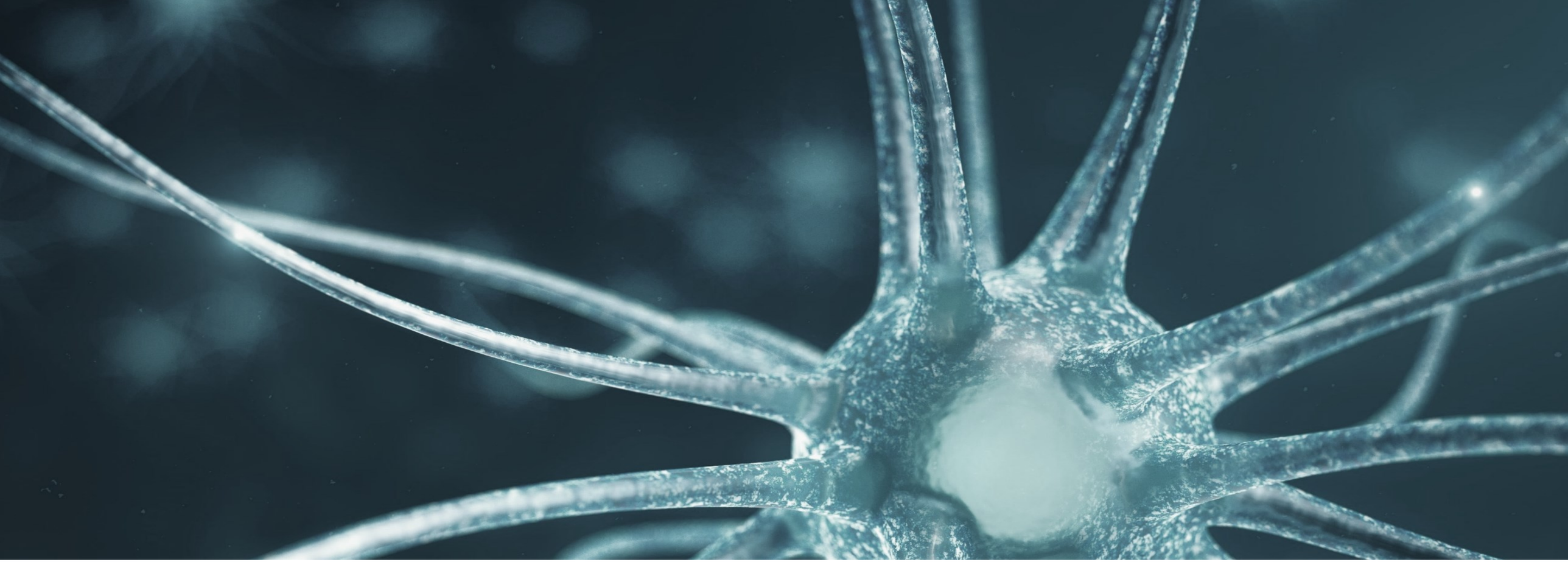

DEVELOPMENT OF TDP-43 IMMUNOTHERAPY BLOCKING TRANSMISSION OF SEEDING-COMPETENT SPECIES FROM ALS/FTD

Tariq Afroz, PhD | AD/PD™ 2023 | 30 March

AC Immune

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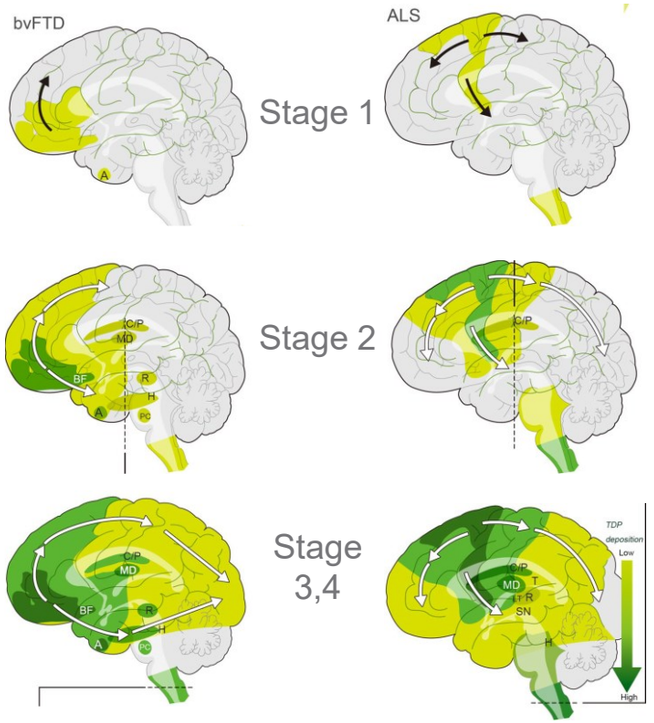
Conflict of interest disclosure

Tariq Afroz is an employee of AC Immune entitled to stock options

TDP-43 immunotherapy for ALS[1] and FTD[2]

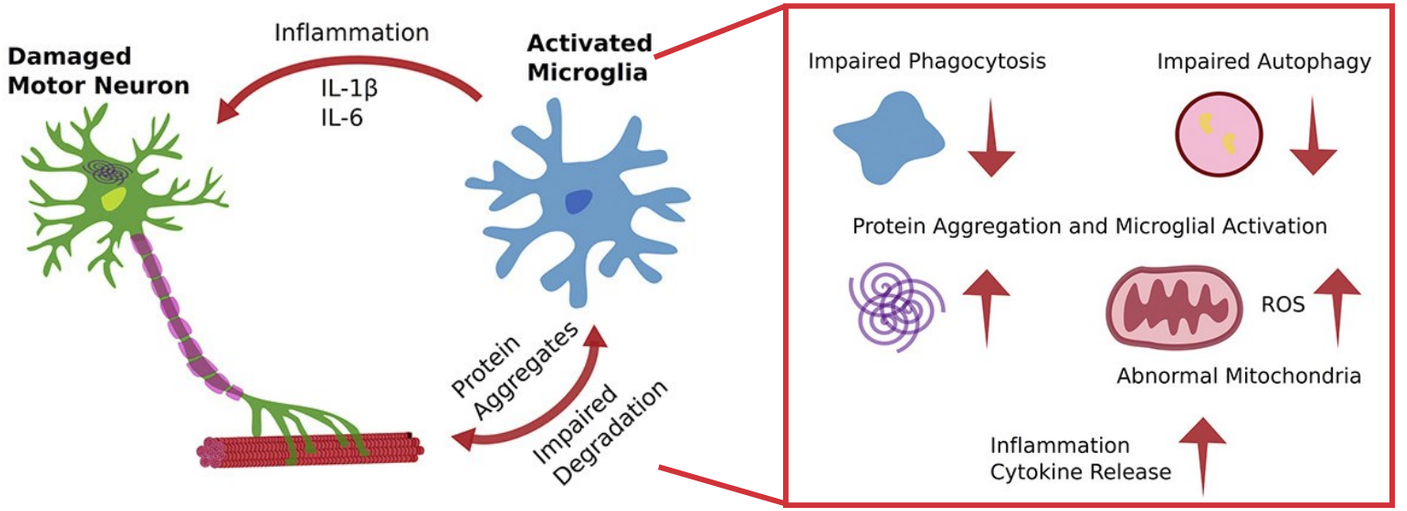
To mitigate TDP-43 pathology and ameliorate associated cellular dysfunctions

Pattern of TDP-43 pathology spreading



Kawakami et al., 2019

Microglial dysfunction



Haukedal et al., 2019

- Extracellular TDP-43 species involved in spreading are promising targets for an antibody-based therapeutic approach

[1]ALS – Amyotrophic lateral sclerosis, [2]FTD – Frontotemporal dementia

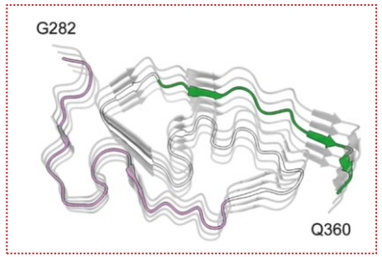
C-terminal targeting mAbs highly active *in vitro*

Two pan-TDP-43 mAbs binding to the low complexity domain

TDP-43 mAbs

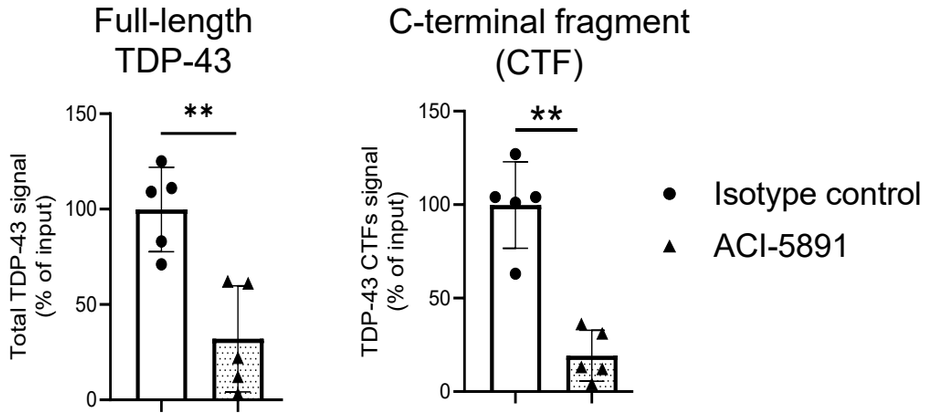
ACI-5891
ACI-6677

C-terminal low complexity domain harbors amyloid core in patient brains



Arseni et al., 2021

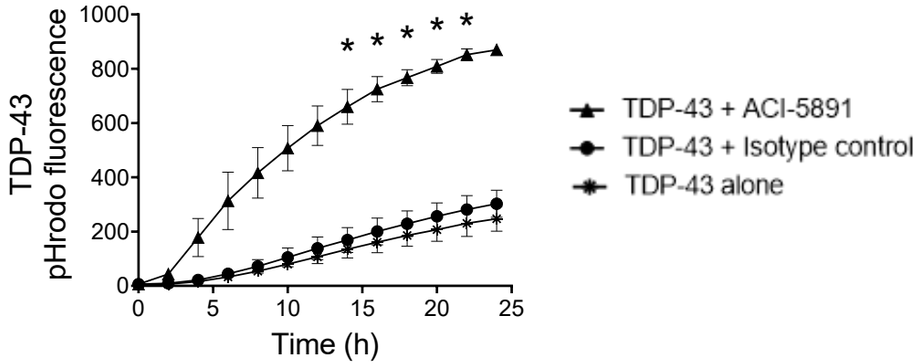
Immunodepletion of TDP-43 seeds from patient brains



mAb binding characteristics and potency

mAb	K_D TDP-43 (nM)	Immunohistochemistry		% inhibition of TDP-43 aggregation
		Aggregated TDP-43	Nuclear TDP-43	
ACI-5891	0.18	+++	++	98
ACI-6677	0.38	+++	++	97.4

TDP-43 aggregates uptake by ALS microglia



T. Afroz et al., Neurobiology of disease, 2023

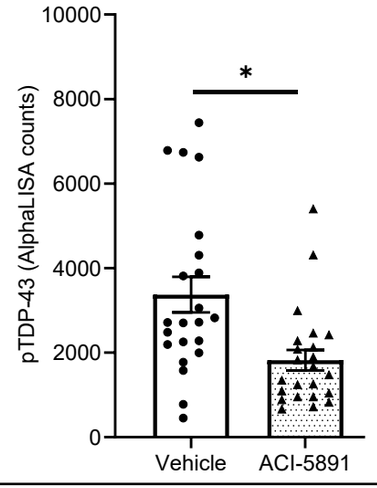
- C-terminal mAbs binding with sub-nanomolar affinity inhibit aggregation, deplete seeds from patient brains and facilitate uptake and clearance of TDP-43 by microglia

C-terminal mAbs reduce pathology conferring neuroprotection

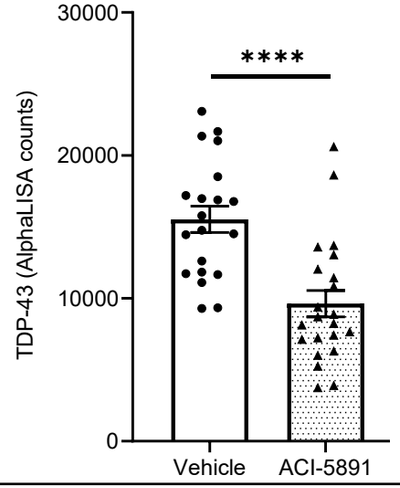
In mouse models of TDP-43 proteinopathies

NEFH – hTDP-43 NLSm (rNLS8 model)

Phosphorylated TDP-43 (in cortex, RIPA-insoluble)

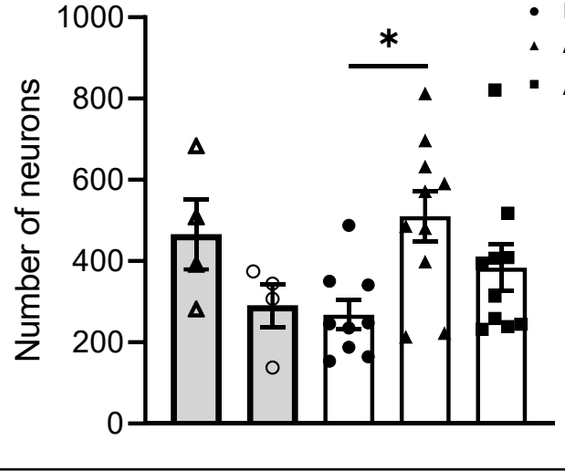


Aggregated TDP-43 (in cortex, RIPA-insoluble)

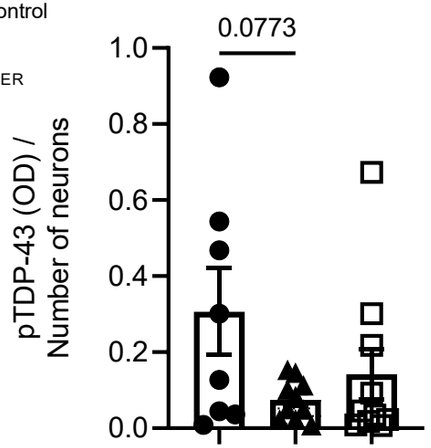


CamKIIa – hTDP-43 NLSm (with FTLD-TDP[1] brain-extract injection)

Neuronal number (Dentate gyrus)



pTDP-43 pathology (Dentate gyrus)



Statistics: One-way ANOVA followed by a tukey post-hoc test. Data represent mean ± SEM. *p < 0.05, ****p < 0.0001.

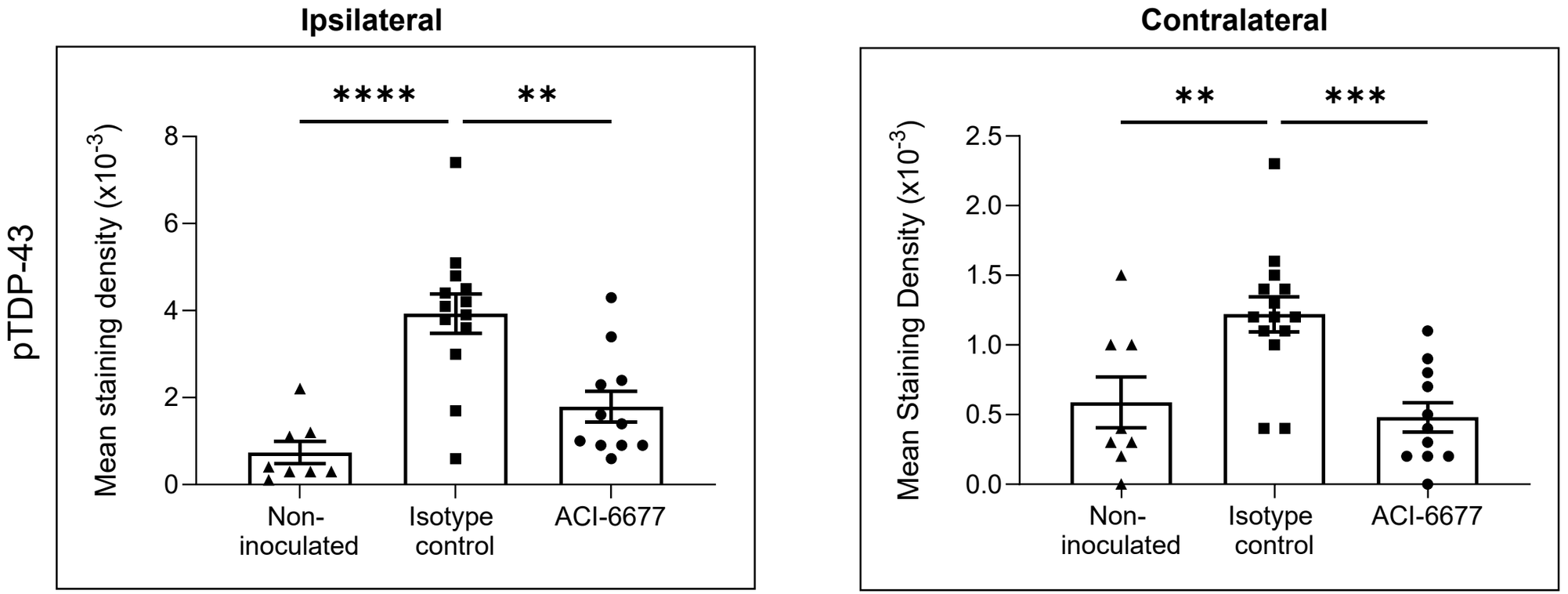
- Two *in vivo* models of TDP-43 pathology demonstrated:
  - A significant reduction in pTDP-43 and neuronal loss with ACI-5891 on a wildtype IgG
  - Involvement of Fc-mediated clearance and microglia
- Based on these data, ACI-5891 selected for development as clinical candidate, ACI-5891.9

[1]FTLD-TDP – Frontotemporal lobar degeneration with TDP-43 pathology

T. Afroz *et al., Neurobiology of disease, 2023*

C-terminal mAbs reduce spreading of TDP-43 neuropathology

In CamKIIa – hTDP-43 NLSm model (inoculated with FTLD-TDP[1] brain-extracts)



Statistics: One-way anova with Tukey's test for posthoc analysis. Data represent mean ± SEM
*p < 0.05, **p – 0.01, ***p < 0.001, ****p < 0.0001

- Phosphorylated TDP-43 (pTDP-43) pathology observed in contralateral side confirming spreading
- ACI-6677 significantly reduces pTDP-43 in both ipsilateral and contralateral brain regions
- These data demonstrate the relevance of targeting extracellular TDP-43 by passive immunotherapy

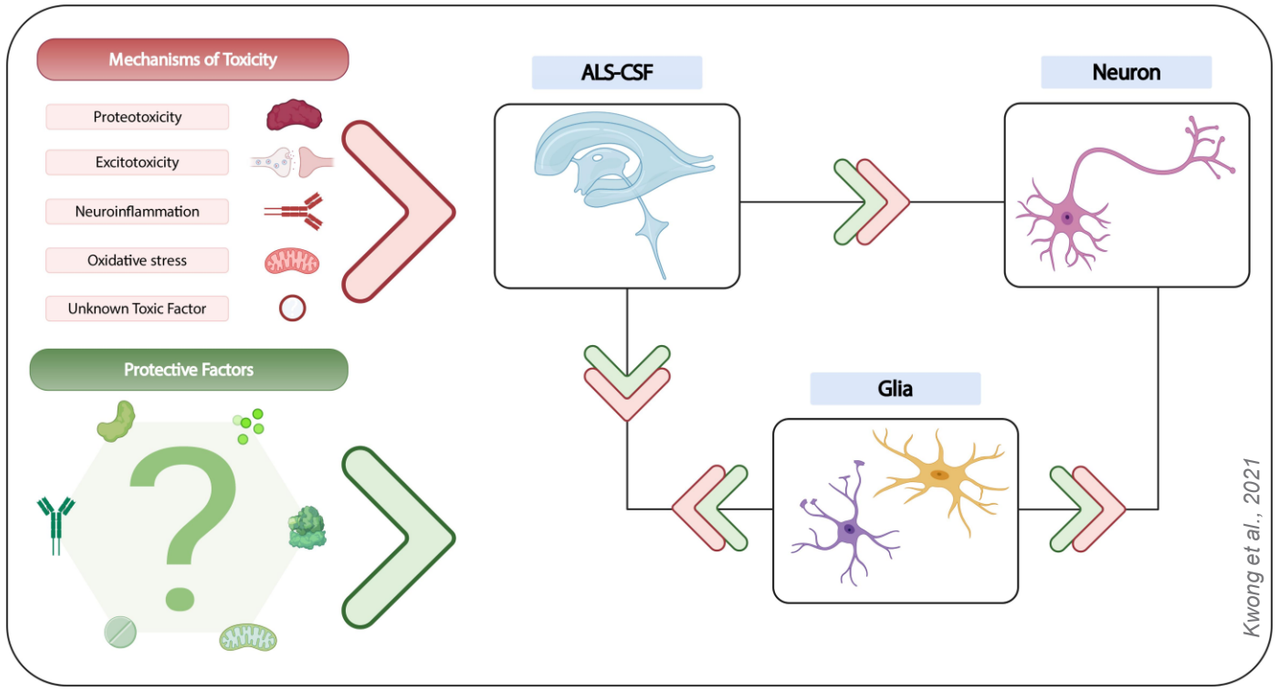
[1]FTLD-TDP – Frontotemporal lobar degeneration with TDP-43 pathology

Ref: AC Immune unpublished data

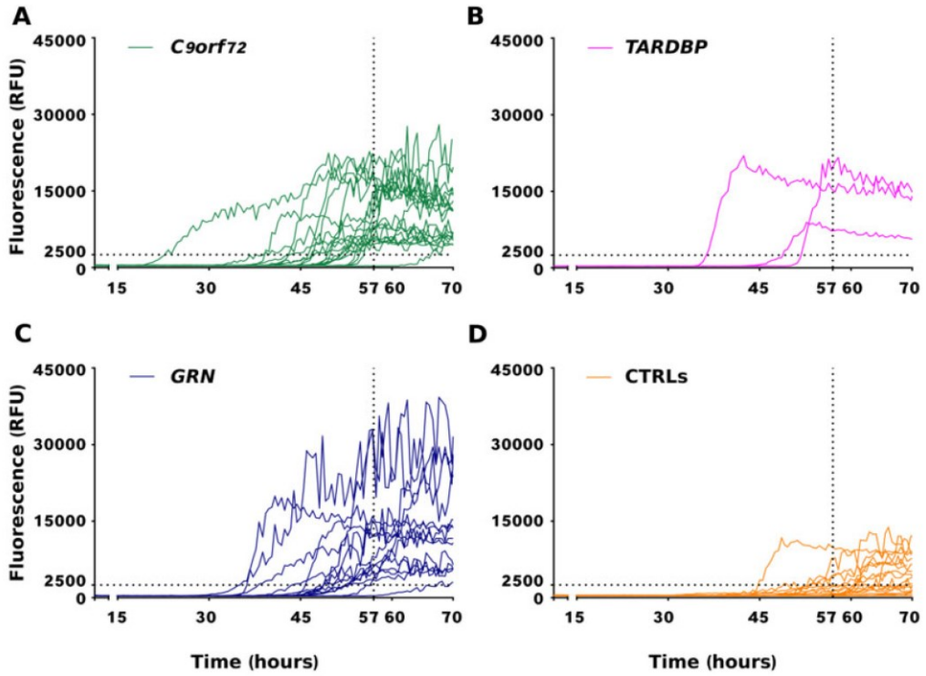
Contribution of CSF to non-contiguous progression of pathology

Evidence from bench and clinical research

CSF toxicity in ALS



Confirmation of seeding-active extracellular TDP-43 in patient CSF using RT-QuIC[1]



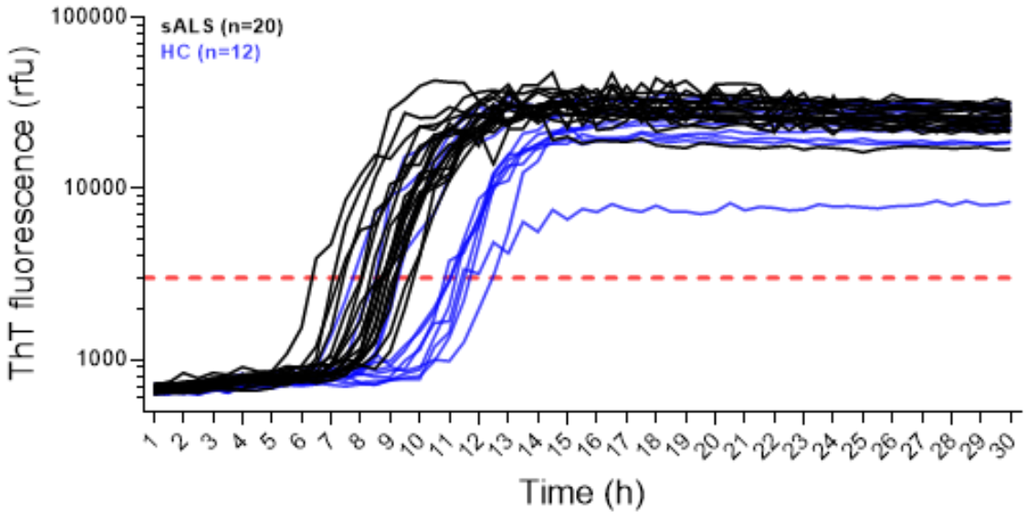
- Spreading through CSF proposed as a mechanism for multi-centric ALS onset
- RT-QuIC assay shows accelerated aggregation in ALS/FTLD-TDP CSF as compared with healthy controls demonstrating the presence of seeding competent TDP-43 species in patients

[1]RT-QuIC – Real time quaking induced conversion

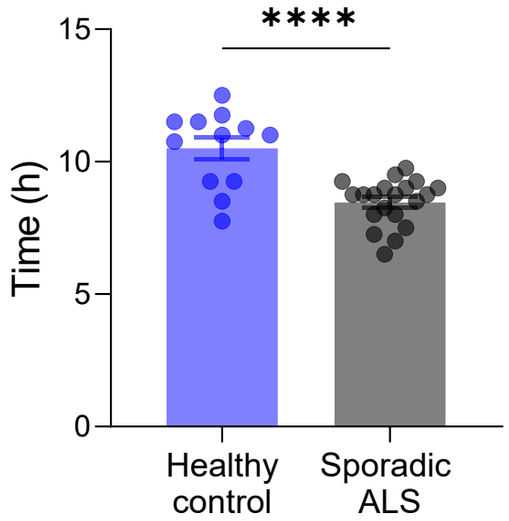
Confirmation of seeding-competent extracellular TDP-43 in patients

Using sporadic ALS (sALS) cerebrospinal fluid (CSF)

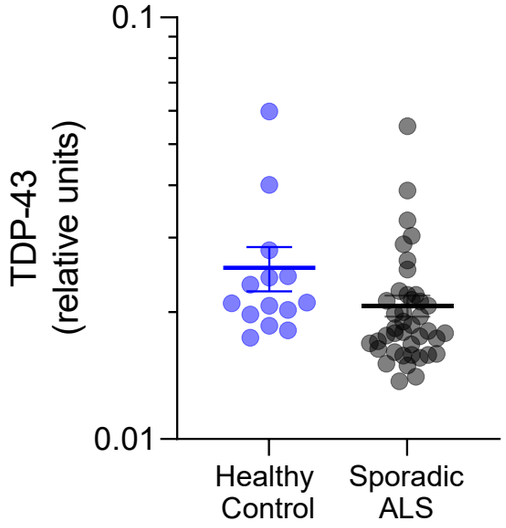
Aggregation kinetics



Time to reach 3000 rfu[1]



TDP-43 levels in CSF using an in-house SIMOA®[2] assay



Ref: AC Immune unpublished data

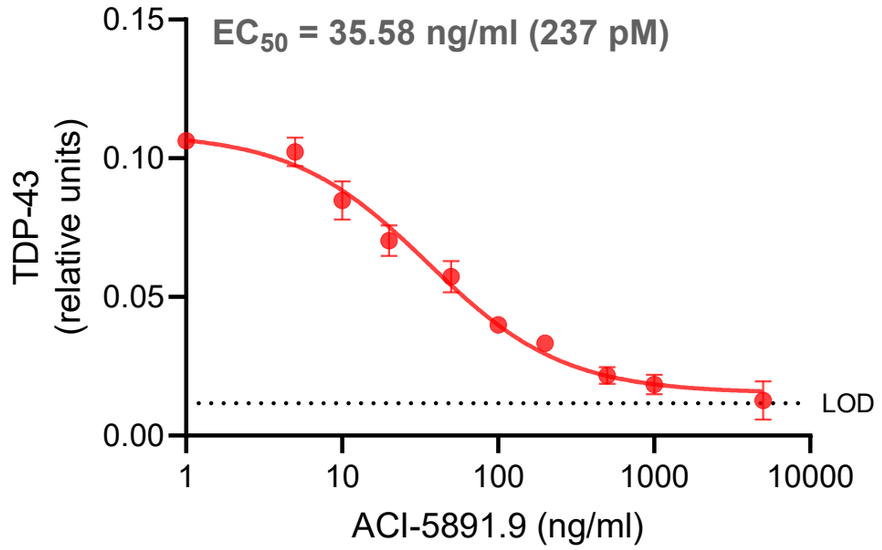
- A robust RT-QuIC assay established for potential biomarker evaluation in clinical trials
- CSF from sporadic ALS donors accelerate the aggregation of the recombinant substrate compared to healthy controls demonstrating the presence of pathologic seeding species in ALS CSF
- No significant difference in the total TDP-43 levels in the CSF quantified using a SIMOA®[2] assay

[1]rfu – relative fluorescence units, [2]SIMOA – Single molecule array

ACI-5891.9 levels achieved for target saturation in CSF

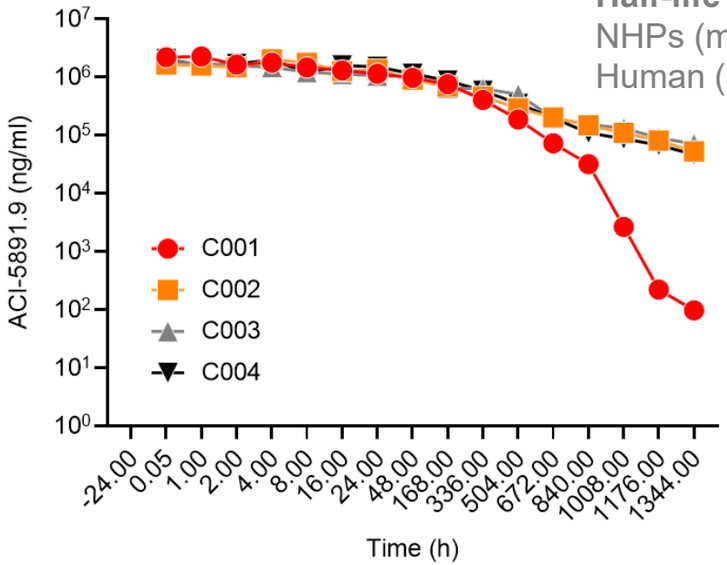
Established a novel assay to study pharmacodynamics in preclinical and clinical studies

mAb binding potency in human CSF



Single-dose (40 mg/kg) PK profile in non-human primates (NHPs)

Half-life ($t_{1/2}$):
NHPs (measured) – 12.7 days
Human (predicted) – 27-30 days



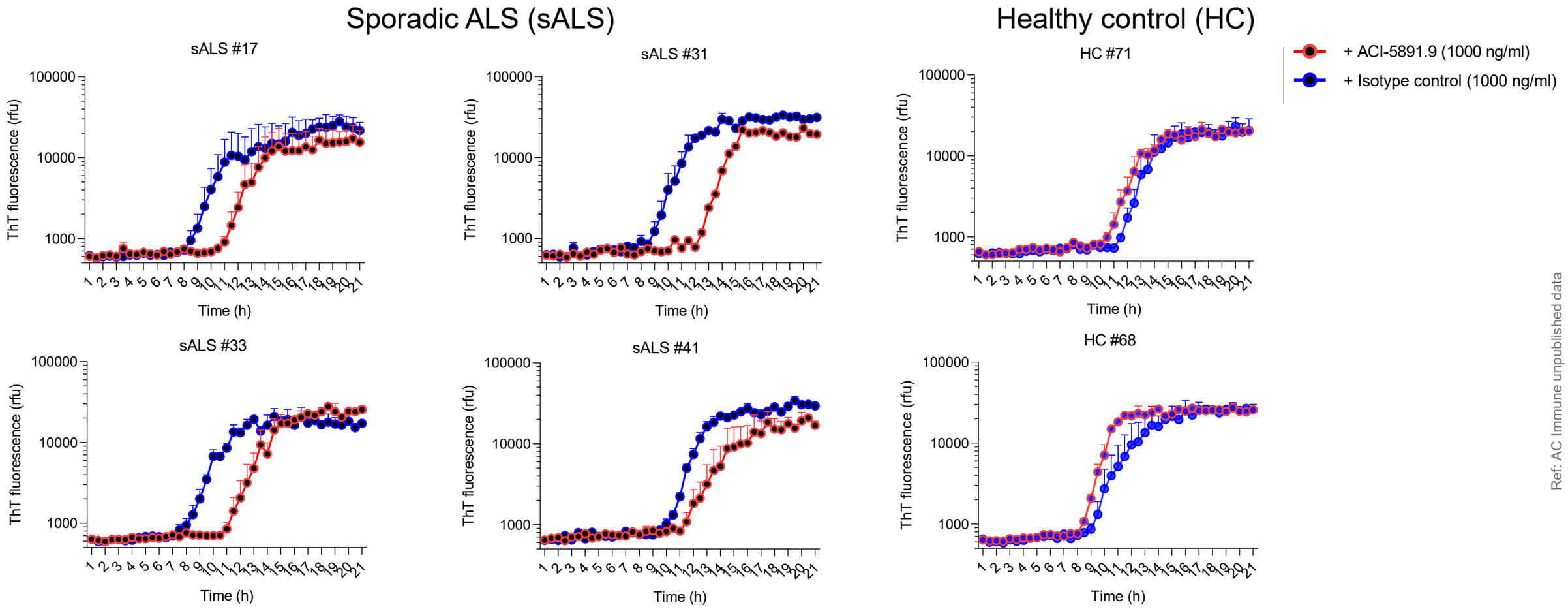
Predicted mAb CSF concentration in NHP at Day 28: 200 ng/ml (assuming 0.1% brain penetration from serum)

Ref: AC Immune unpublished data

- ACI-5891.9 binds with high affinity to TDP-43 in human CSF
- >80% target saturation in CSF is achieved at mAb concentrations 200-1000 ng/ml
- Excellent PK profile in NHPs with predicted mAb concentration in CSF sufficient for target saturation >80% for 28 days upon single administration at 40 mg/kg

ACI-5891.9 neutralizes TDP-43 seeding species in patient CSF

Evaluated using in-house developed RT-QuIC



Ref: AC Immune unpublished data

- Pre-incubation of the CSF with 1000 ng/ml of ACI-5891.9 neutralizes the seeding-competent TDP-43 present in sALS CSF

Summary

1

- A panel of TDP-43 mAbs with broad epitope coverage obtained using the SupraAntigen® platform

2

- Targeting C-terminal domain of TDP-43 is key to achieving efficacy *in vitro* and *in vivo:*
  - Inhibits aggregation by 98% and depletes patient-derived seeds to decrease templated aggregation within cells
  - Decreases pTDP-43 pathology, inhibits spreading and provides neuroprotection in mouse models of ALS/FTD
- Using ALS patient samples
  - Confirmed presence of extracellular seeding species in patient CSF
  - Demonstrated neutralization with ACI-5891.9 of TDP-43 seeding species in CSF
  - Rescued phagocytic impairments with microglia derived from ALS patients by creating immune complexes

3

- Two novel assays established to evaluate target engagement in CSF for preclinical and clinical studies
- Excellent PK profile predicts with a single 40 mg/kg dose a >80% target saturation for 28 days in CSF
- Proven safety:
  - ACI-5891 does not alter intracellular functions of TDP-43
  - Four once-weekly intravenous infusions up to 360 mg/kg in NHPs well tolerated
- GLP IND enabling toxicology study to start July 2023

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AC Immune

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

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