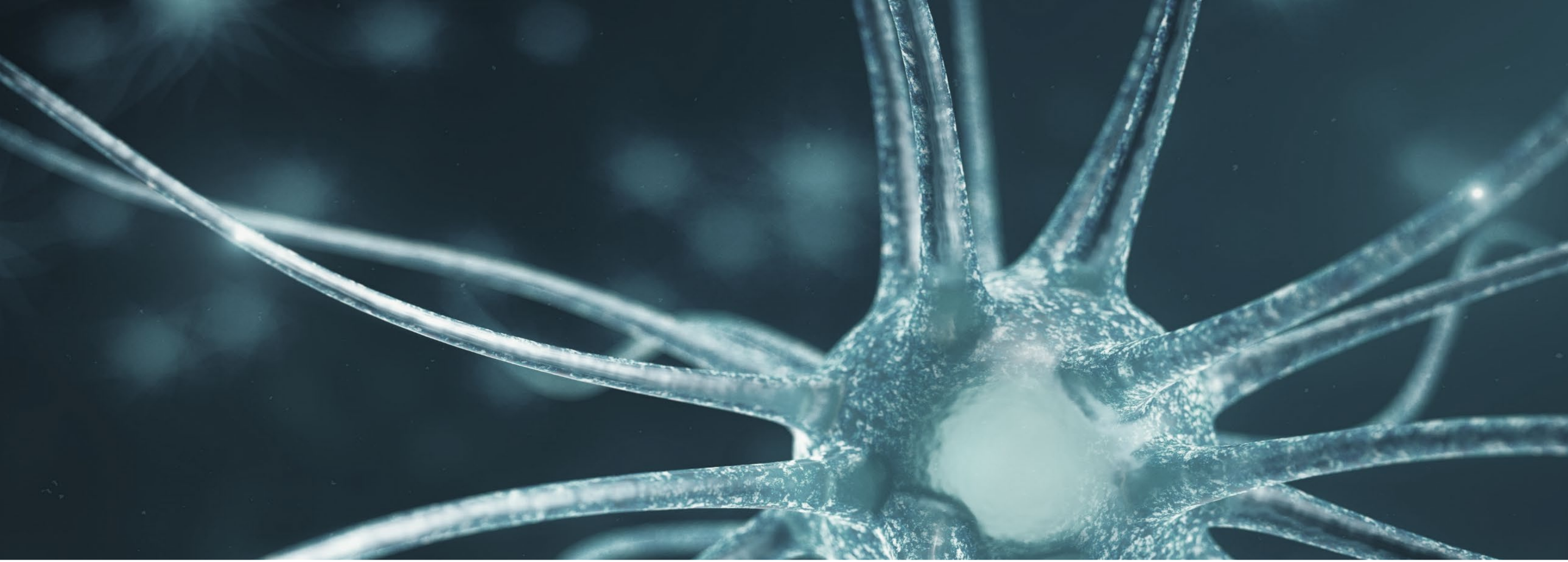

DEVELOPMENT OF TDP-43 IMMUNOTHERAPY BLOCKING TRANSMISSION OF SEEDING-COMPETENT SPECIES FROM ALS/FTD

Tariq Afroz, PhD | AAIC 2023 | 17 July

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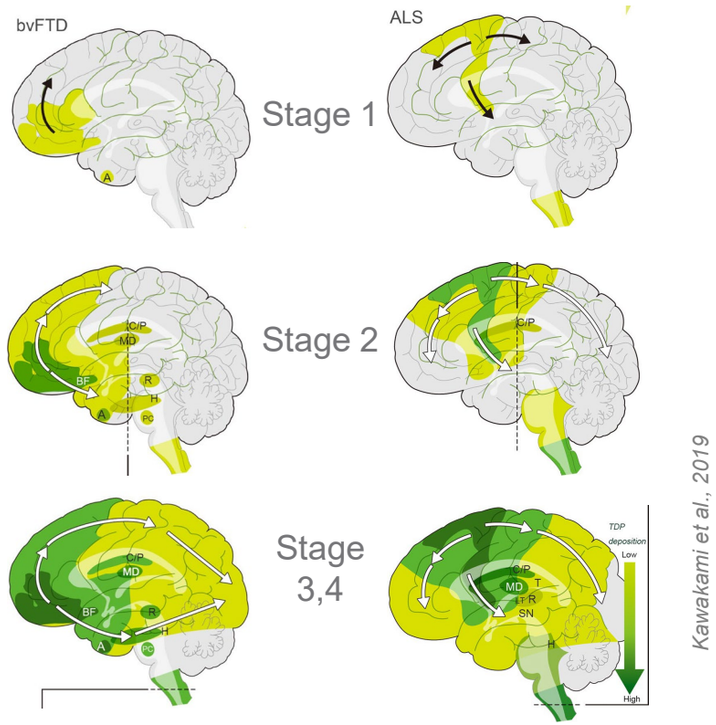
Conflict of interest disclosure

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

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

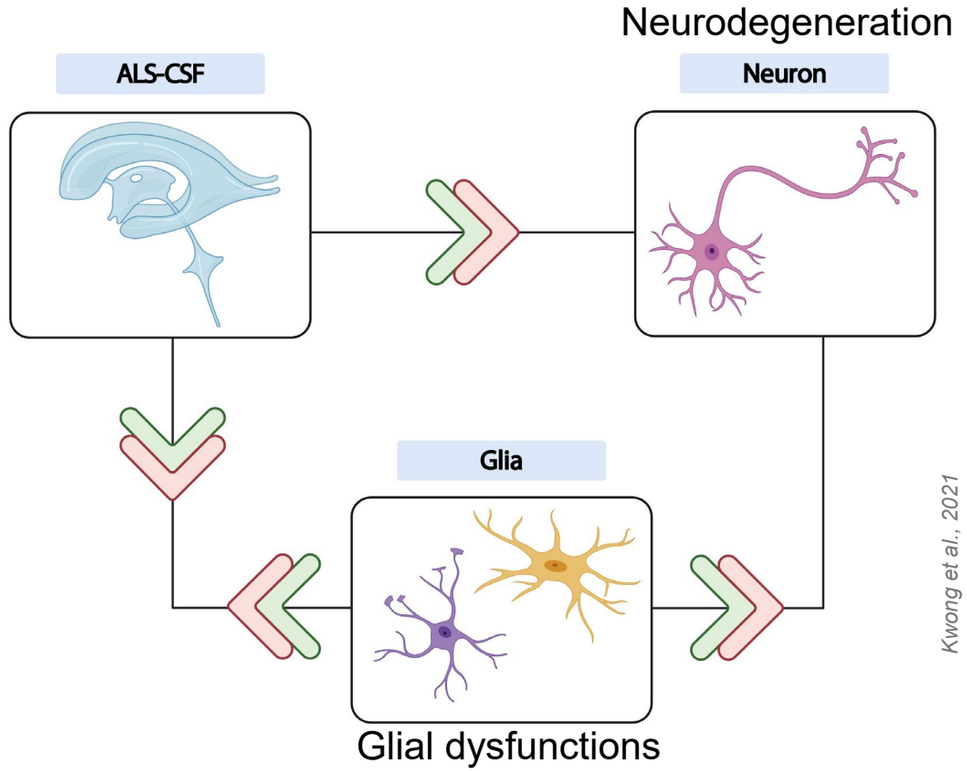
To mitigate TDP-43 pathology and ameliorate associated cellular dysfunctions

Pattern of TDP-43 pathology spreading



Kawakami et al., 2019

CSF[3] contribution to pathology spreading and cellular toxicity



Kwong et al., 2021

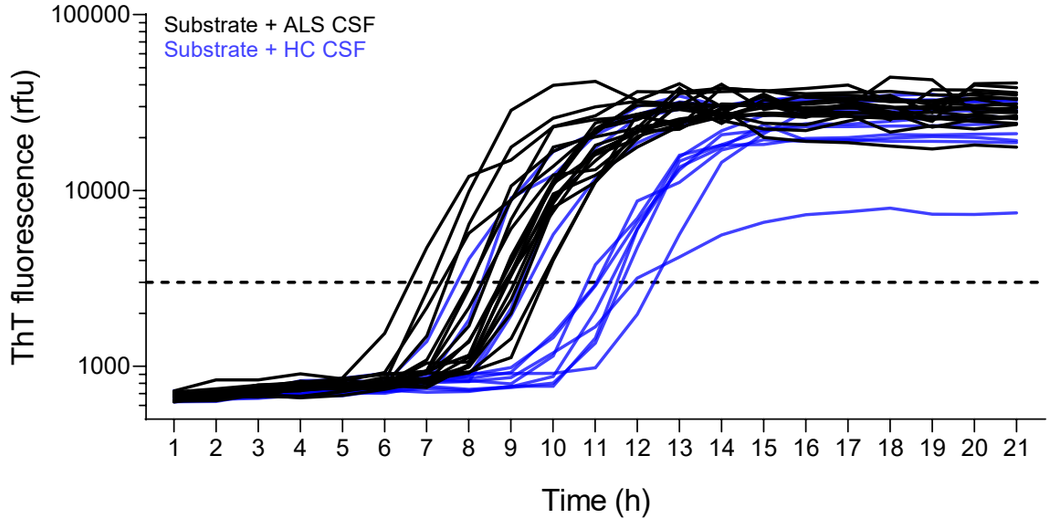
- Extracellular TDP-43 species involved in spreading are promising targets for an antibody-based therapeutic approach

1: ALS – Amyotrophic lateral sclerosis; 2: FTD – Frontotemporal dementia; 3: Cerebrospinal fluid

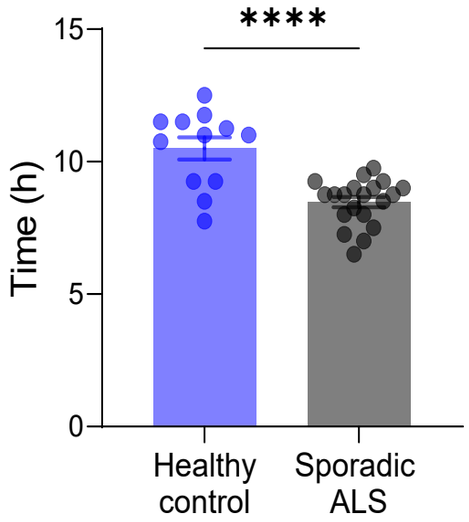
Confirmation of seeding-competent extracellular TDP-43 in patients

Using sporadic ALS (sALS) cerebrospinal fluid (CSF) and optimized seed amplification assay

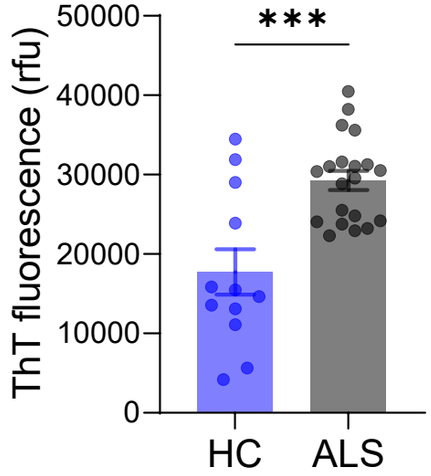
Aggregation kinetics



Time to reach 3000 rfu[1]



Aggregation (13 h)



Statistics: Unpaired Student's t-test (two-tailed), ***p<0.001 ****p<0.0001

M. Audrain et al., manuscript in review

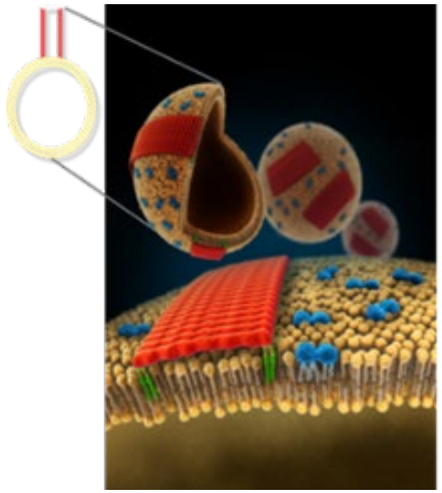
- A robust seed amplification assay (SAA) established as a promising biomarker in clinical trials
- CSF from sporadic ALS donors accelerate the aggregation of the assay substrate compared to healthy controls demonstrating the presence of seeding-competent species

1: rfu – relative fluorescence units

TDP-43 C-terminal targeting mAbs selected

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

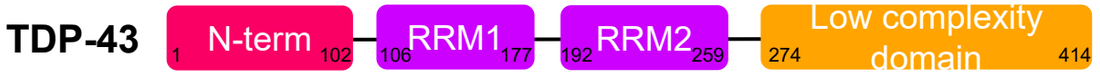
SupraAntigen® platform



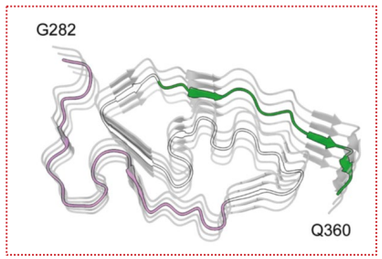
Hickman et al., 2011

pan-TDP-43 mAbs

ACI-5891
ACI-6677



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



Arseni et al., 2021

Binding affinity

mAb	K_D TDP-43 (nM)
ACI-5891	0.18
ACI-6677	0.38

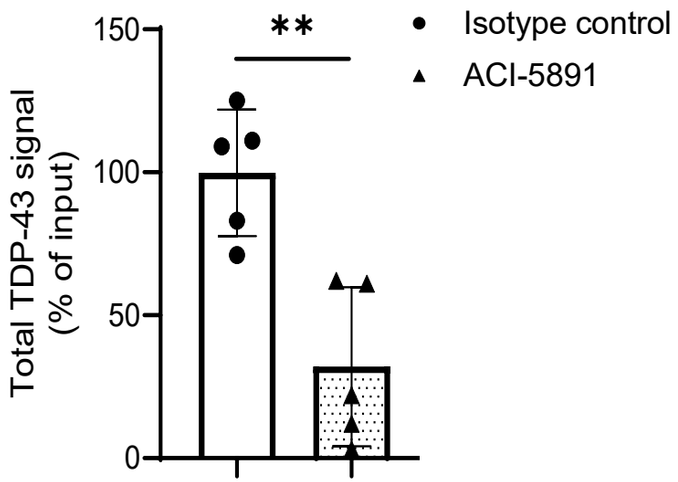
T. Afroz et al., Neurobiology of disease, 2023

- C-terminal, pan-TDP-43 mAbs binding with sub-nanomolar affinity selected

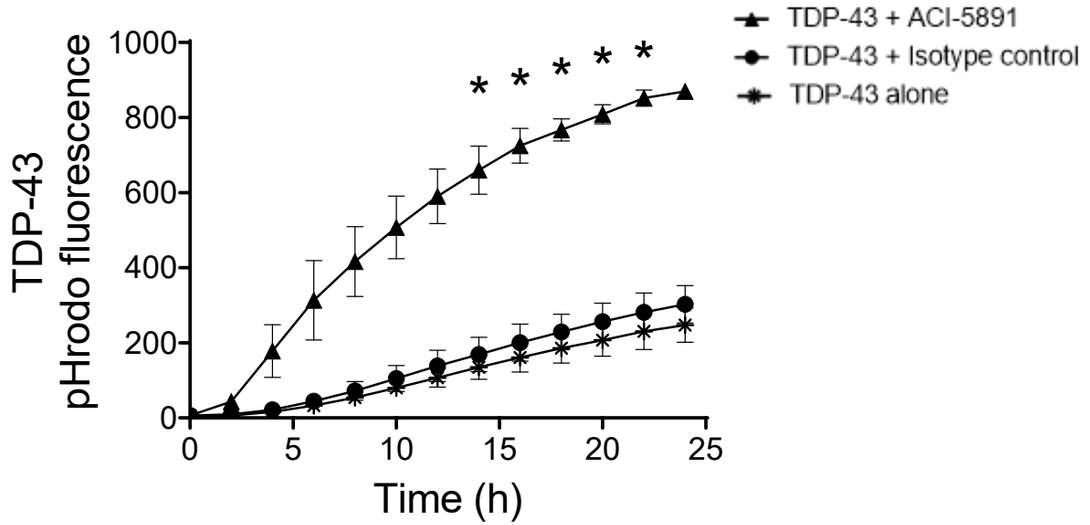
C-terminal targeting mAbs highly active *in vitro*

Using patient brain-derived extracts and ALS microglia

Immunodepletion of TDP-43 seeds from FTLD-TDP brain extracts



TDP-43 aggregates uptake by ALS microglia



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

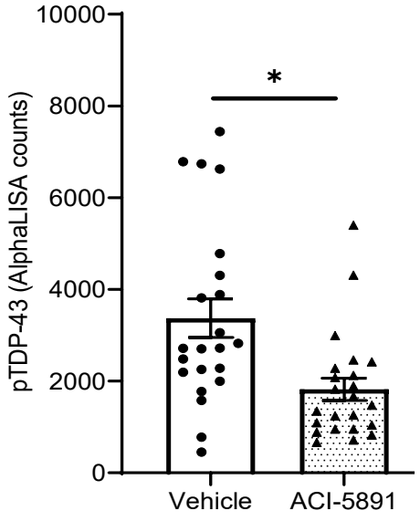
- ACI-5891 binding in C-terminal region of TDP-43 -
  - efficiently depletes TDP-43 seeds from FTLD-TDP brain extracts
  - facilitate uptake and clearance of TDP-43 by ALS microglia

C-terminal mAbs reduce TDP-43 spread to confer neuroprotection

In mouse models of TDP-43 proteinopathies

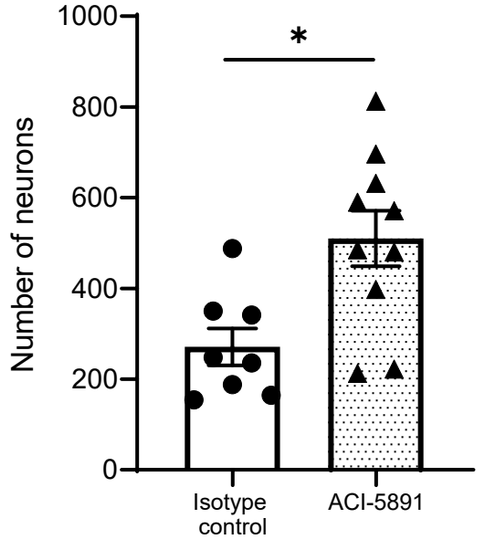
Phosphorylated TDP-43

NEFH – hTDP-43 NLSm[1]
(rNLS8 model)



Neuroprotection

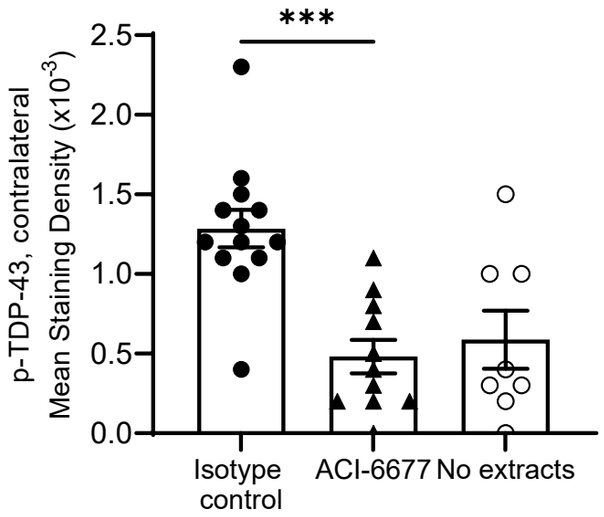
CamKIIa – hTDP-43 NLSm
(with FTLD-TDP[2] brain-extract injection)



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

Spreading

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



Ref: AC Immune unpublished data

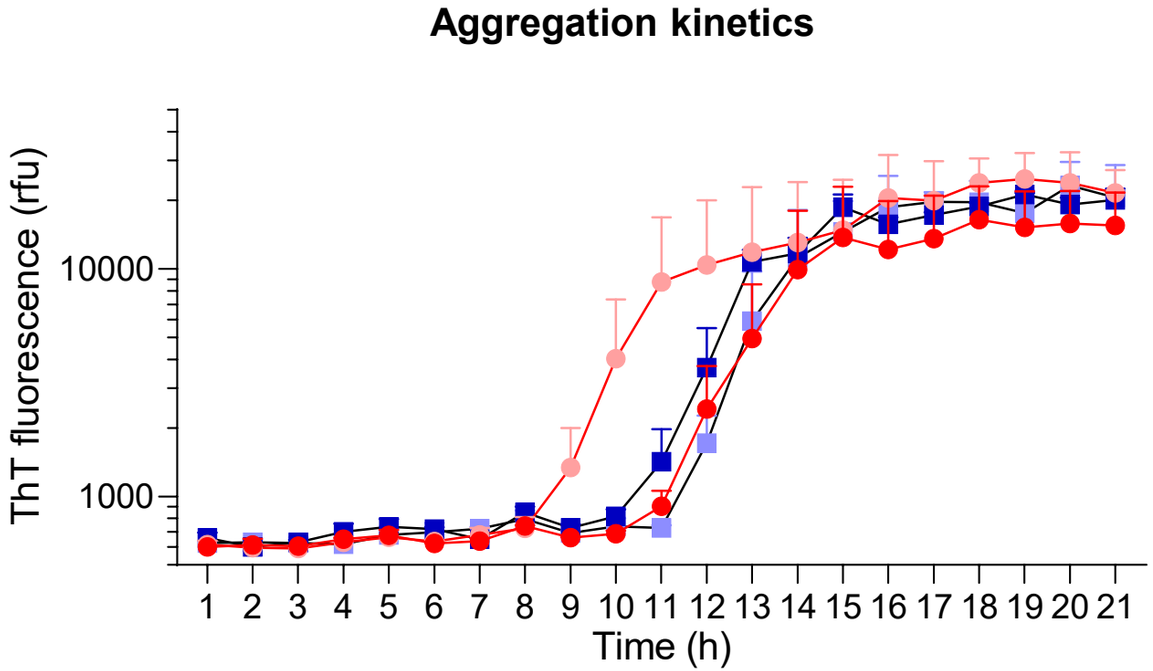
Statistics: One-way anova with Tukey's test for posthoc analysis. Data represent mean ± SEM, *p < 0.05, ***p < 0.001

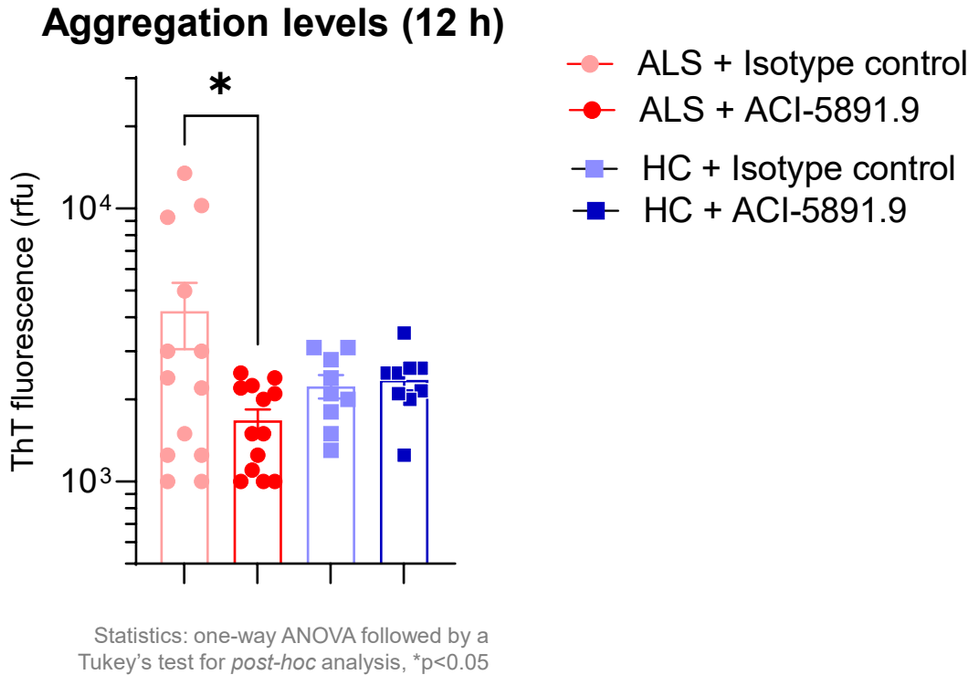
- Two *in vivo* models of TDP-43 pathology demonstrated a significant reduction in:
  - pTDP-43 pathology and neuronal loss
  - spreading of pathology to contralateral side
- ACI-5891 selected for development as clinical candidate, ACI-5891.9

1: NLSm – Nuclear localization signal mutant; 2: FTLD-TDP – Frontotemporal lobar degeneration with TDP-43 pathology

ACI-5891.9 neutralizes TDP-43 seeding species in patient CSF[1]

Evaluated using ACI's optimized seed amplification assay





Statistics: one-way ANOVA followed by a Tukey's test for *post-hoc* analysis, *p<0.05

M. Audrain et al., manuscript in review

- Using TDP-43 mAb confirmed that the seeding in CSF of ALS patients is driven by extracellular TDP-43
- TDP-43 immunotherapy will neutralize the seeding-competent TDP-43 present in the patient CSF

1: Cerebrospinal fluid; 2: Seed amplification assay; 3: Average enzymes per bead

Summary

1	▪ TDP-43 seed amplification assay confirmed the presence of seeding-competent species in CSF of ALS patients

2	▪ Targeting C-terminal domain of TDP-43 is key to achieving efficacy *in vitro* and *in vivo*
	  ▪ By depletion of patient brain-derived seeds to decrease templated aggregation
	  ▪ Decrease of pTDP-43, inhibition of spreading and conferring neuroprotection in mouse models of ALS/FTD
	▪ Using ALS patient samples
	  ▪ 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	▪ The TDP-43 seed amplification assay will serve as a pharmacodynamic biomarker during clinical trails
4	▪ IND/CTA-enabling toxicology study for ACI-5891.9 to start in Q4 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

Web: https://www.acimmune.com/

Social media: www.linkedin.com/company/ac-immune

Presenter: tariq.afroz@acimmune.com

Business development: bd@acimmune.com

Investors and Media: communications@acimmune.com