ProMIS™ Neurosciences

Rational Design of a Vaccine Against TDP-43 Proteinopathies Using a Pathogenic Epitope of Misfolded TDP-43

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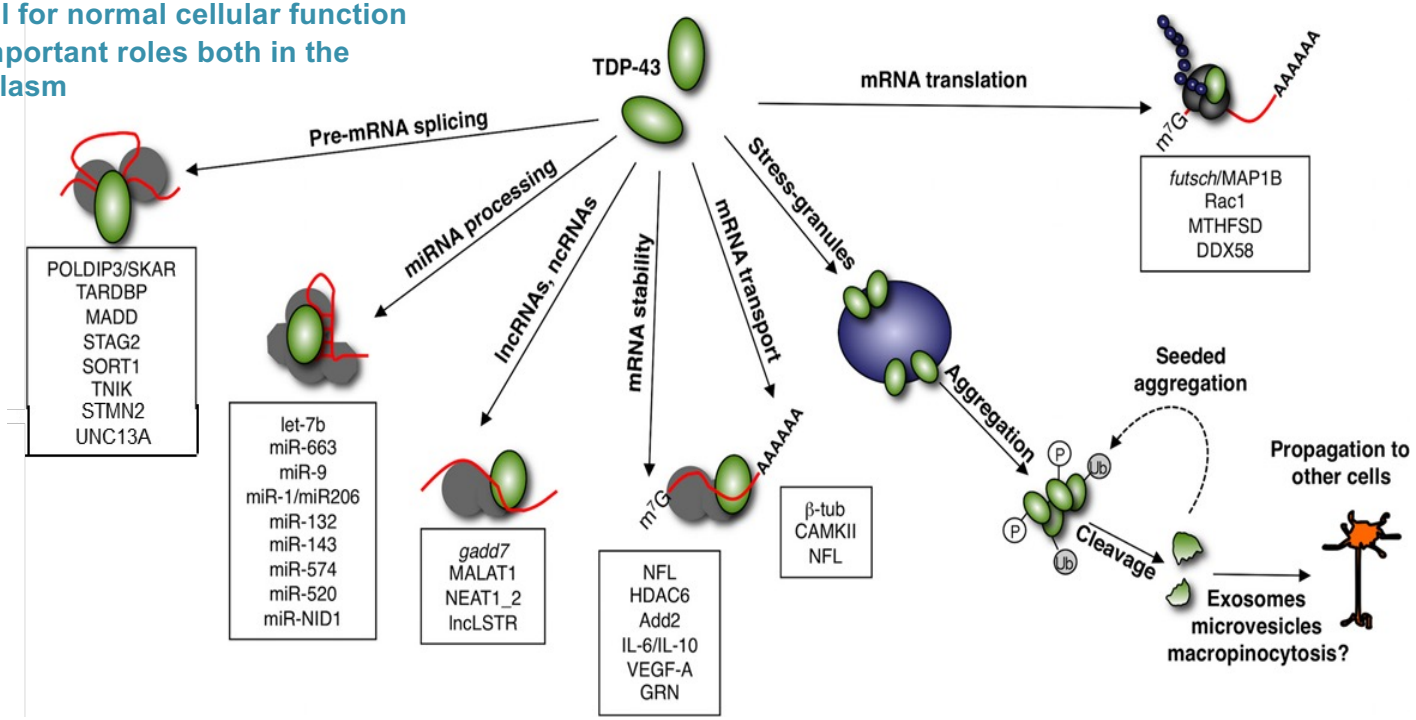
*Disclosure: Employee of ProMIS Neurosciences

TAR DNA-Binding Protein 43 (TDP-43) is essential for normal cellular function and for neuronal survival

TDP-43 is essential for normal cellular function and plays many important roles both in the nucleus and cytoplasm



- TDP-43 is normally present in the nucleus of cells and performs an essential role in RNA splicing, transport, and stability
- Under stress conditions (e.g. oxidative stress) normal TDP-43 also forms protective stress granules in the cytoplasm[1]

1. de Boer, EMJ et al, 2020, J Neurol Neurosurg Psychiatry 2. Figure adapted from Ratti A and Buratti E, 2016, J Neurochem, DOI: 10.1111/jnc.13625

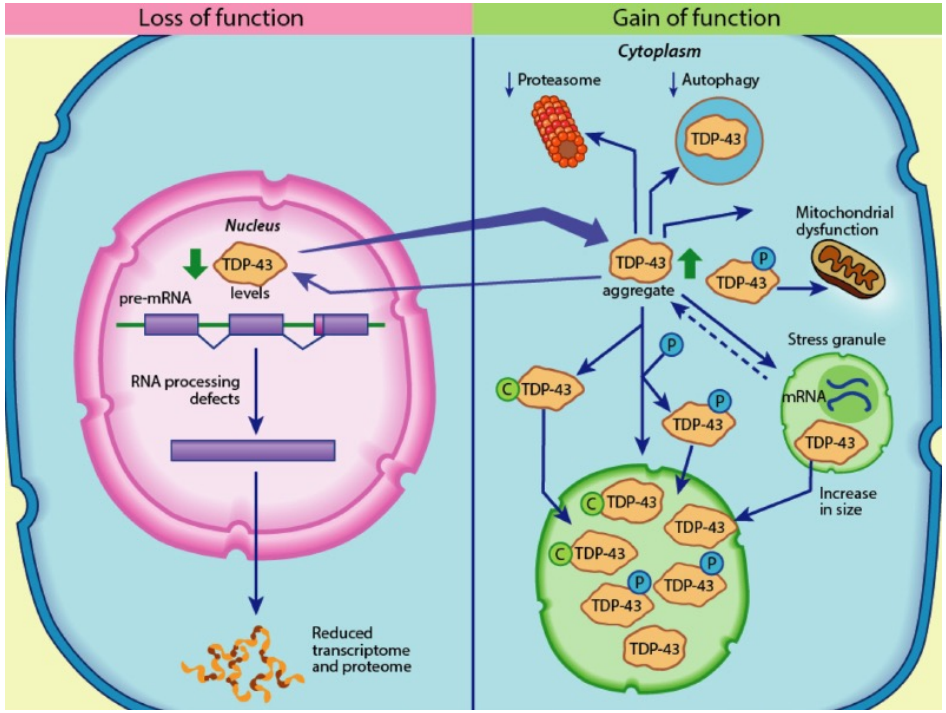
Misfolded and aggregated TDP-43 disrupts normal cellular function

Misfolded TDP-43 gives rise to both loss of function and toxic gain of function[1]

Loss of function: under disease conditions, misfolding of TDP-43 causes formation of mis-localized cytoplasmic aggregates. Nuclear depletion leads to defective splicing and transport of mRNA.

Toxic gain of function: cytoplasmic aggregates of misfolded TDP-43 are toxic and interfere with physiologic stress granule function. They also induce misfolding of other proteins into pathogenic aggregates[2-4] "TDP-43 Pathological Interactome"

Targeting of pathogenic TDP-43 requires stringent selectivity for the misfolded form of the protein to avoid safety concerns



de Boer et al[1]

- **Left:** Misfolded TDP-43 leads to nuclear depletion, ultimately leading to defective nuclear TDP-43 function
- **Right:** Cytoplasmic TDP-43 aggregates disrupt normal TDP-43 cytoplasmic function and cause other proteins to aggregate, ultimately leading to disruption of numerous cytoplasmic protein functions

1de Boer, EMJ et al, 2020, J Neurol Neurosurg Psychiatry; 2Pokrishevsky et al, 2016, Scientific Reports; 3Chou et al, 2018, Nat Neurosci; 4Endo et al, 2018, Biological Psych

Application of EpiSelect™ for generation of antibodies selective for the misfolded toxic form of TDP-43

Because TDP-43 has essential nuclear and cytoplasmic functions, it is vital to selectively target the pathogenic, misfolded form of TDP-43 to avoid safety concerns

EpiSelect™: Epitope prediction

Computational modeling to identify regions of misfolded epitopes likely to be exposed in pathogenic forms of the protein

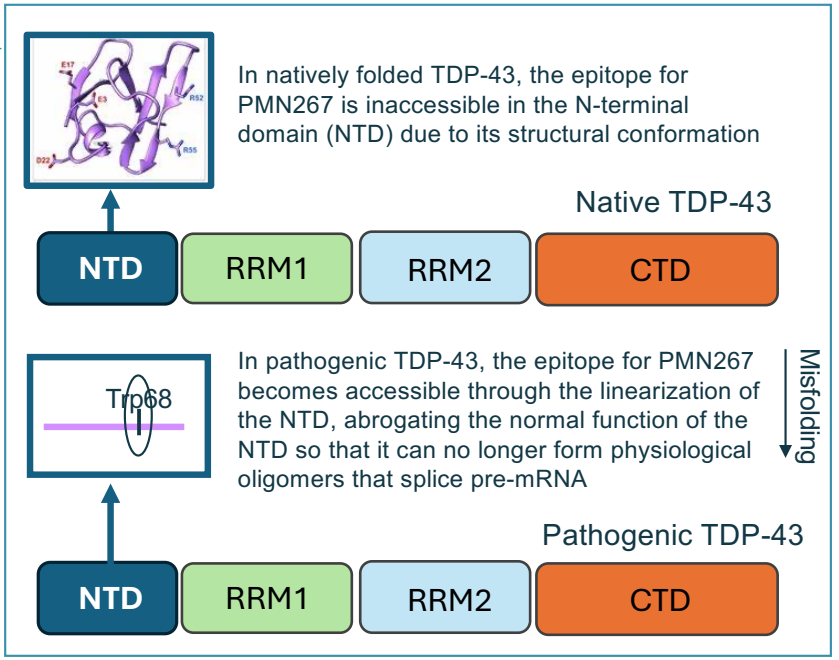
Epitope construction

Construct peptide immunogens mimicking the epitope as exposed in misfolded but not healthy forms of the protein

- ☑ Neutralize the toxic misfolded form of TDP-43
- ☑ Avoid the normal form, critical for brain health

Immunization to generate selective monoclonal antibodies

PMN267



Specificity and selectivity is achieved by targeting an epitope (N-terminal domain containing Trp68 residue) inaccessible in the natively folded state of TDP-43

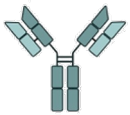
PMN267: Providing optionality in targeting pathogenic TDP-43 with a selective extracellular antibody and a selective intrabody

PMN267

- ✓ Two candidate options targeting toxic TDP-43
- ✓ High affinity for target epitope
- ✓ Selective for misfolded TDP-43
- ✓ No binding to TDP-43 in physiological stress granules

Monoclonal Antibody

- Monoclonal antibody raised against an epitope only exposed on the pathogenic form of TDP-43 (Containing Trp68 in the N-terminal domain of TDP-43)
- Goal: to block cell-to-cell propagation of toxic misfolded TDP-43 to inhibit progression of disease



Vectorized Intrabody*

- Vectorized intrabody encoding a single chain (scFv) intrabody version of PMN267 against an epitope only exposed on the pathogenic form of TDP-43 (Containing Trp68 in the N-terminal domain of TDP-43)
- Goal: to promote degradation of toxic cytoplasmic aggregates of pathogenic TDP-43 intracellularly without affecting cell viability

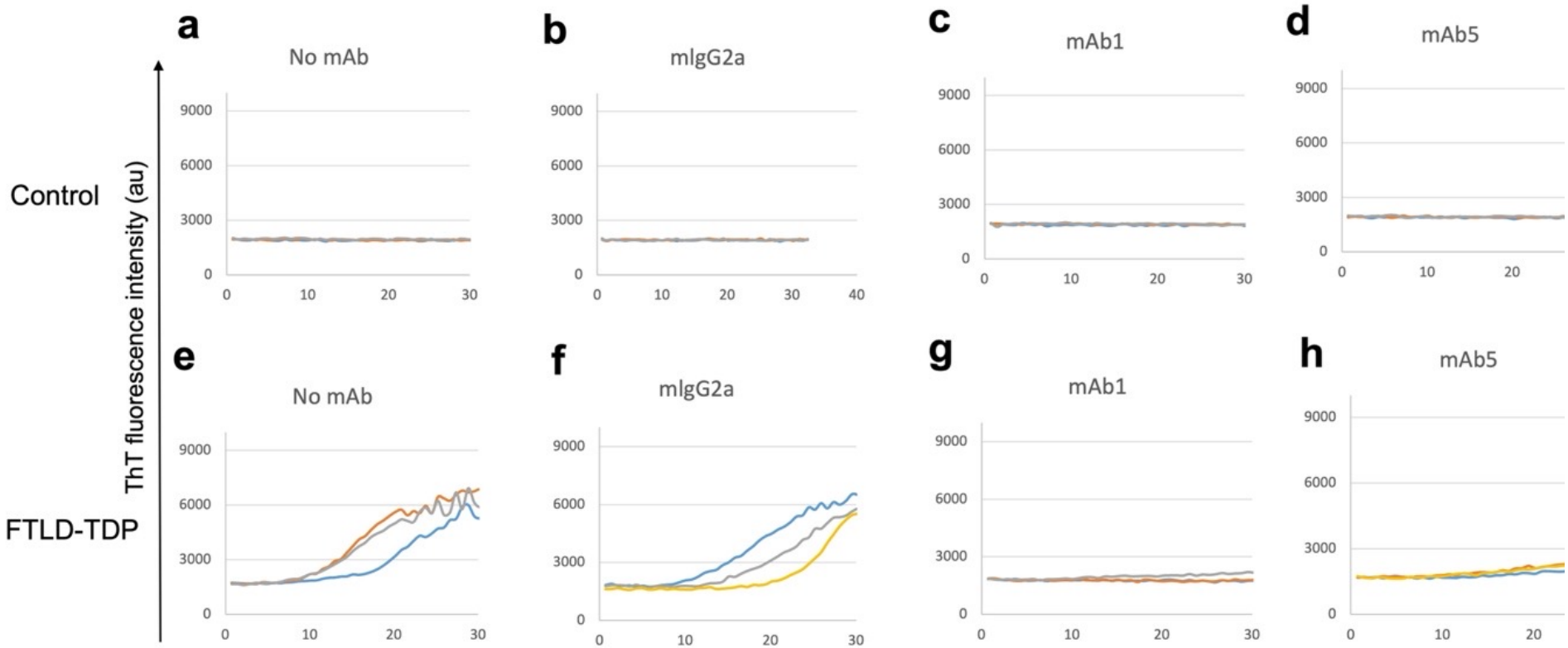
Many misfolded pathogenic proteins that drive neurodegenerative disorders such as TDP-43 form aggregates that propagate from cell to cell but are primarily intracellular

Intracellular targeting with intrabodies or via uptake of extracellular antibodies requires selectivity for the toxic form to preserve function of the normal form of the protein

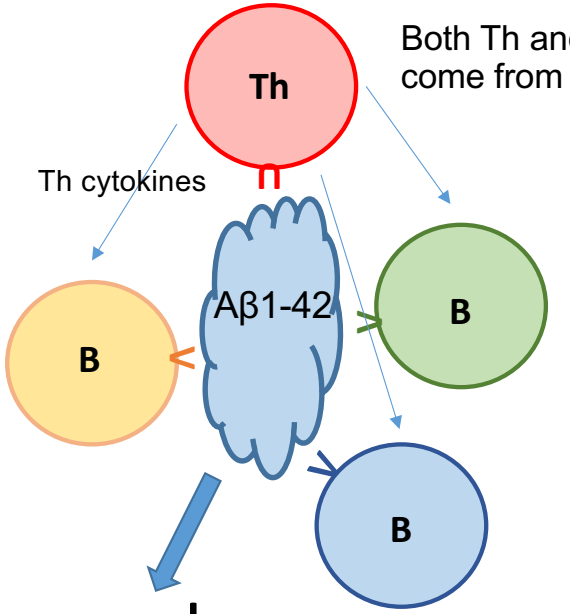
Selectivity is critical to avoid interference with essential cellular function for optimal safety and efficacy

*PMN267 in its current form requires a neuron-targeted vector to deliver the intrabody sequence intracellularly

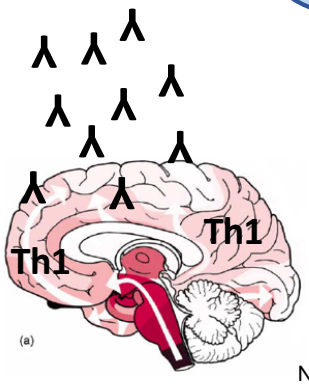
TDP-43 RT-QuIC massive seeding particle: blocked by NTD mAbs



First generation Aβ vaccine (Elan)



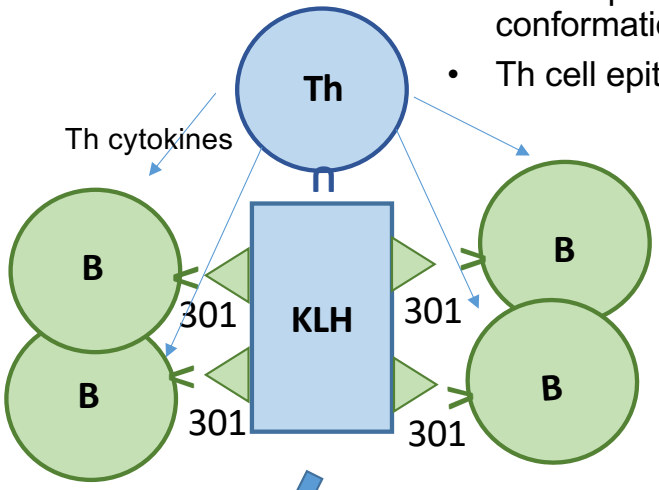
Both Th and B cell epitopes come from Aβ protein

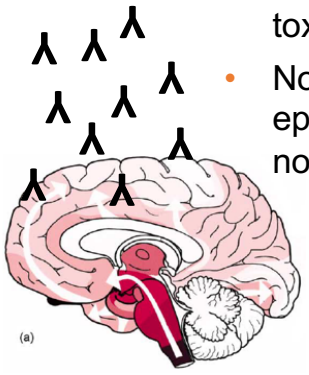


- Aβ B cell epitopes -> Non-selective antibody response to all forms of Aβ
- Aβ T helper epitopes -> Th1-driven meningoencephalitis upon recognition of epitope in the brain

Second generation ProMIS Aβ vaccine

- B cell epitope: ProMIS Aβ conformational peptide
- Th cell epitopes from KLH

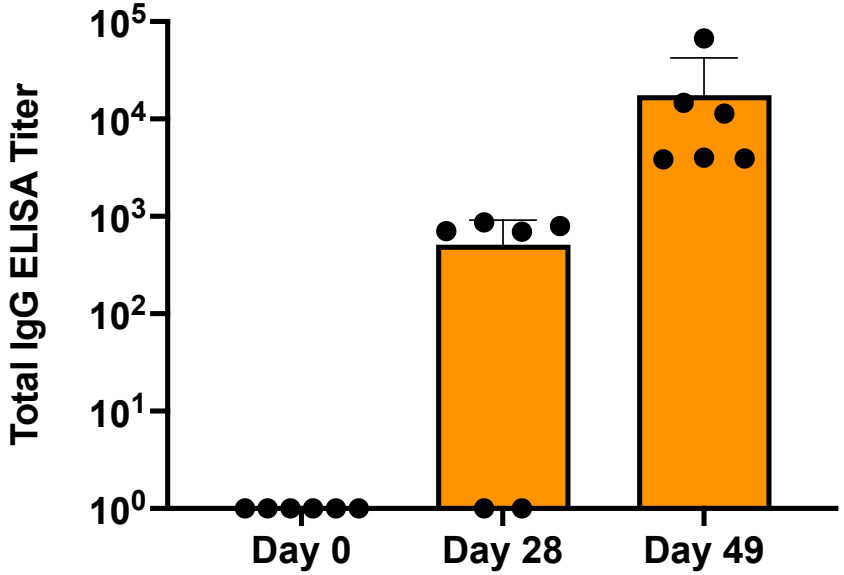


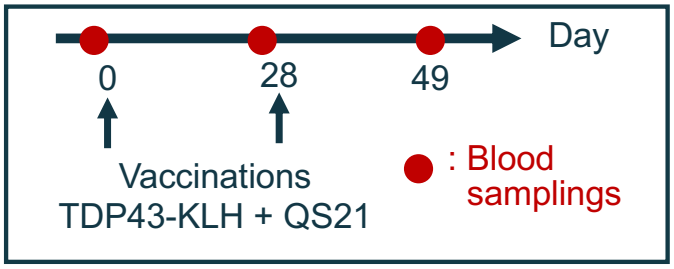


- Aβ conformational B cell epitope -> Antibody response selective for toxic Aβ oligomers
- No Aβ Th epitopes – KLH T helper epitopes not present in the brain, no meningoencephalitis

Note: T helper epitopes are presented on the surface of antigen-presenting cells in association with MHC Class II after uptake and processing of the vaccine. B cell epitopes in the vaccine are presented directly to B cells.

Vaccination with misfolded TDP-43 epitope elicits a robust antibody response

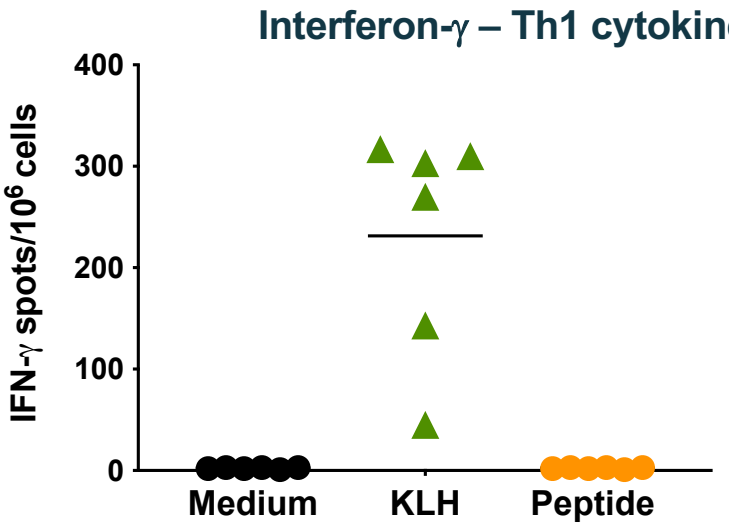


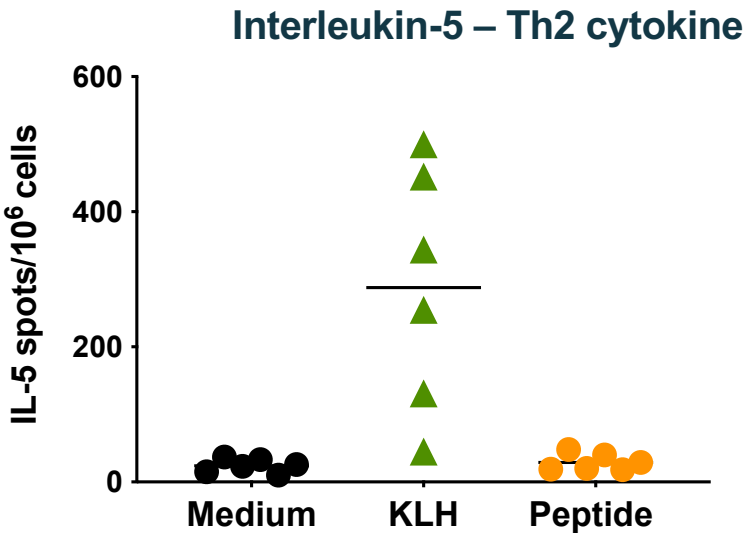


Total IgG ELISA titers

- Vaccination with an N-terminal epitope exposed on misfolded TDP-43 elicited robust antibody titers

Only the KLH carrier protein, not the misfolded TDP-43 peptide epitope, elicits Th cell cytokines in ELISPOT assay – No detrimental inflammatory T cell response to TDP-43





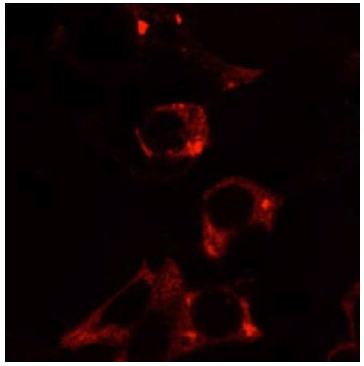
- The production of T helper cytokines in response to KLH stimulation confirms that KLH provides effective Th cell epitopes to support anti-pathogenic TDP-43 peptide antibody responses
- The background production of T helper cytokine in response to stimulation with the misfolded TDP-43 epitope confirms that the peptide does not contain any Th cell epitope, only a B cell epitope

Spleens at day 49

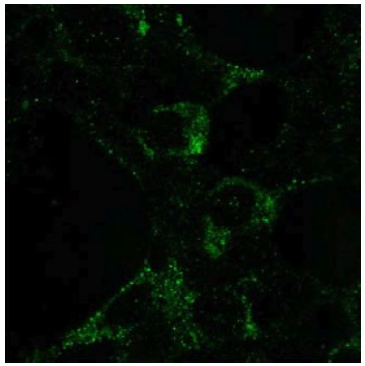
Antibodies induced by misfolded TDP-43 epitope selectively react with TDP-43 in cytoplasmic aggregates and not normal nuclear TDP-43 in HEK-293 cell system

- Immune IgG reacts with misfolded ΔNLS-TDP-43 in cytoplasmic aggregates
- No reactivity with endogenous nuclear TDP-43

ΔNLS-TDP-43



Immune IgG



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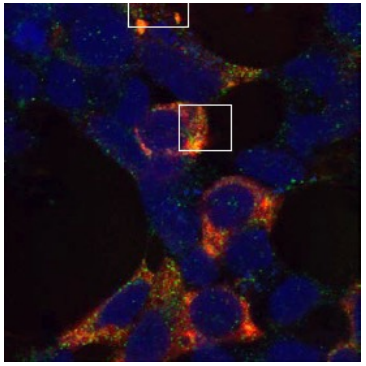
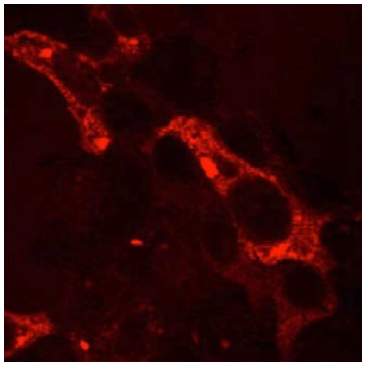
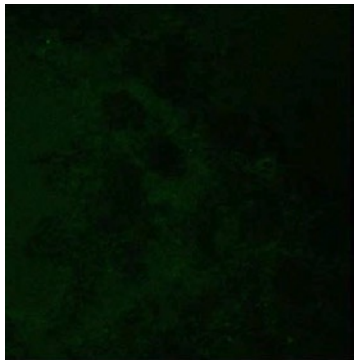


- No reactivity of control mouse IgG with ΔNLS-TDP-43 or nuclear TDP-43

ΔNLS-TDP-43



Control mouse IgG



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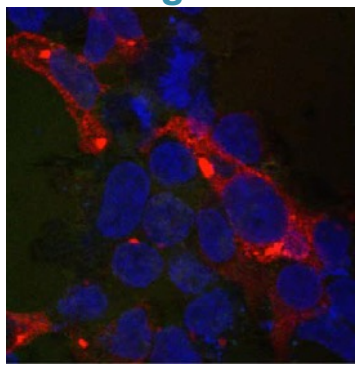
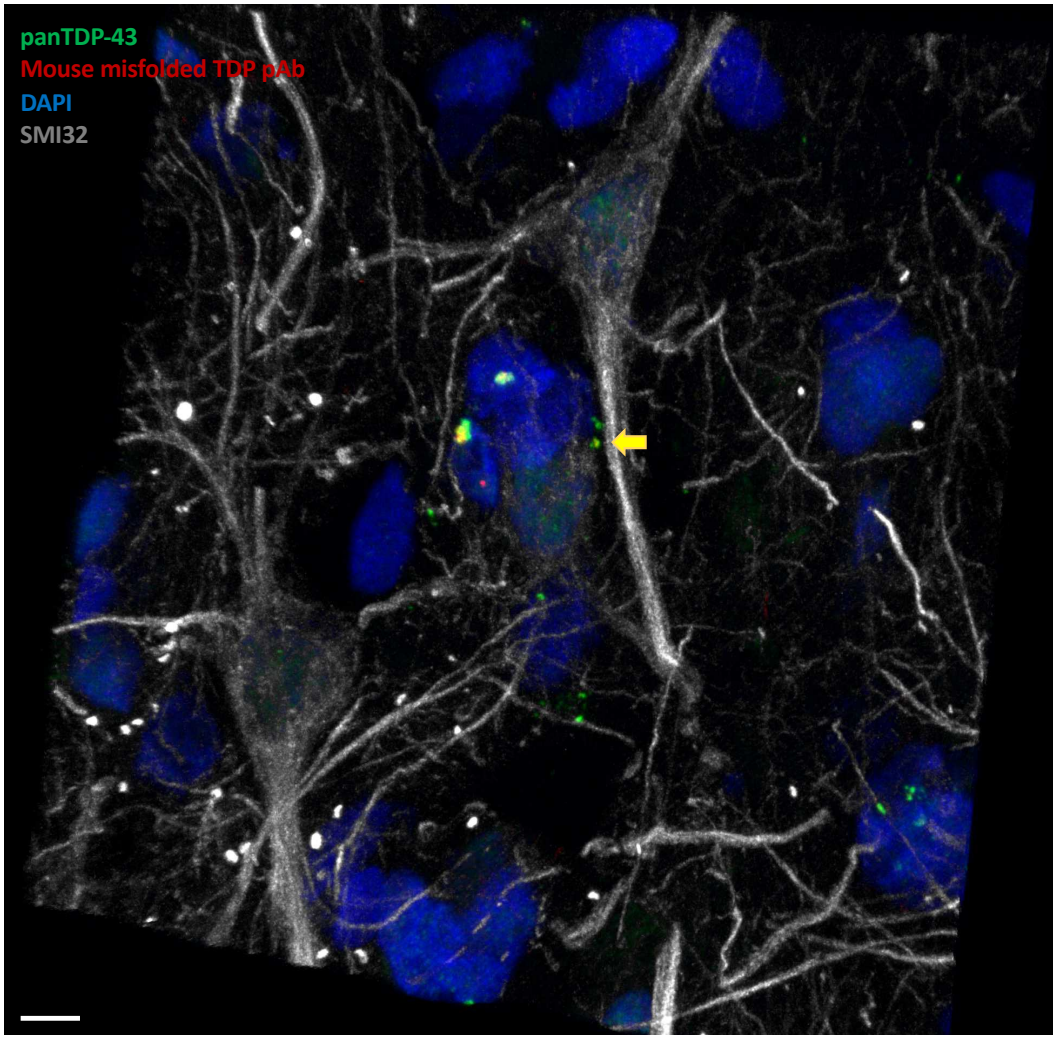
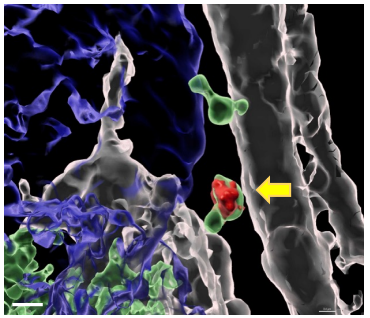
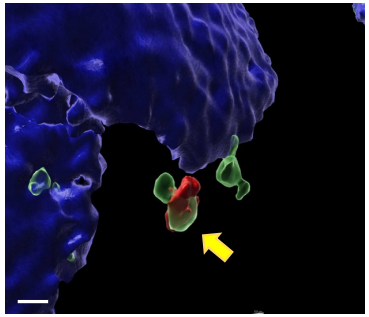


- 5 μg/ml antibody
- 40X magnification
- HA tag stain for ΔNLS-TDP-43

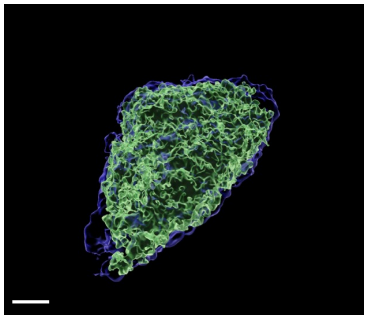
Immune IgG FTLD-TDP brain: cytoplasmic aggregates and extracellular “particles”

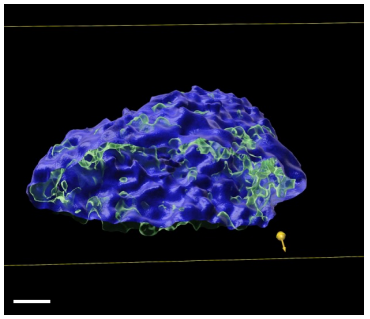


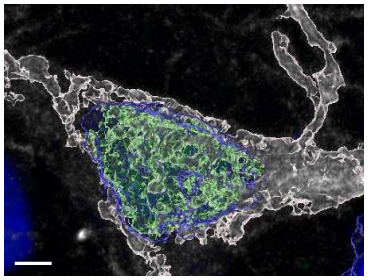




Normal TDP-43 in nucleus of some cells







Sekiguchi et al, JNNP 2013
Ding et al, Oncotarget 2015
Mishra et al, ANPC 2020

Conclusions

We have identified a TDP-43 misfolding-specific epitope centered around Trp68 in the N-terminal domain, which becomes unfolded and antibody-accessible in disease (ALS/FTLD-TDP, and co-pathologies in Alzheimer and Parkinson disease)

Whole monoclonal antibodies against the NTD target block TDP-43 RT-QuIC seeding by FTLD brain homogenate, estimated at least 1 million Da

A KLH-coupled peptide vaccine for the NTD target is immunogenic in mice, with strong Th2 (humoral) activity with T-cell help focused on KLH, without CNS Th1 activity

Vaccine IgG appears to be partially directed at a potential massive extracellular seeding particle, estimated at 50 million Da

Blockade of extracellular seeding particles may have utility in prevention and/or therapeutic slowing of disease progression

Acknowledgements

Co-Authors: Erin Scruten[3], Kanika Verma[2], Florian Pernin[2], Scott Napper,[3] Johanne Kaplan[1]

[1]ProMIS Neurosciences, Cambridge, MA; [2]University of British Columbia, Canada;
[3]University of Saskatchewan, VIDO, Canada

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