ProMIS™ Neurosciences

RATIONAL DESIGN OF ALZHEIMER'S VACCINE TO MAXIMIZE SELECTIVE TARGETING OF TOXIC AMYLOID-BETA OLIGOMERS

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Designing an optimal amyloid-beta vaccine

A vaccination strategy presents several advantages:

- Small number of doses
- Sustained, long term anti-disease activity
- Ease of use in prevention setting in conjunction with diagnostic/predictive biomarkers

A first generation vaccine from Elan consisting of aggregated human $A\beta_{1-42}$ induced antibody production but elicited meningoencephalitis and had to be discontinued for safety[1]

Lesson learned: T helper cell epitopes in the Aβ vaccine gave rise rise to a pro-inflammatory Th1-type response against the same Aβ epitopes in the brain

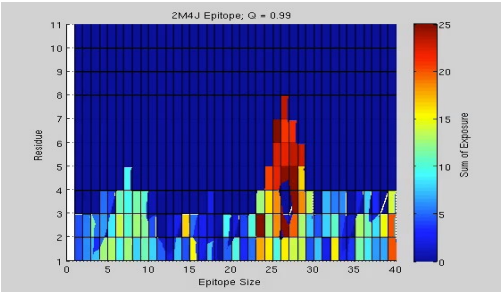
ProMIS approach:

- T helper epitopes provided by a carrier protein (KLH) not expressed in the brain
- Use conformational Aβ epitopes exposed only on toxic Aβ oligomers (AβO), the main driver of pathogenesis
  - Maximizes the dose of antibody reaching the AβO target -> No antibody wasted to cross-reactivity with abundant monomers in blood and CNS
  - AβO selectivity also expected to reduce the risk of brain edema (ARIA-E) and microhemorrhages (ARIA-H) associated with plaque binding

[1]Orgogozo et al, 2003, Neurology

ProMIS platform applied to Aβ oligomer vaccine design

Computational Modeling



Identification of regions (conformational epitopes) likely to be exposed in misfolded toxic Aβ oligomers but not in monomers or fibrils

Vaccination with conformational AβO epitopes

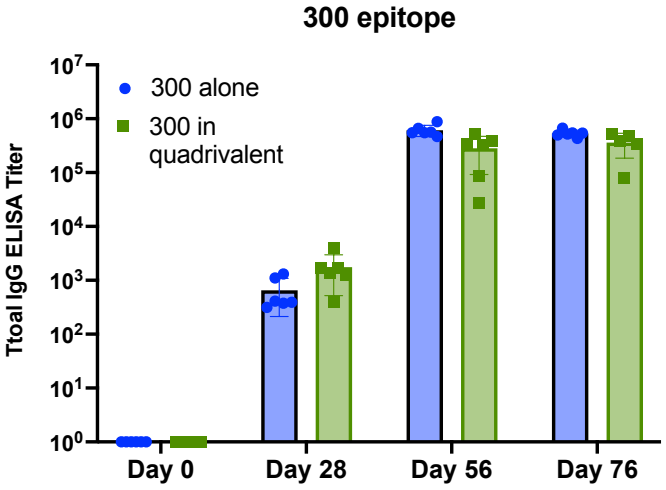
300: $_{25}$GSNK$_{38}$
301: $_{13}$HHQK$_{16}$
303: $_{6}$HDSG$_{9}$
305: $_{15}$QKLV$_{18}$

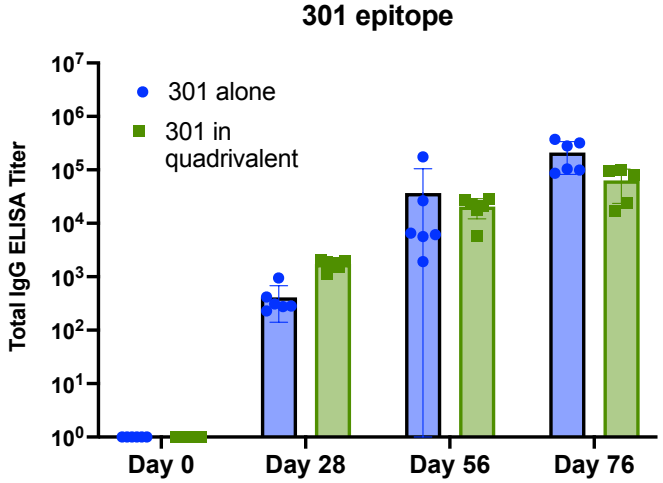
- AβO epitope locations
- Conformation reproduced with cyclized peptides
- Coupled to KLH for T cell help
- QS-21 adjuvant

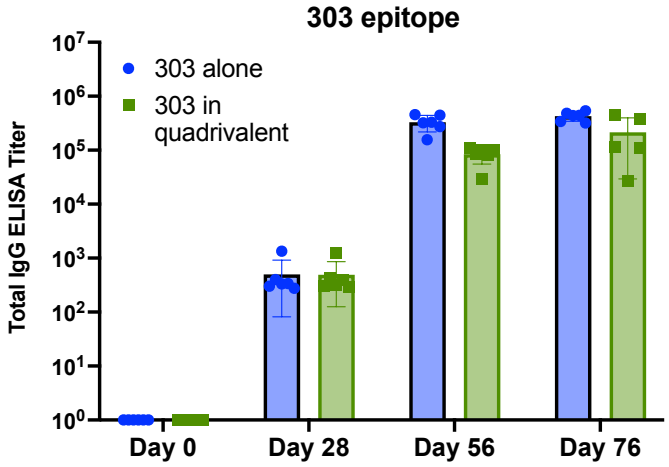
Read-outs

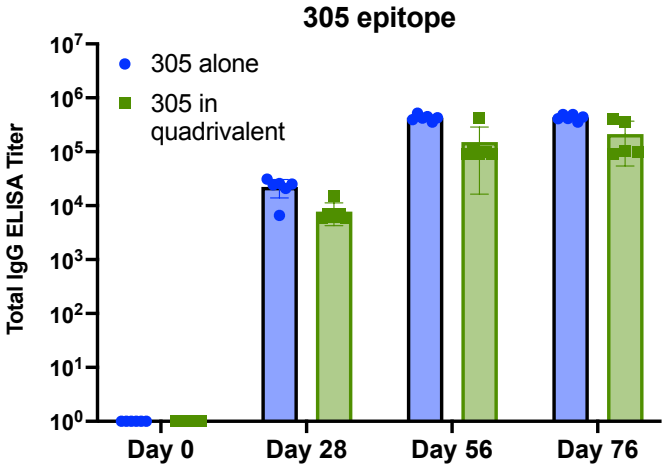
- ELISA IgG titers
- ELISPOT – Th cytokines
- Selectivity profile
  - Oligomers vs monomers (SPR)
  - Plaque (IHC)
- Selection of optimal vaccine design
  - Reactivity of immune IgG with toxic oligomers from AD brain (SPR)

AβO conformational peptide epitopes elicit a robust antibody response when administered individually or in a quadrivalent combination



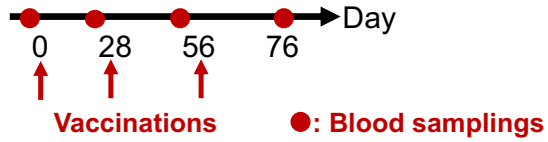




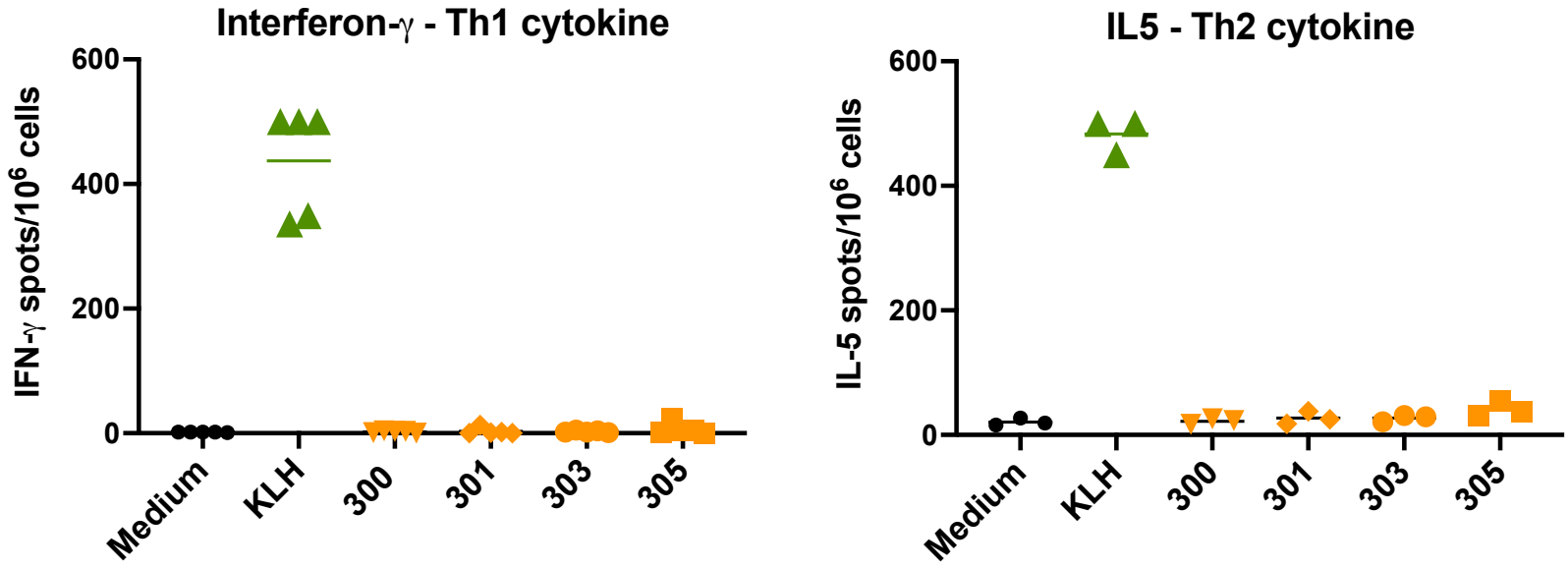


Total IgG ELISA titers

- All 4 AβO conformational peptide epitopes elicit robust antibody titers
- Antibody titers are comparable for peptide epitope delivered alone or as part of a quadrivalent vaccine suggesting a lack of antigenic competition amongst the epitopes



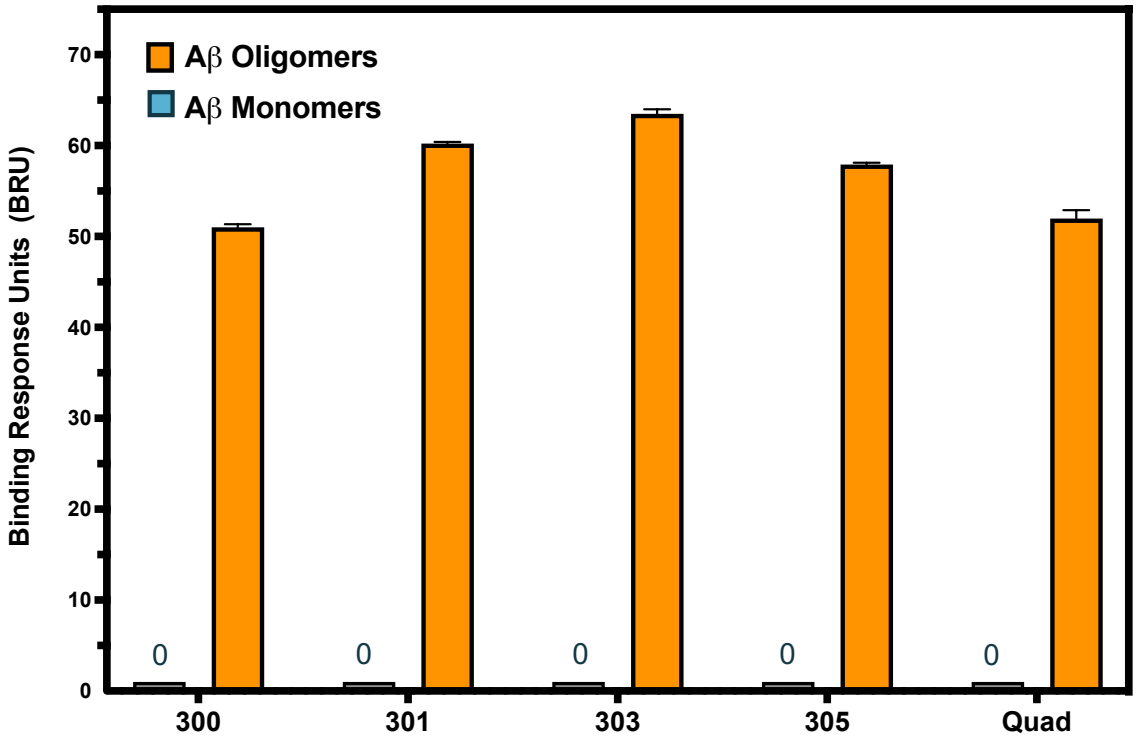
Only the KLH carrier protein, not conformational AβO epitopes, elicits Th cell cytokines in ELISPOT assay – No detrimental inflammatory T cell response to Aβ



- The production of T helper cytokines in response to KLH stimulation confirms that KLH provides effective Th cell epitopes to support anti-AβO peptide antibody responses
- The lack of T helper cytokine production in response to stimulation with conformational AβO epitopes confirms that the peptides do not contain any Th cell epitope, only a B cell epitope

Spleens at day 76, quadrivalent vaccine shown here
Same pattern was observed with the 4 monovalent vaccines

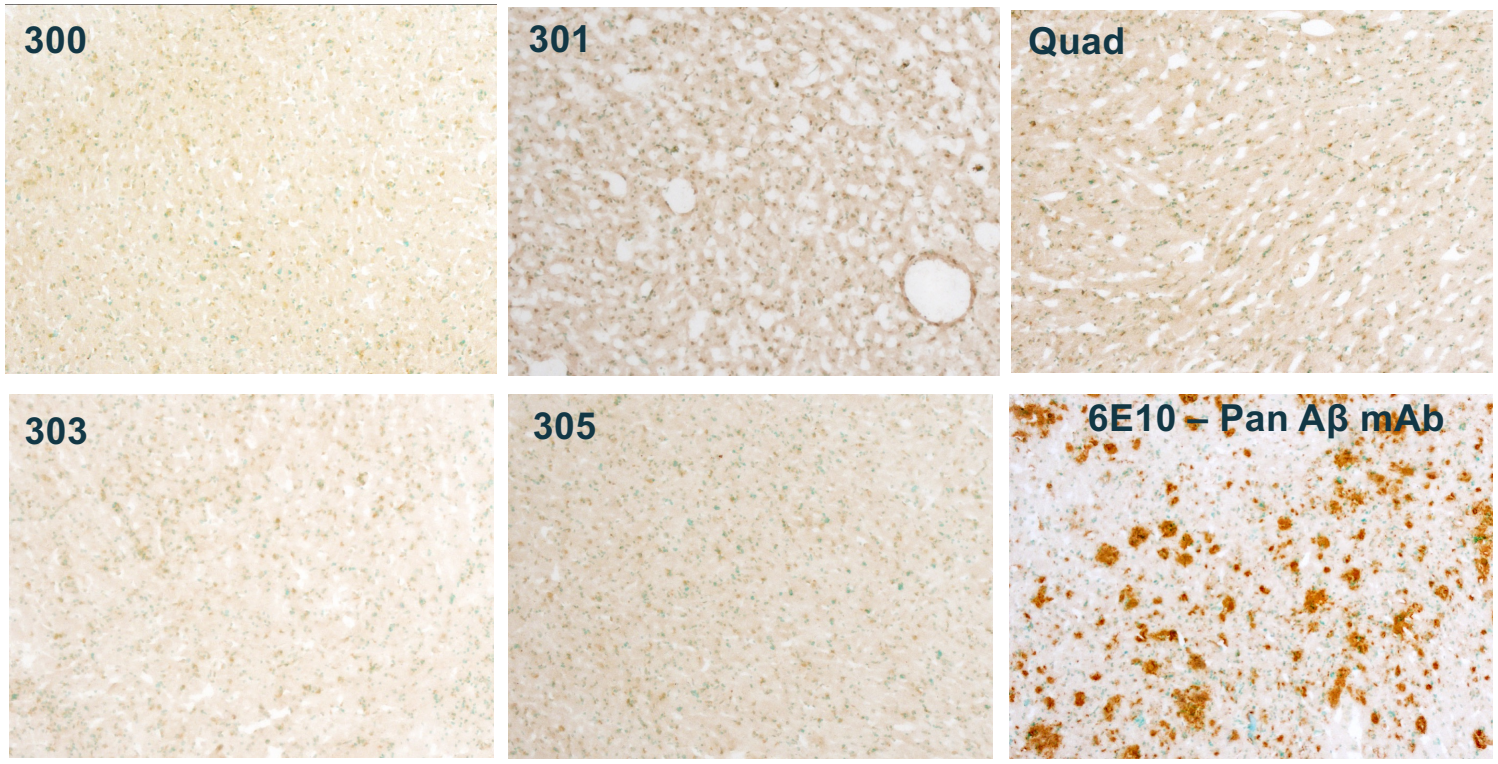
The antibodies induced by conformational AβO epitopes are selective for oligomers vs monomers



Antibodies in immune sera bind Aβ oligomers and not monomers by surface plasmon resonance (SPR)

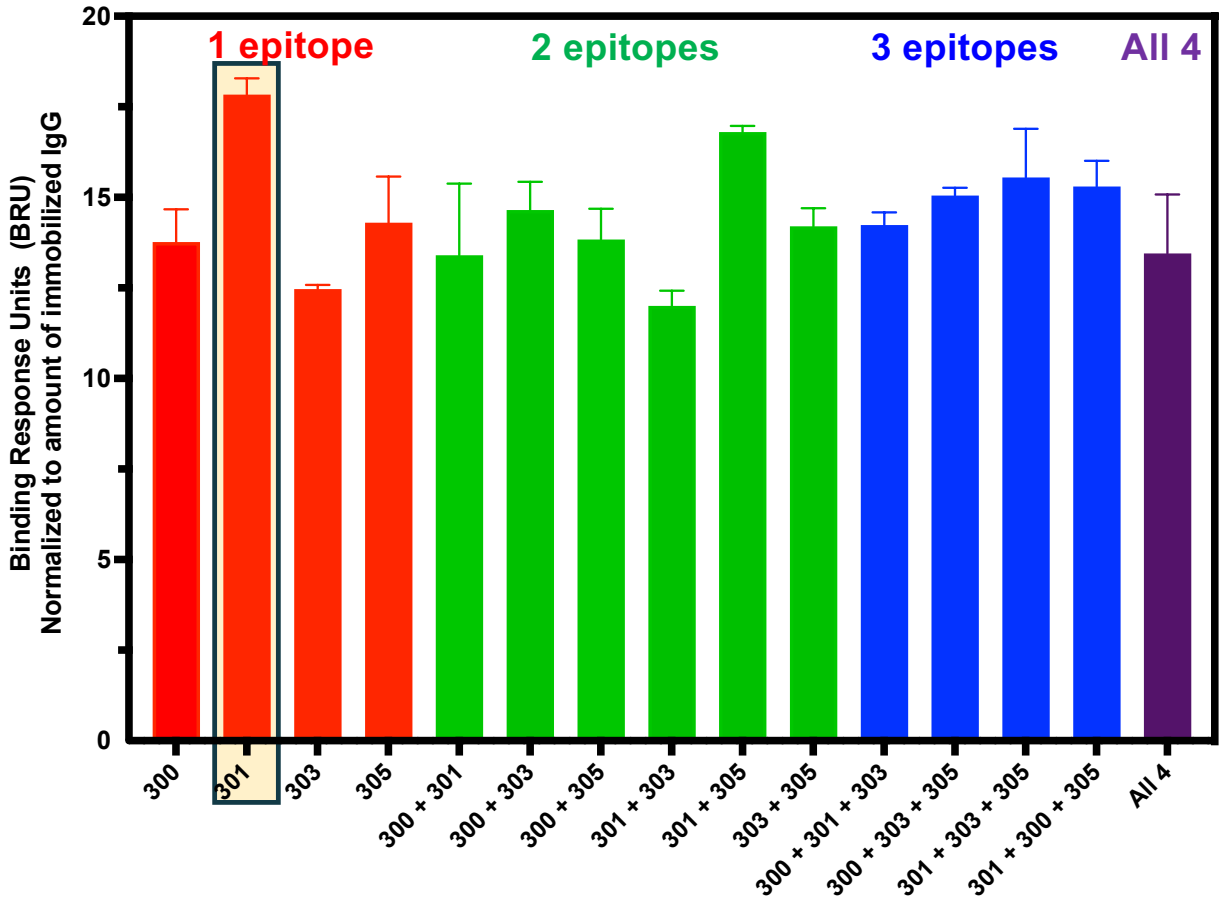
- Day 76, purified immune IgG immobilized on sensor chip
- Monomers or oligomers injected over the surface
- Quad = Quadrivalent vaccine

The antibodies induced by conformational AβO epitopes do not bind plaque in AD brain –> Oligomer-selective antibody response



- Day 76 antisera
- Quad = Quadrivalent vaccine
- Positive control: 6E10, pan-Aβ mAb
- 10X magnification
- No signal on normal, control brain

Maximal reactivity with AD brain toxic oligomers is achieved with conformational epitope 301 alone - No advantage of additional epitopes



Evaluation of 15 possible vaccine configurations

- IgG from immune serum of monovalent vaccines vs mixtures of 2, 3 or 4 sera were tested by SPR for binding to a toxic oligomer-enriched fraction of AD brain
- Maximal reactivity was achieved with immune IgG against the monovalent vaccine containing epitope 301 (target of clinical-stage PMN310 antibody).
- Immune IgG against additional epitopes did not provide any advantage.

- Day 76, purified immune IgG immobilized on sensor chip
- Toxic oligomer-enriched fraction of soluble AD brain extract (MW ~8-70 kDa by SEC) injected over the surface
- Binding response units normalized to the actual amount of immobilized IgG for each combination

Summary

- A robust antibody response was elicited by vaccination with 4 different conformational AβO peptide epitopes conjugated to KLH and formulated with QS-21, an adjuvant approved for human use
- No potentially deleterious T helper responses to any of the conformational AβO peptide epitopes were detected. As expected, T helper responses were induced by the protein carrier (KLH) -> Reduced risk of meningoencephalitis
- The serum antibodies elicited were selective for Aβ oligomers with no detectable binding to monomers or plaque -> Response focused on pathogenic AβO + Reduced risk of ARIA
- Evaluation of all 15 possible combinations of immune IgG to the 4 conformational epitopes indicated that maximal reactivity with toxic oligomers from AD brain was achieved with immune IgG against conformational epitope 301 alone (target of clinical-stage PMN310 antibody).

❖ Under the conditions tested, conformational AβO epitope 301 is the lead vaccine candidate

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