



Targeting TDP-43 with a vectorized full-length antibody decreases neuropathology in a model of ALS/FTD



Damien Nevoltris, PhD | AD/PD™ 2024 | 8th March

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Conflict of interest disclosure

Damien Nevoltris is an employee of AC Immune entitled to stock options

TDP-43 mediated pathology in ALS¹ and FTD²

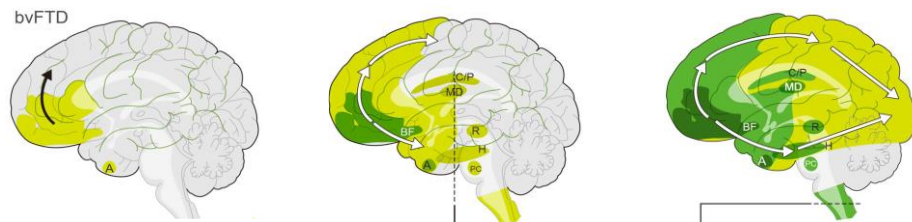
Progression and spreading of pathology

TDP-43 in ALS, FTD patients and pattern of brain spreading

ALS



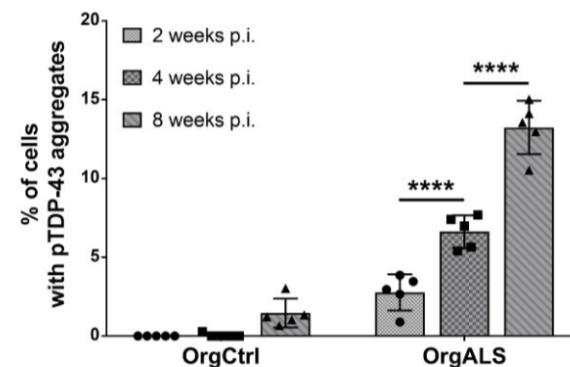
FTD



Adapted from Kawakami et al., 2019

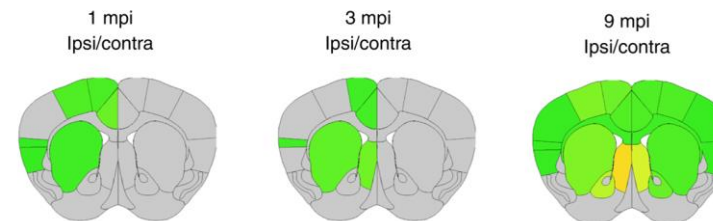
Prion-like spreading recapitulated in disease models

ALS cerebral organoids injected with ALS spinal cord extracts



Tamaki et al., 2023

Tg mice injected with FTLD-TDP³ brain extracts



Porta et al., 2018

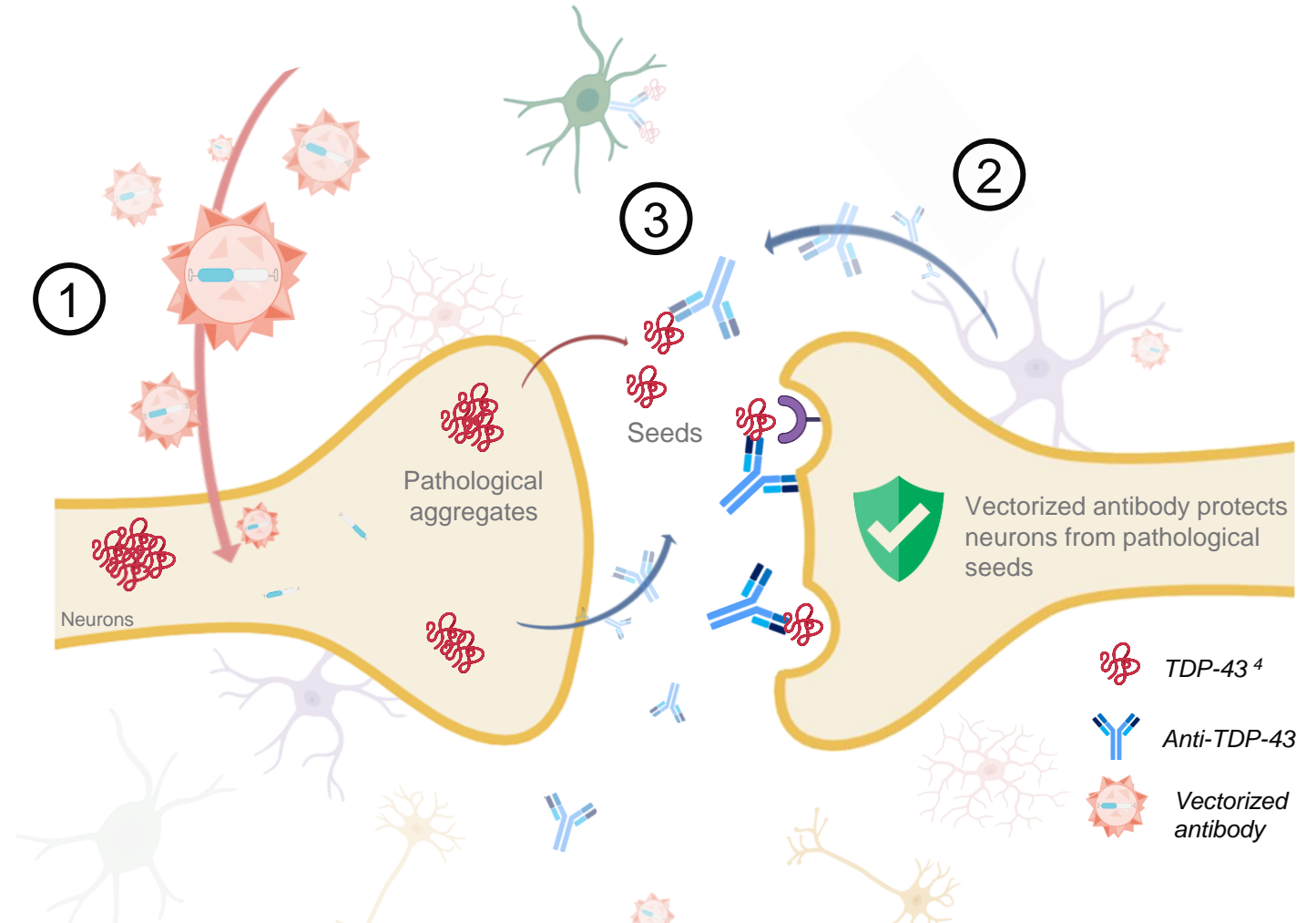
- Extracellular TDP-43 species involved in spreading are promising targets for an antibody-based therapeutic approach

(1): ALS – Amyotrophic lateral sclerosis; (2): FTD – Frontotemporal dementia; (3): FTLD-TDP - Frontotemporal lobar degeneration with TDP-43-immunoreactive pathology

Addressing limited mAb¹ exposure in brain by vectorized antibody

Local antibody production in the CNS²

- 1 AAV³ vectors deliver antibody genes (vectorized antibody) in brain cells
- 2 Local and long-term antibody expression (months, years), with single dose administration
- 3 Antibodies neutralize pathological seeds, effector function of full-length antibody promote microglia-mediated clearance



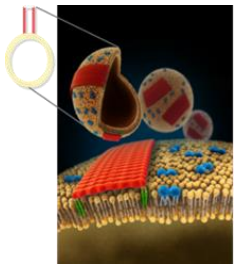
- Vectorized Antibody: antibody genes are delivered by AAV vectors to improve delivery in CNS
- Single dose administration affords long term exposure and pathological seed clearance

(1): mAb: monoclonal antibody; (2): Central Nervous System; (3): AAV - Adeno-associated virus; (4): TDP-43: TAR DNA-binding protein 43

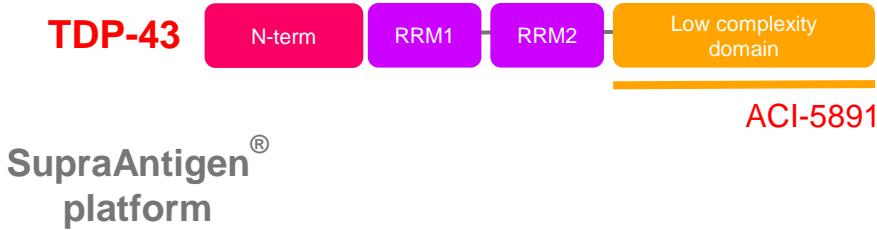
Generated anti-TDP-43 mAb suitable for vectorization

AAV packaging size is a bottleneck to vectorized antibody

Proprietary mAb targeting C-terminal domain of TDP-43

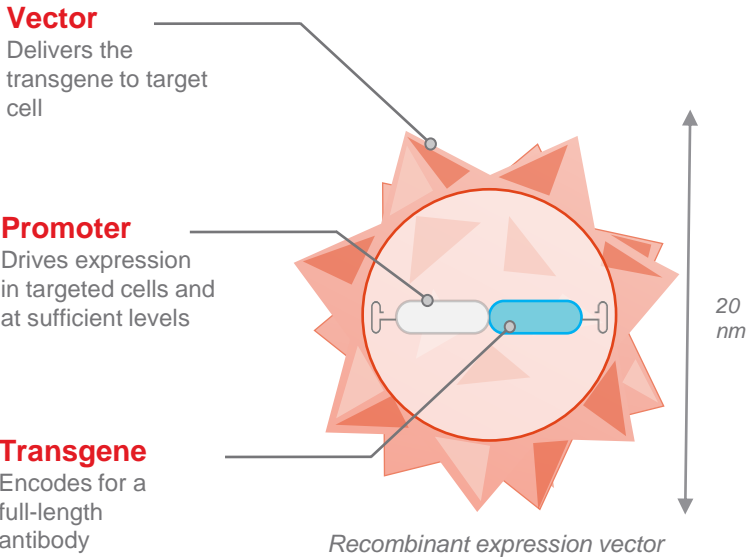


Hickman et al., 2011



Afroz et al., 2023

mAb	K _D TDP-43 (nM)	<i>In vitro</i> % inhibition of TDP-43 aggregation	<i>In vivo</i> Reduction of pTDP-43 in ALS/ FTD model
ACI-5891	0.18	98	Yes



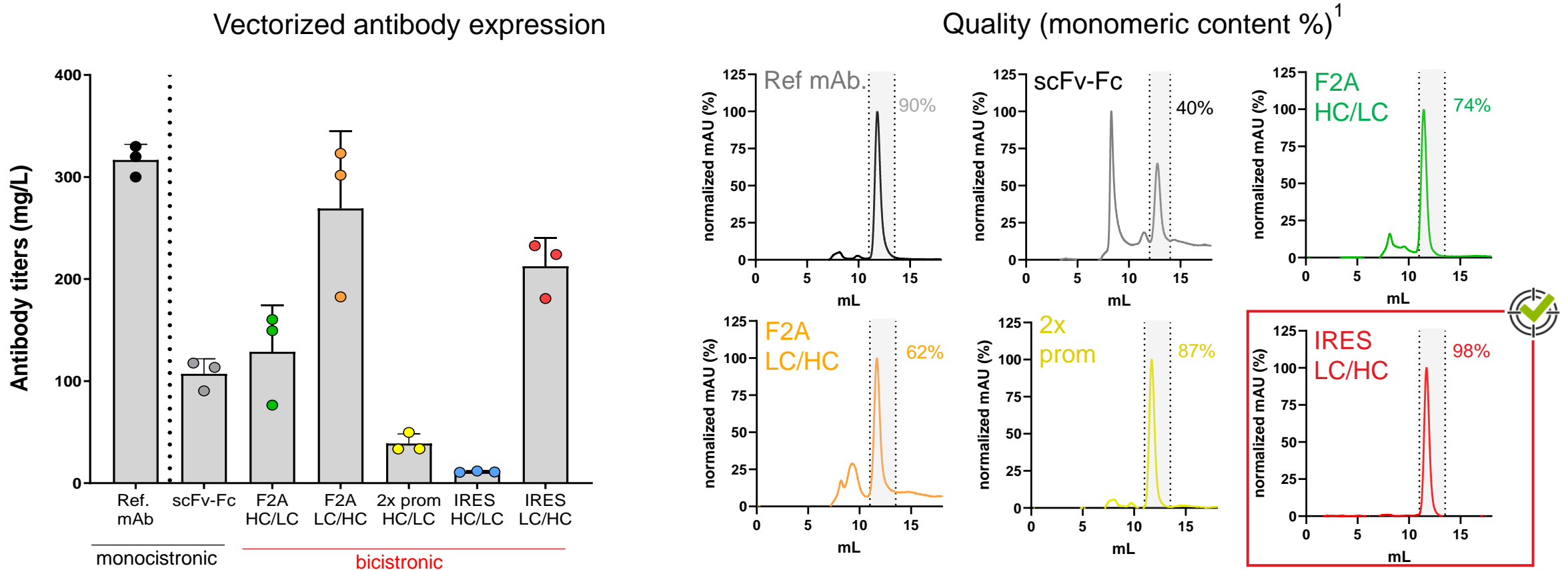
Maximum capacity: 4.7 kb
promoter + antibody genes + regulatory elements



- ACI-5891, a potent blocker of TDP-43 pathology used as proof of concept for vectorization
- Multiple designs of antibody transgene evaluated to address constraints of AAV packaging

IRES-based construct provides high-quality vectorized antibody

Expression titers and monomeric content



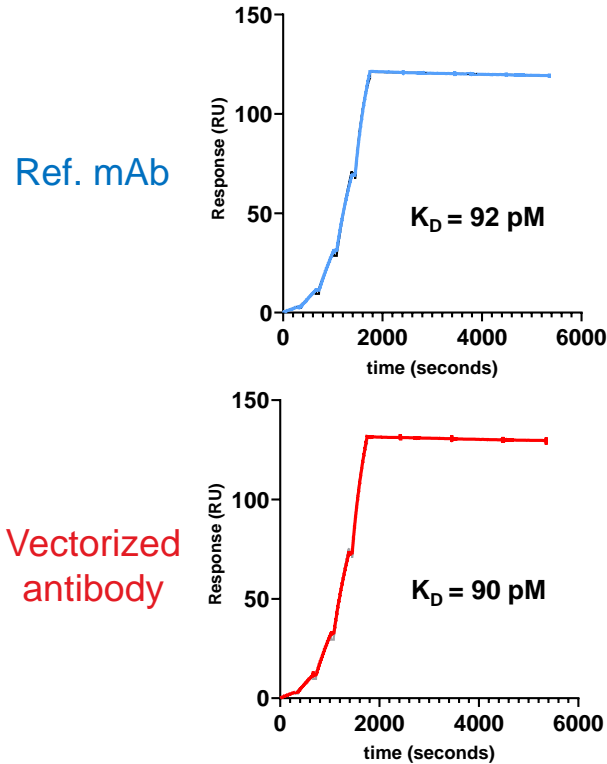
- High expression titer (>200mg/L) and excellent antibody quality (98% monomers) obtained with IRES LC/HC construction
- Key to providing potency and lowering risk of immunogenicity

(1): measured by size-exclusion chromatography; IRES: Internal ribosome entry sites; scFv-Fc – single-chain Fv-Fc; HC: Heavy chain; LC: Light Chain; F2A: Furin-2A; 2xprom: two promoters

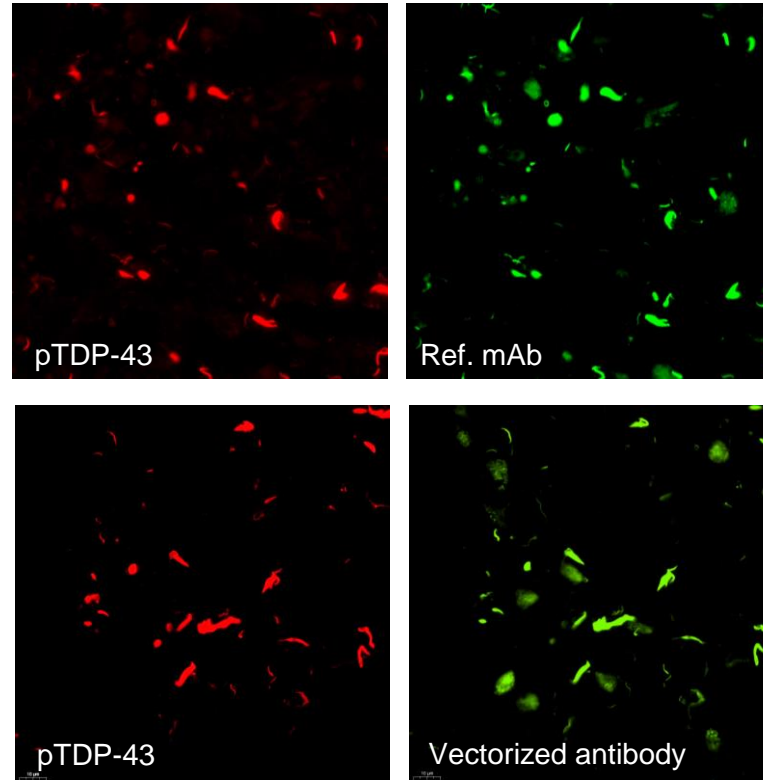
Vectorized antibody retains pico-molar binding affinity and potency

In vitro characterization: binding and aggregation inhibition

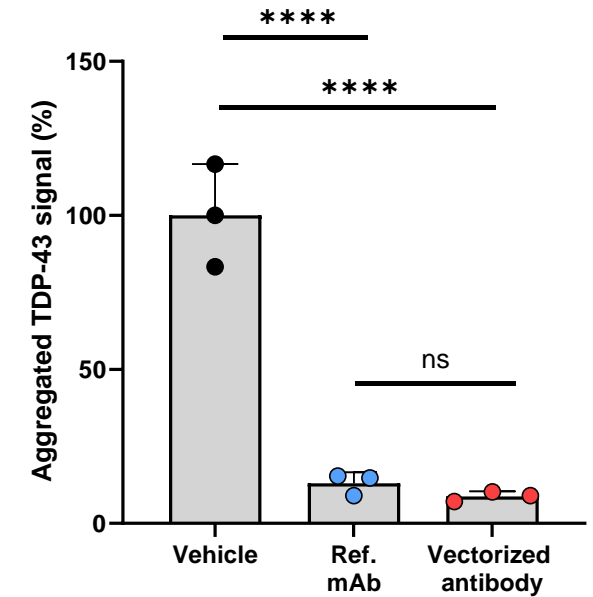
Binding to recombinant TDP-43



Target engagement on human FTLD-TDP¹ brain sections



Aggregation inhibition of TDP-43

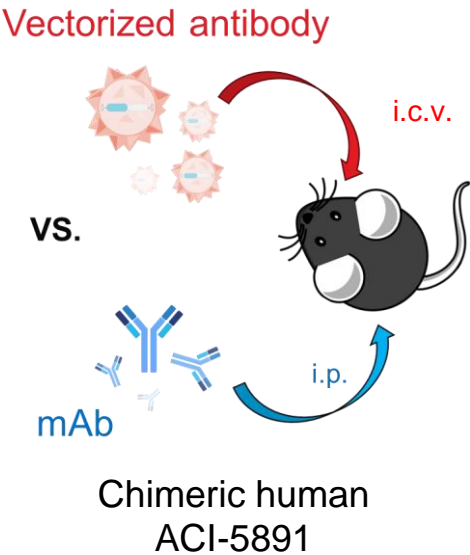


- Vectorized antibody presents equivalent potency and binding properties to TDP-43 compared to parental mAb antibody ACI-5891

(1) FTLD-TDP - Frontotemporal lobar degeneration with TDP-43-immunoreactive pathology

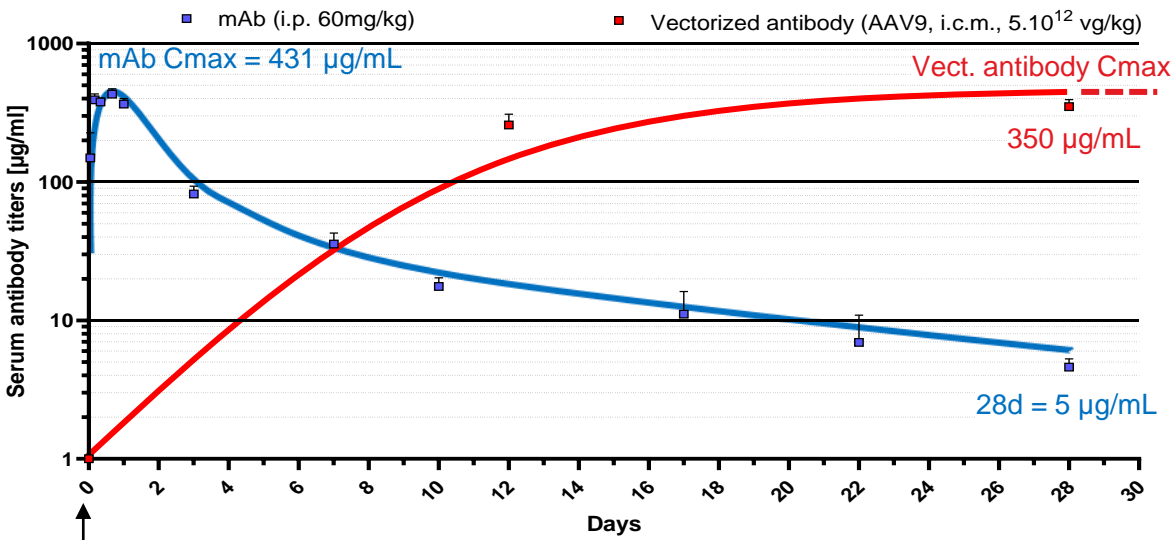
Functional vectorized antibody produced *in vivo*

Vectorized antibody vs bolus mAb administration



Readout at 28 days:

- Antibody levels in serum and CSF measured by target mediated binding assay



Exposure (AUC over 28 days)	Serum (µg/mL.day)	CSF (ng/mL.day)
mAb (60mg/kg)	1309	3885
Vectorized antibody	9800	10976

- Single administration of AAV9 (5.10^{12} vg/kg) supports long-term production of functional vectorized anti-TDP-43 antibody and provides higher exposure compared to bolus mAb administration

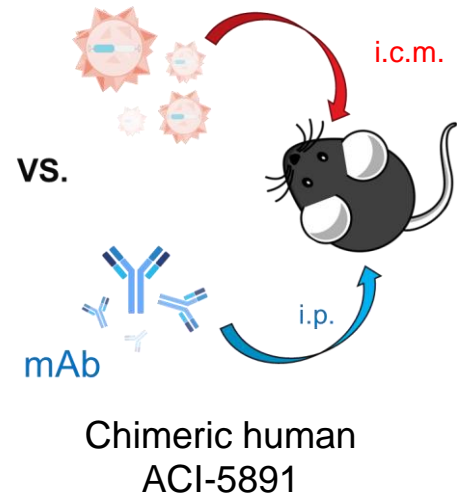
(i.p.) : Intraperitoneal; (i.c.v.): Intracerebroventricular; (AUC): Area under the curve

Vectorized antibody are expressed in brain

Vectorized antibody vs bolus mAb administration

Readout at 28 days:

Vectorized antibody



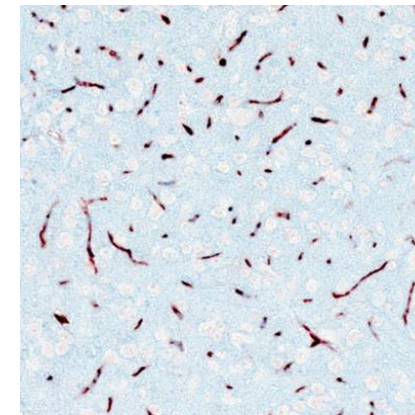
- Antibody levels in plasma and CSF measured by target mediated binding assay
- Brain Immuno-histochemistry

Detection: anti-human IgG-HRP

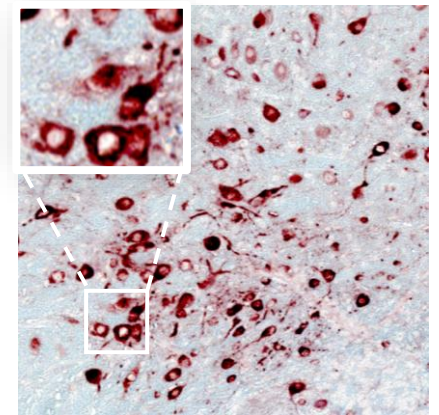
Vehicle



mAb (Cmax)



Vectorized antibody (AAV9)



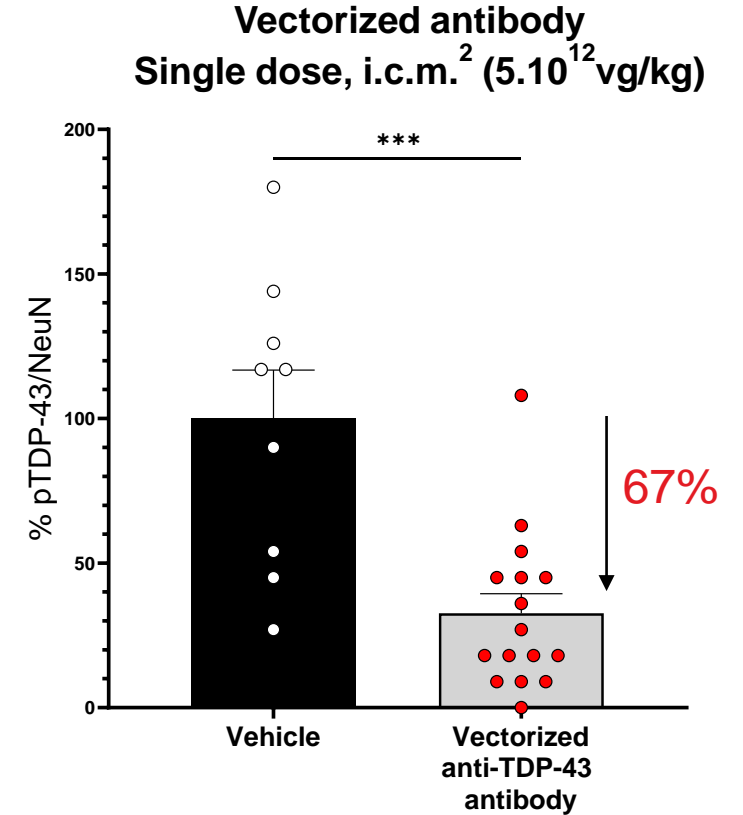
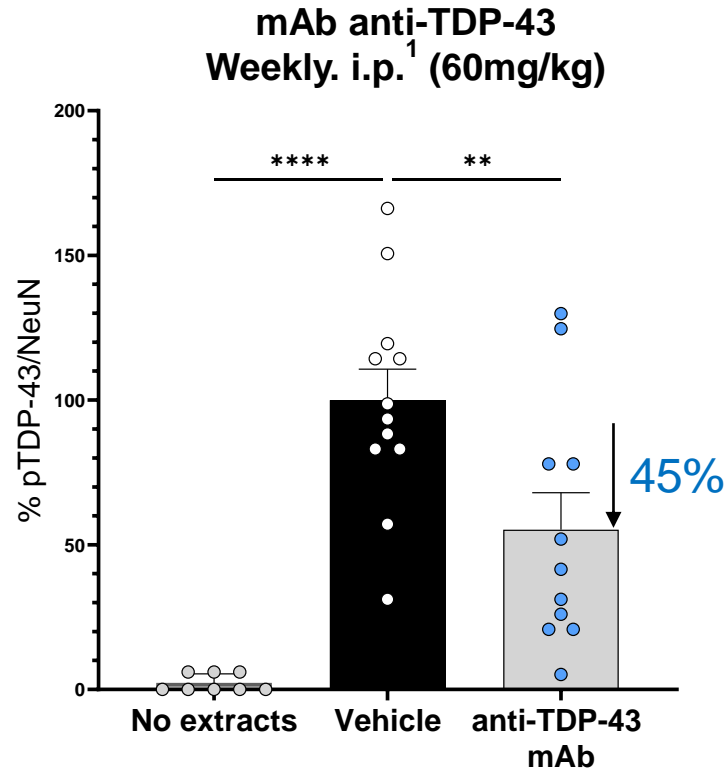
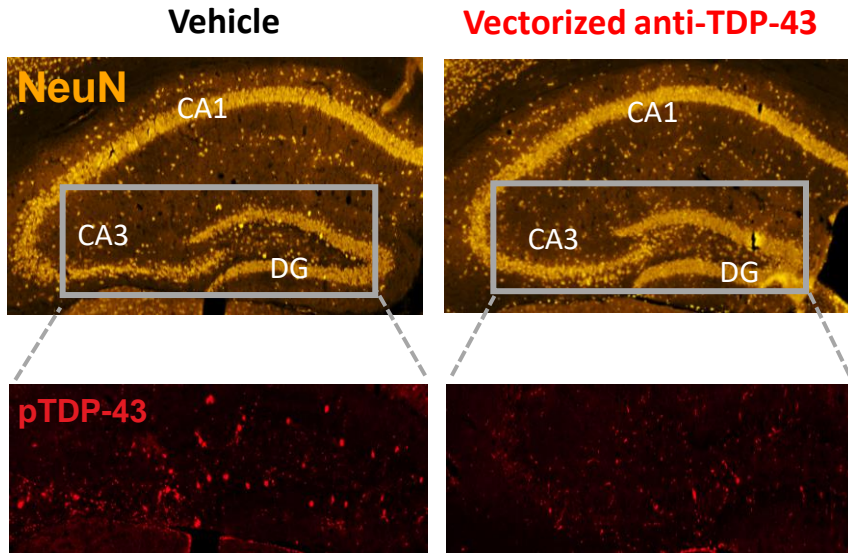
- Ip injected mAb are mostly present in capillaries 24h post administration
- Brain cells provide sustained production of functional antibody
- No vectorized antibody detected within cell nucleus where endogenous TDP-43 is mostly present

(i.p.) : Intraperitoneal; (i.c.m.): Intra cisterna magna

Vectorized antibody reduces pathological species of TDP-43

CamKIIa-hTDP-43_{NLSm} mice – 3 months post extract administration

Immunohistochemistry (Hippocampus)



- Vectorized antibody delivered by AAV9 significantly reduced pTDP-43 levels by 67% compared to control cohort, with a single dose administration, offering a promising alternative to conventional immunotherapy

(1) i.p.: Intraperitoneal; (2) i.c.m.: Vectorized antibody delivered by AAV9 administered intracisternal

Summary and conclusions

Platform technology

- Established a “plug and play” vectorized antibody platform:
 - High expression of excellent antibody quality
 - Retained binding affinity to target
 - Comparable potency to mAb

In vivo production

- *In vivo*, single administration of AAV supports long-term *in situ* production of functional vectorized anti-TDP-43 mAb (up to 4 months)
- Provides higher exposure compared to bolus mAb administration

Proof-of-concept

- First time demonstration that vectorized full-length antibody decreases pathological TDP-43 (67%) in mouse model of ALS/FTD
- Offers a promising alternative to conventional immunotherapy

Validated approach

- Data validate the approach for targeting NDD¹, optimized delivery can be achieved by:
 - Engineered capsids
 - Selective promoters
 - Transgene expression silencing in off-target tissues

(1) Neurodegenerative diseases

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



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