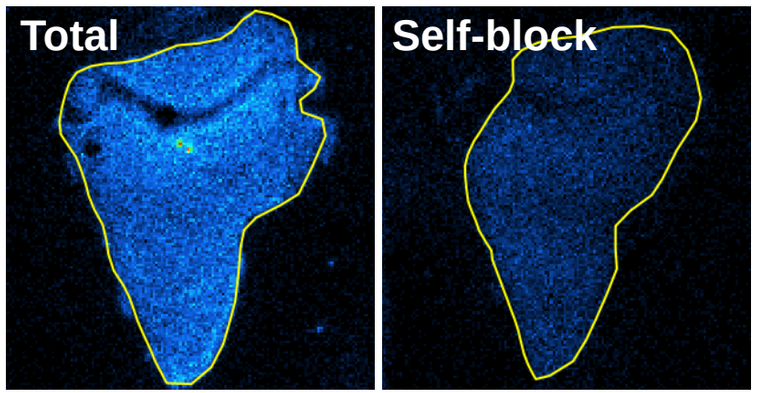
Classical autoradiography on FTLD-TDP[1] brain sections

ACI-19278 Autoradiography

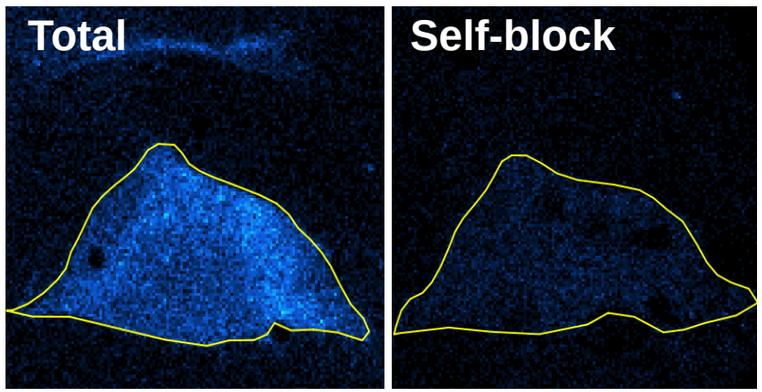
Non-demented control

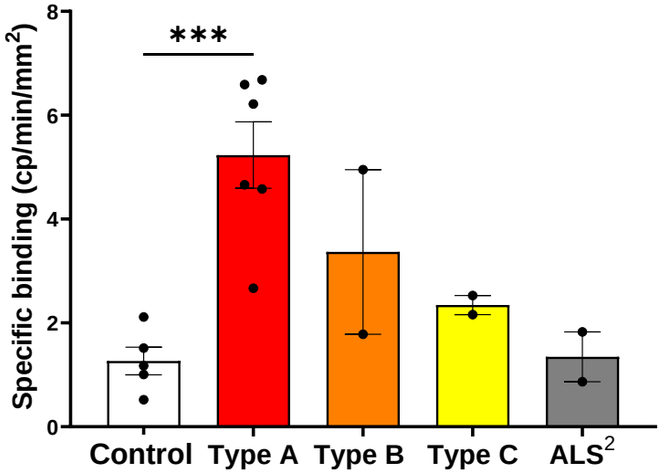


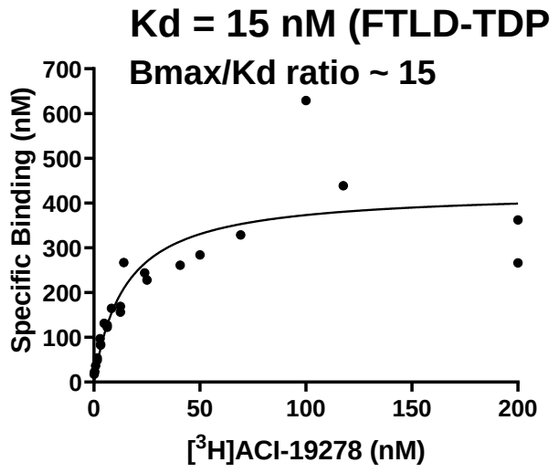
FTLD-TDP Type A



FTLD-TDP Type B (abundant pathology)







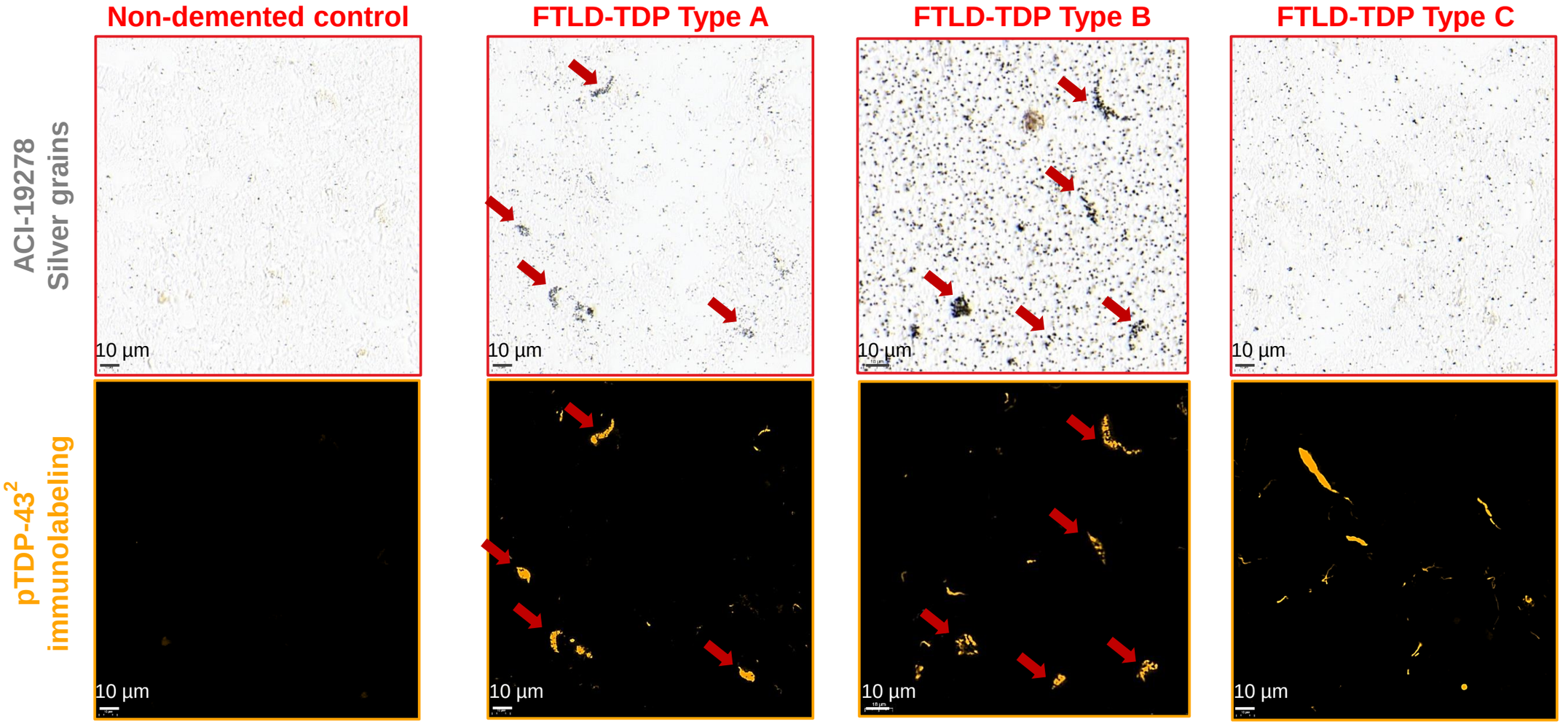
Ref: ACI unpublished data

- Low nanomolar binding affinity and the first proof of target engagement on brain samples with FTLD-TDP type A pathology by a method with the resolution translatable to human PET
- FTLD-TDP type A pathology is commonly found in brains of FTLD-TDP GRN[3], LATE[4] and AD[5]

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

[^{3}H]ACI-19278 target engagement on FTLD-TDP^1 pathology types

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



Ref: ACI unpublished data

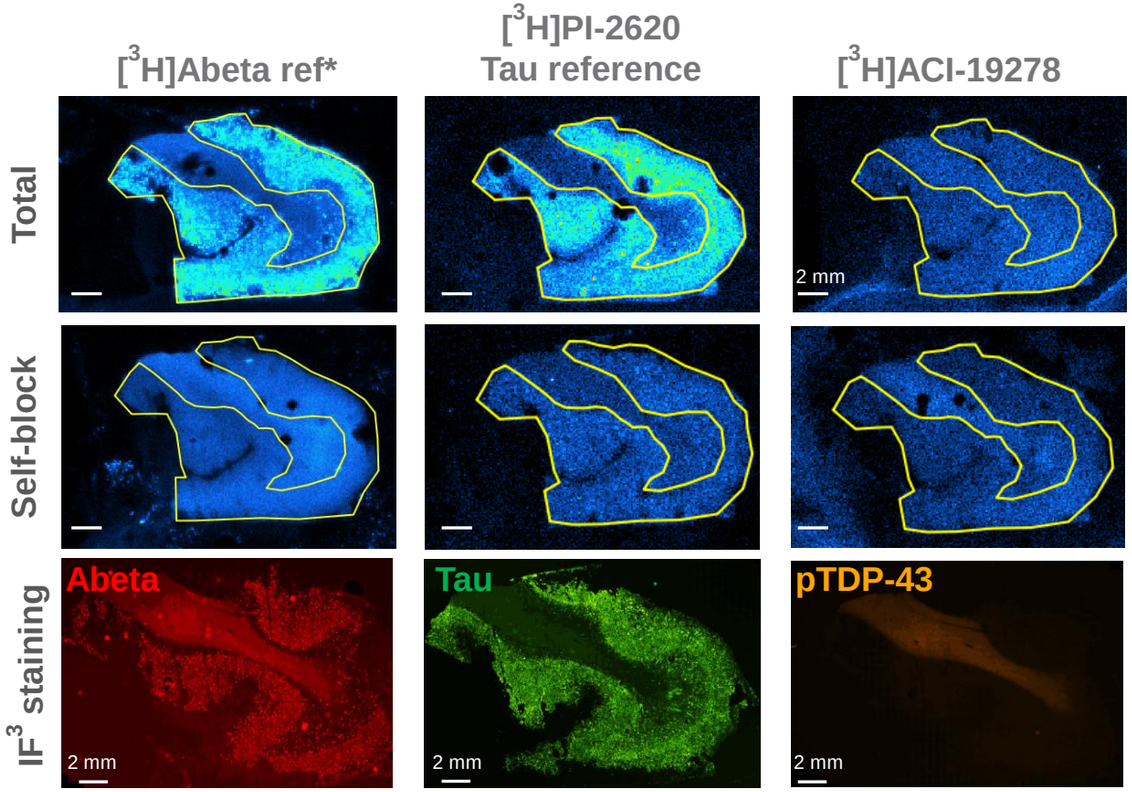
- Strong target engagement on human brain samples with FTLD-TDP type A and B pathology, showing compound co-localization with pTDP-43 antibody labeling

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

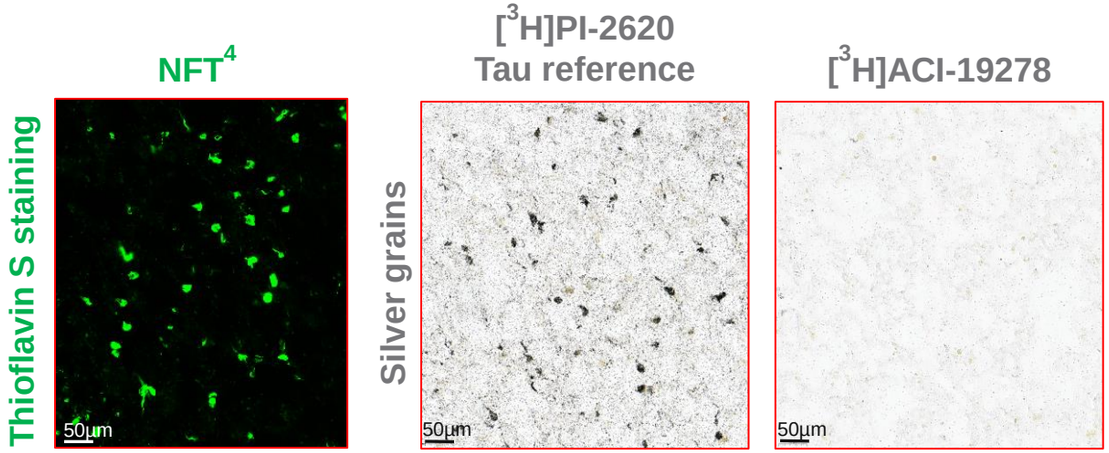
[3H]ACI-19278 is selective over Abeta and pathological Tau

Selectivity on tissue sections from brains of Alzheimer's disease

Autoradiography in AD[1] tissue sections



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



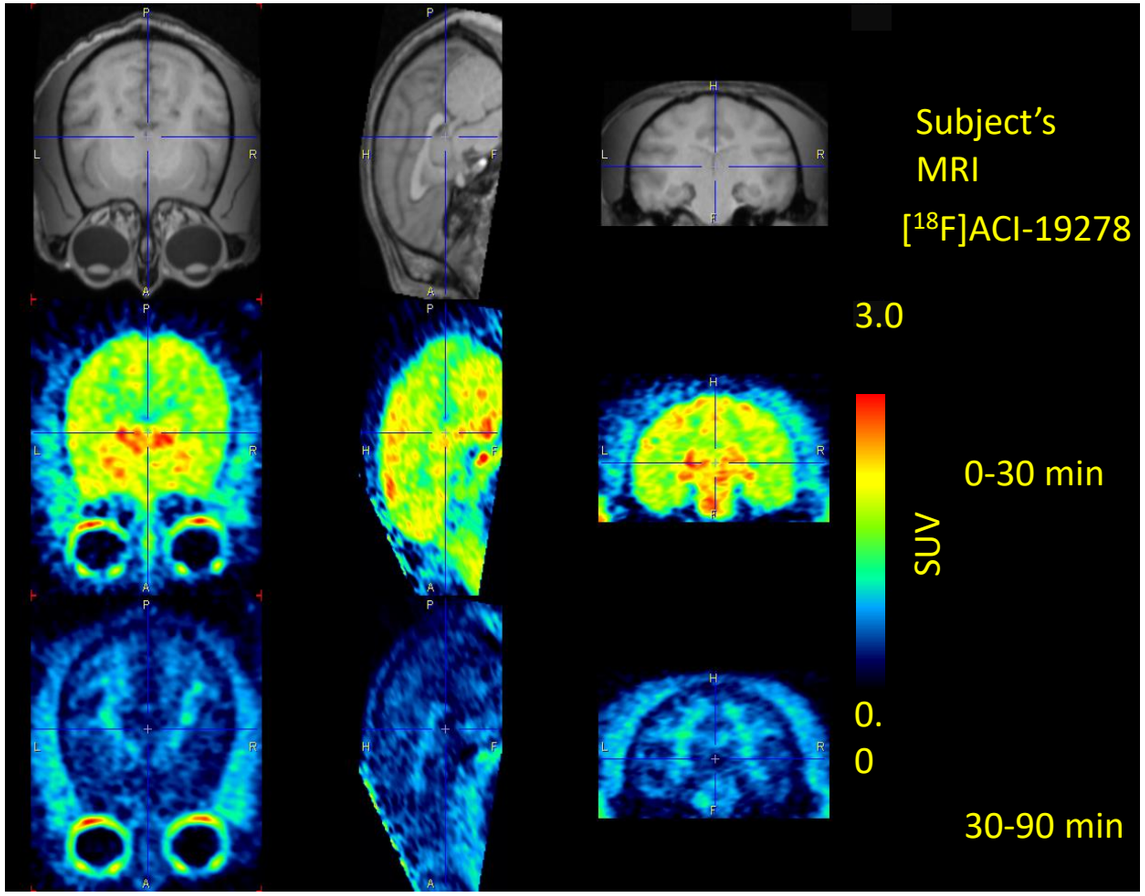
Ref: ACI unpublished data

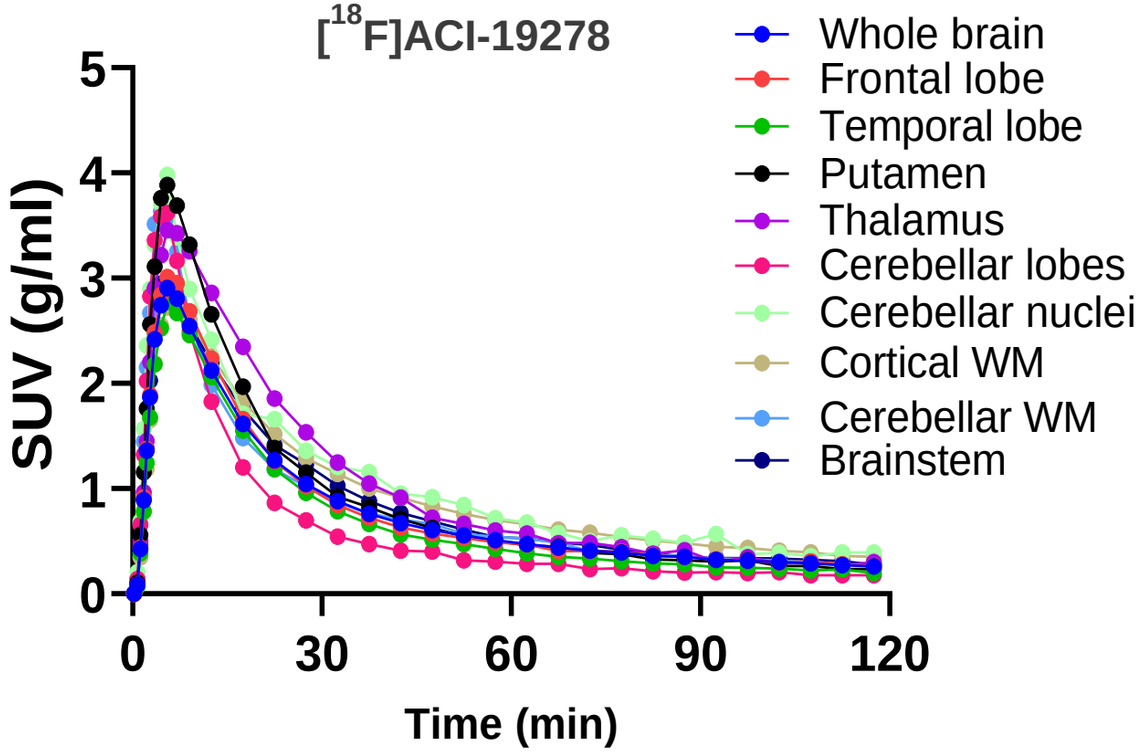
- ACI-19278 displays selectivity over co-pathologies such as Abeta and Tau in AD brain tissue sections

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

[18F]ACI-19278 pharmacokinetic profile

[18F] PK profile in brain after intravenous administration in non-human primates





Ref: ACI unpublished data

- [18F]ACI-19278 readily entered NHP brain upon intravenous administration
- Peak whole-brain standardized uptake value (SUV) > 2.5 % injected dose
- Fast washout suitable for human PET

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

Conclusions

1	▪ Building on our extensive experience in tracer development, several series with distinct chemical scaffolds identified that bind specifically to pathological TDP-43 aggregates
2	▪ First-in-class TDP-43 ligand ACI-19278 shows: ▪ Low nM Kd on FTLD-TDP brain tissue ▪ Potential to detect TDP-43 pathology in various indications, including FTLD-TDP, ALS, AD and LATE ▪ Selectivity over common co-pathologies including Abeta, Tau and a-synuclein ▪ Robust brain uptake and fast washout in non-human primates ▪ Analogs with similar binding profile available
3	▪ First-in-human evaluation to start in Q2 2024
4	▪ Medicinal chemistry optimization continues to explore SAR and enrich our TDP-43 PET tracer library with additional candidates

Ref: ACI unpublished data

Acknowledgements

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**

Efthymia Vokali
Nicolas Dreyfus
Elodie Chevalier
Tariq Afroz
Monisha Ratnam
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Mathieu Clavel
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Francesca Capotosti
Andrea Pfeifer
Johannes Streffer
Marie Kosco-Vilbois

Prof. John Trojanowski

JPND research
EU Joint Programme – Neurodegenerative Disease Research
ImageTDP43
Dr. Harro Seelaar

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
Grant ID: MJFF-022232

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