IMAGE TDP-43
Imaging heterogeneous TDP-43 neuropathologies

JPND final symposium

Tamara Seredenina, PhD

2024 | November 28th

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Disclosures

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

IMAGE TDP-43 consortium

Aims and impact on the therapeutic development for neurodegenerative diseases

JPND research
EU Joint Programme – Neurodegenerative Disease Research

Aims: **Improve understanding of TDP-43 biology and pathology**
Clinical trial for 1st generation TDP-43 imaging agent in FTD

Dates: **January 2021 – December 2023** **Extension to July 2026**

Benefits of TDP-43 brain PET tracer:

- Patient stratification, focused recruitment and monitoring for better clinical trials
- Differentiation of frontotemporal dementia (FTD) subtypes
- May enable combination treatment of co-pathologies., e.g. in Alzheimer's disease (AD)

IMAGE TDP-43 consortium

Partners and external collaborators

JPND research
EU Joint Programme – Neurodegenerative Disease Research

PET imaging experts

Oskar Hansson

John van Swieten

Ruben Smith

Harro Seelaar

Region Skåne

Erasmus MC
Universitair Medisch Centrum Rotterdam

TDP-43 biology experts

Magdalini Polymenidou

University of Zurich[UZH]

Emanuele Burrati

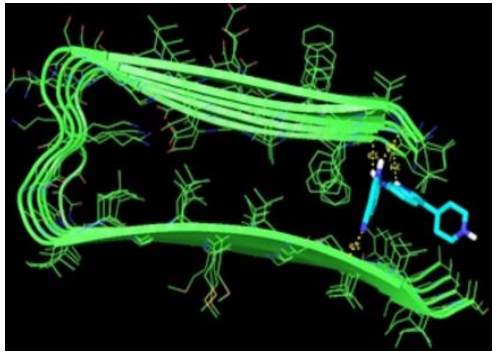
International Centre for Genetic Engineering and Biotechnology

Patrizia Longone

Santa Lucia Neuroscienze e Riabilitazione

Biotech pioneering precision medicine for neurodegeneration

AC Immune



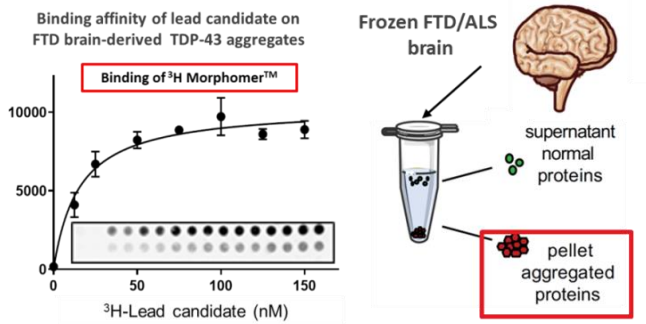
Morphomer® platform delivered:

- Tau PET tracer PI-2620
- A-syn PET tracer ACI-12589
- **First-in-class TDP-43 PET tracers**

IMAGE TDP-43 consortium

Plan of work

Molecular assays



JPND research
EU Joint Programme – Neurodegenerative Disease Research

Cellular assays

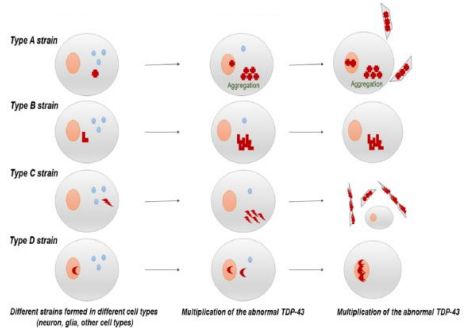
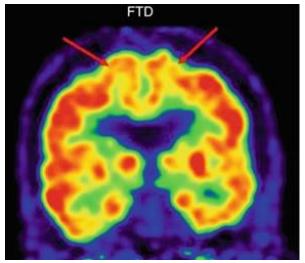
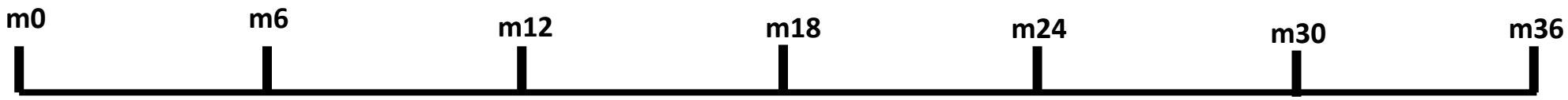


IMAGE TDP-43



Clinical Trial



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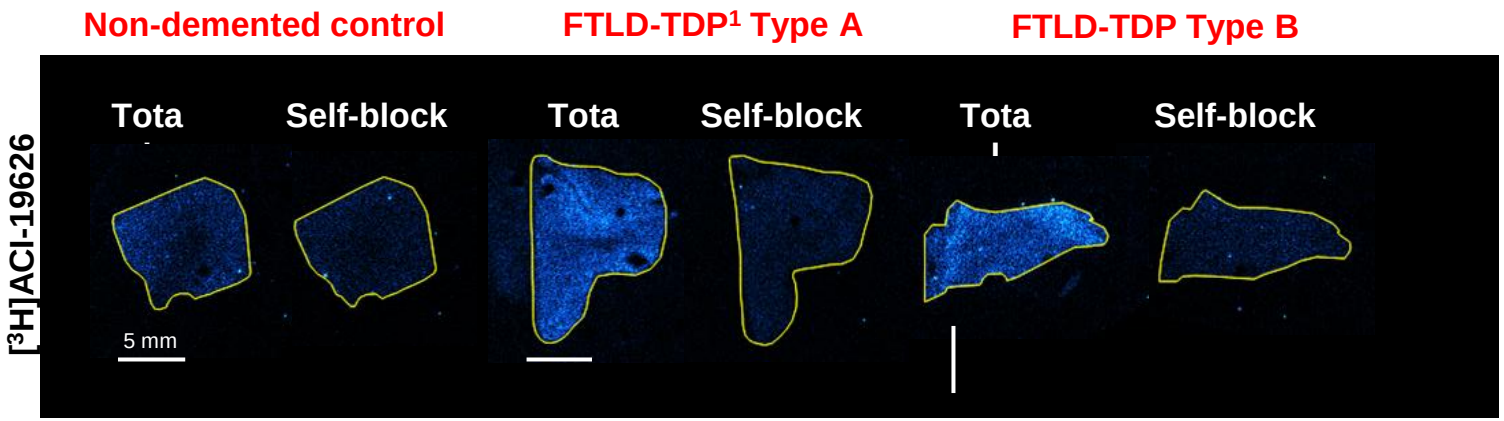
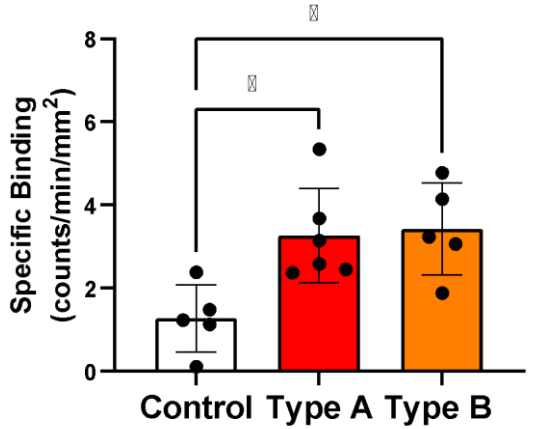
First-in-class ACI's TDP-43 PET tracer ACI-19626

Characterization in patient brain material





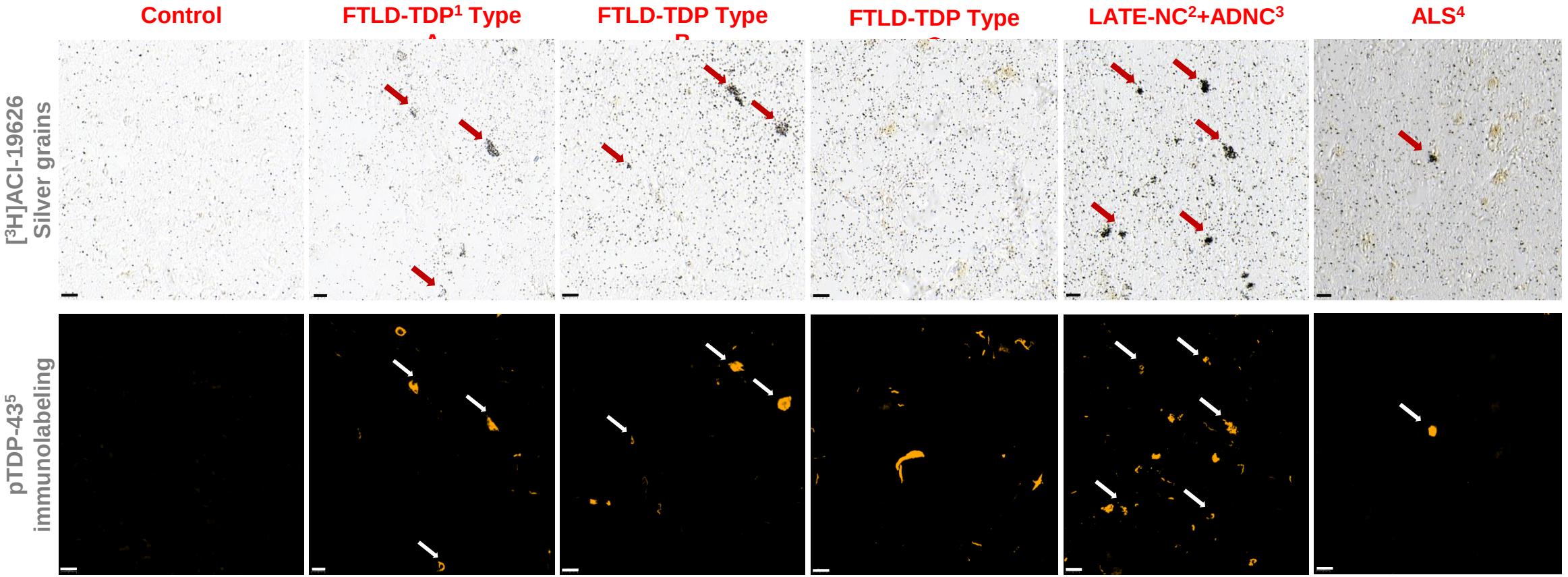
- High affinity binding (Kd=10-20 nM) on brain sections with FTLD-TDP pathology
- Selectivity over Abeta, Tau and α-syn; clean off-target profile (e.g. MAO-A, MAO-B)
- Rapid brain uptake and fast washout in non-human primates

- The first proof of target engagement on FTLD-TDP brain samples using 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 FTLD-MND[5] and ALS[6]
- FIH study to commence in Q4 2024

(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

ACI-19626 target engagement

High resolution autoradiography on brain section with TDP-43 proteinopathies



Ref: ACI unpublished data

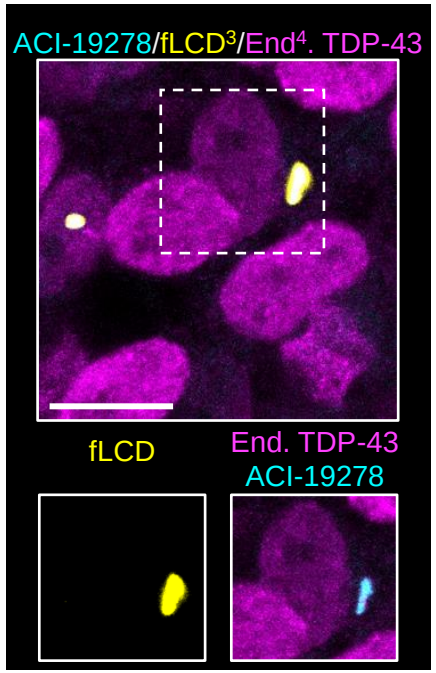
- ACI-19626 shows strong target engagement on human brain samples with FTLD-TDP[1] Type A and B pathology and TDP-43 inclusions in LATE and ALS brain tissue

(1) Frontotemporal lobar degeneration with TDP-43 pathology; (2) Limbic-predominant age-related TDP-43 encephalopathy neuropathological change; (3) Alzheimer's disease neuropathologic change; (4) Amyotrophic lateral sclerosis; (5) phospho-TDP-43 pS409/410

Binding specificity to aggregated TDP-43

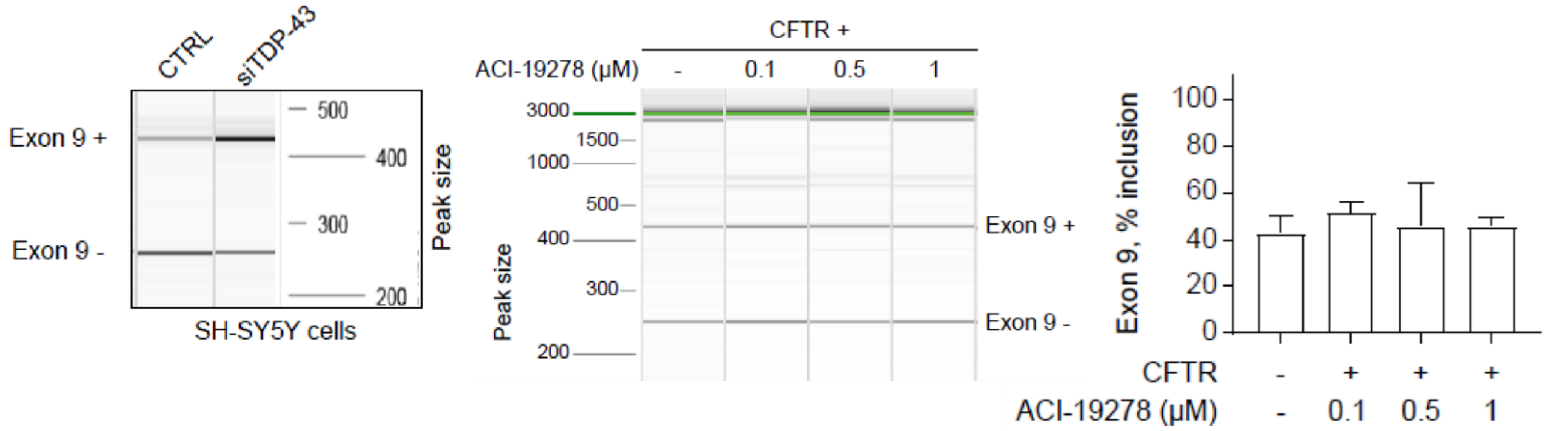
Characterization of ACI-19278, a close analog of ACI-19626

Cellular model



Carlo Scialo, Polymenidou lab

CFTR[1] exon 9 splicing assay in SH-SY5Y cells



Sara Capelli, Buratti lab

Ref: ACI unpublished data

- ACI-19278 shows binding specificity to aggregated TDP-43 *versus* physiological nuclear TDP-43
- No interference of ACI-19278 with the natural TDP-43 controlled RNA splicing of exon 9, suggesting no interference with the physiological function of TDP-43 *in vitro*

(1) Surface Plasmon Resonance: (2) Frontotemporal lobar degeneration with TDP-43 pathology; (3) Fluorescent low complexity domain recombinant TDP-43 fibrils; (4) Endogenous

IMAGE TDP-43

Conclusions and next steps

First-in-class TDP-43 PET ligand ACI-19626

- Low nM Kd on FTLD-TDP brain tissue with no binding to physiological TDP-43
- Detection of TDP-43 pathology in various indications, including ALS, FTD and LATE
- Excellent selectivity over Abeta, Tau and a-synuclein aggregates

Successful collaboration

- Leveraged complementary expertise and knowledge of TDP-43 biology and pathology
- Enabled access to patient brain material and to unique experimental models
- Provided access to a unique clinical trial cohort
- Accelerated translation, improving future therapeutic development for brain diseases with high unmet medical need

Next steps

- First-in-Human study sponsored by AC Immune to start in November 2024
- JPND-sponsored investigator-initiated study at Skane on track to start in 2025

Dissemination

- Manuscript “Development of [18F]ACI-19626, a novel brain PET tracer for imaging TDP-43 pathology” ready for submission to Nature Communications