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ProMIS™ Neurosciences

Rational design of a vaccine for Alzheimer's disease using computationally-derived conformational B cell epitopes to selectively target toxic amyloid-beta oligomers

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Disclosure

Employee of ProMIS Neurosciences

Designing an optimal amyloid-beta vaccine

- A vaccination strategy, as opposed to passive immunization with a therapeutic antibody, presents several advantages:
  - Small number of doses vs chronic administration
  - Sustained, long term anti-disease activity
  - Ease of use in prevention setting in conjunction with diagnostic/predictive biomarkers
- A first generation experimental vaccine from Elan consisting of aggregated human $A\beta_{1-42}$ + QS-21 adjuvant induced antibody production but elicited meningoencephalitis and had to be discontinued for safety
- Lesson learned: T helper epitopes in the Aβ vaccine gave rise rise to a pro-inflammatory Th1-type response against the same Aβ epitopes in the brain
- Our approach:
  - Vaccine to contain Aβ B cell epitopes only, no Aβ T helper epitopes
  - T helper epitopes provided by a carrier protein (KLH) not expressed in the brain

Potential of the ProMIS platform for vaccine application

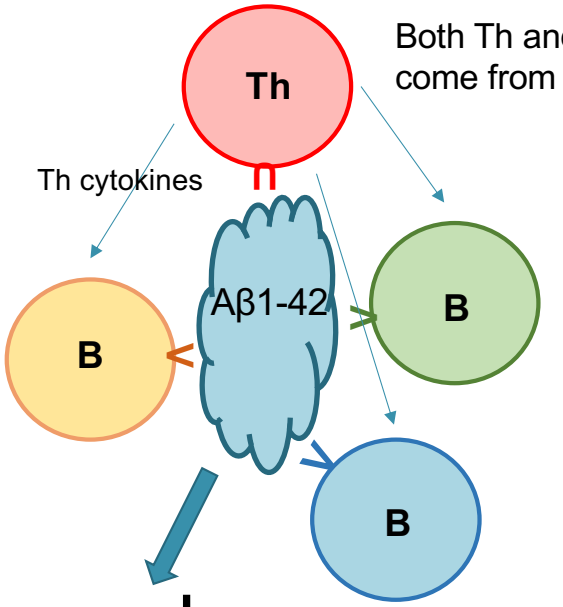
- Using computational modeling, ProMIS has identified conformational epitopes that are exposed on misfolded, toxic Aβ oligomers (AβO) and not monomers or plaque
  - Antibodies raised against these conformational peptide epitopes have demonstrated selectivity and protective activity against toxic AβO[1-3]
  - Monoclonal antibody PMN310 preparing to enter Phase 1 clinical trial (passive immunization)

- Advantages of an oligomer-selective vaccine vs pan-Aβ approach
  - Antibodies elicited are capable of neutralizing and clearing toxic AβO
  - Maximizes the dose of antibody reaching the CNS -> No binding of antibodies to monomers in the blood
  - Once inside the CNS, oligomer-selective antibodies focus the entire dose on toxic oligomers -> No wasted binding to plaque or monomers
  - Reduces the potential risk of brain edema (ARIA-E) observed with plaque-binding antibodies (e.g., aducanumab, lecanemab, donanemab)

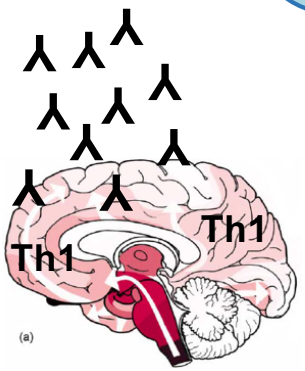
- Vaccination studies conducted in collaboration with VIDO – Vaccine and Infectious Disease Organization, University of Saskatchewan, Canada

[1] Silverman et al. 2016. AAIC poster P4-400; [2]Silverman et al. 2018. ACS Chem Neurosci 9: 1591-1606; [3]Gibbs et al. 2019. Scientific Reports 9:9870

First generation Aβ vaccine (Elan)



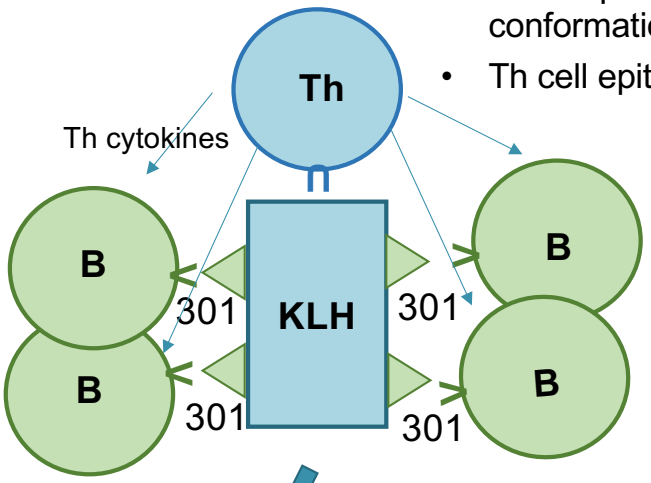
Both Th and B cell epitopes come from Aβ protein

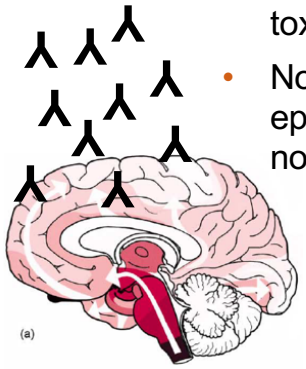


- Aβ B cell epitopes -> Non-selective antibody response to all forms of Aβ
- Aβ T helper epitopes -> Th1-driven meningoencephalitis upon recognition of epitope in the brain

Next generation ProMIS Aβ vaccine

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

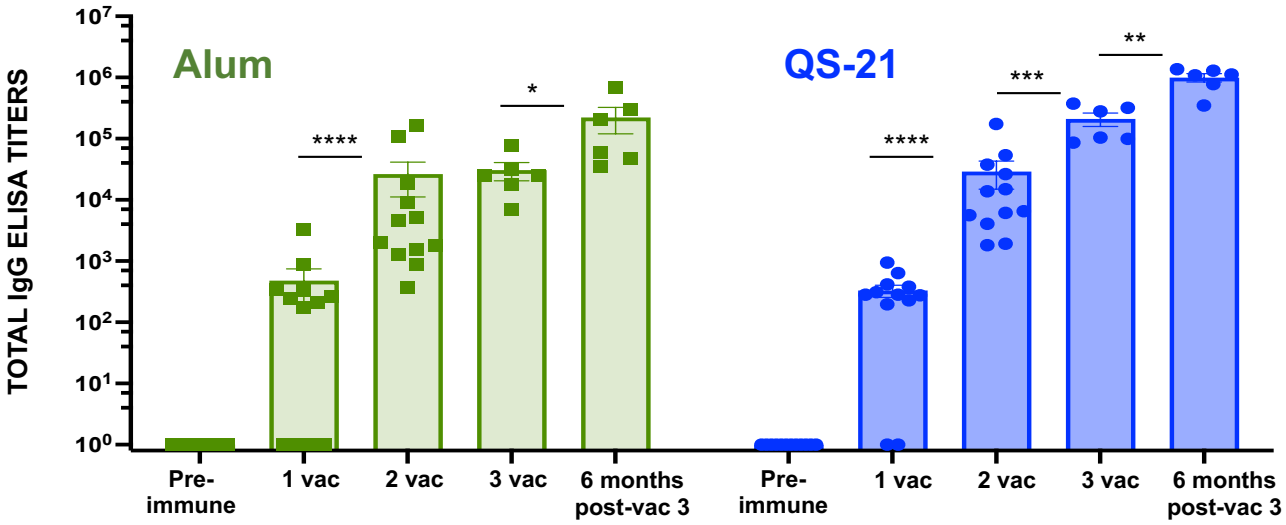




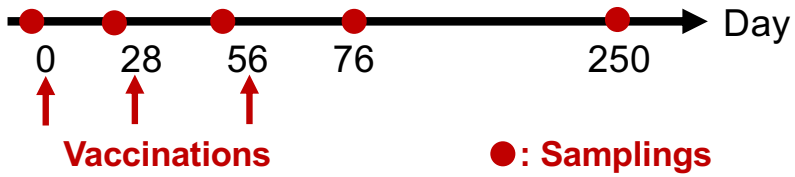
- Aβ conformational B cell epitope -> Antibody response selective for toxic Aβ oligomers
- No Aβ Th epitopes – KLH T helper epitopes not present in the brain, no meningoencephalitis

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 AβO conformational peptide epitope conjugated to KLH elicits a robust and sustained antibody response



*p=0.0152, **p=0.0043, ***p=0.0008, ****p<0.0001

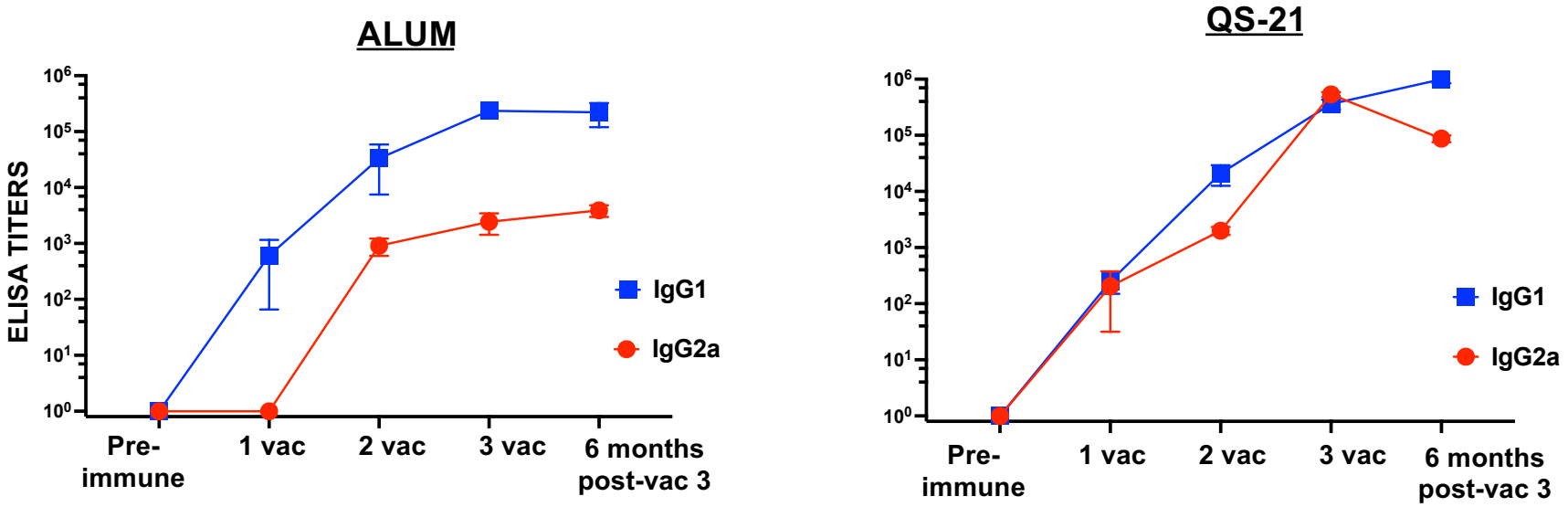


Total IgG ELISA titers

- Comparably high antibody titers achieved after 2 intramuscular vaccinations with either alum or QS-21 as the adjuvant
- Third vaccination provides further increase in titer with QS-21
- High titers sustained and increased out to 6 months after the last vaccination

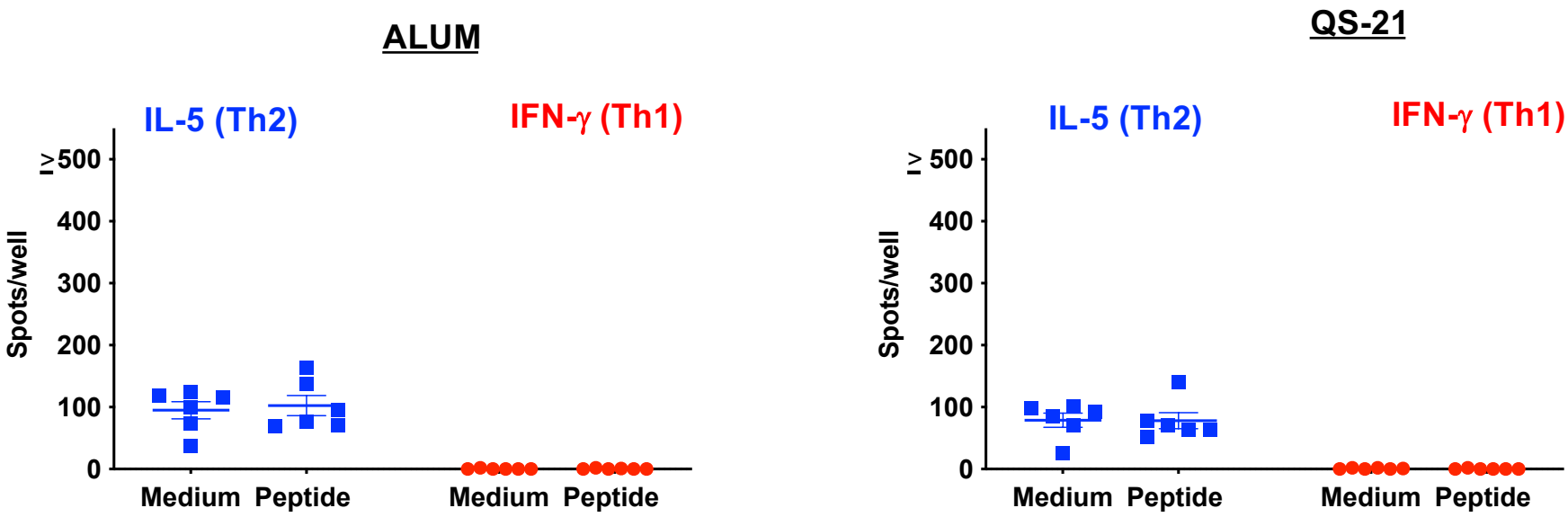
Vac = vaccination

Vaccination elicits both IgG1 and IgG2a antibodies against the conformational AβO epitope



- Alum and QS-21 induce both IgG1 and IgG2a antibody responses to the AβO conformational epitope
- Responses are skewed toward production of IgG1 antibodies (Th2-driven, no effector function) vs IgG2a antibodies (Th1-driven, effector function) with alum
- QS-21 produces more comparable levels of IgG1 and IgG2a

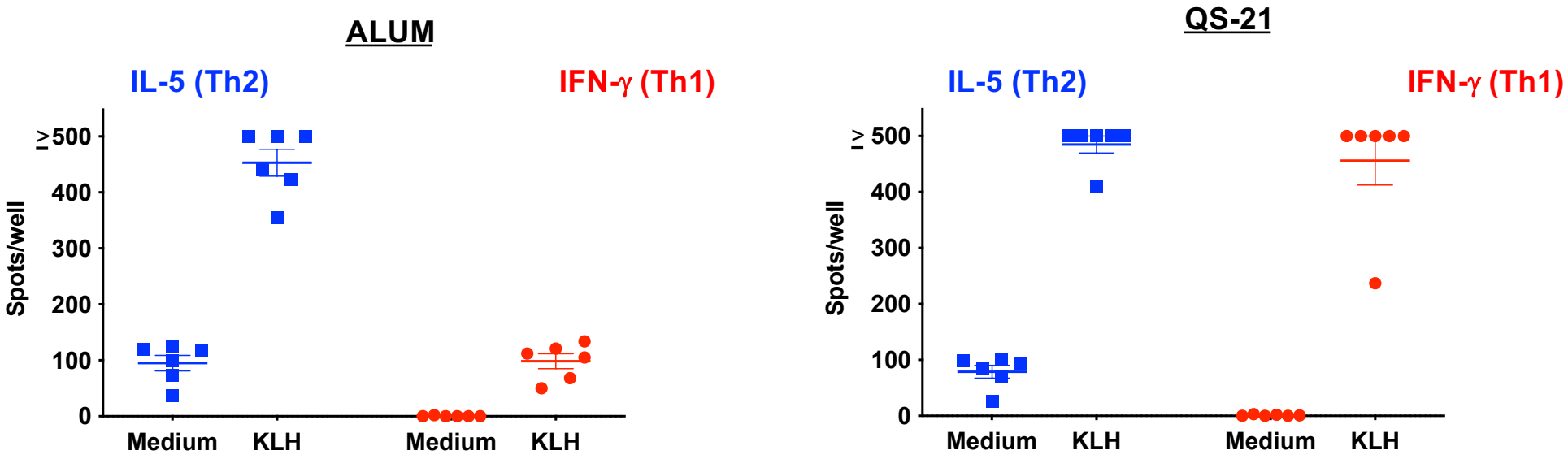
The conformational AβO epitope does not elicit Th cell cytokines in ELISPOT assay – No detrimental inflammatory T cell response to Aβ



The lack of T helper cytokine production above background in response to stimulation with conformational AβO epitope confirms that the peptide does not contain any Th cell epitope, only a B cell epitope

Spleens at 6 months post-vaccination

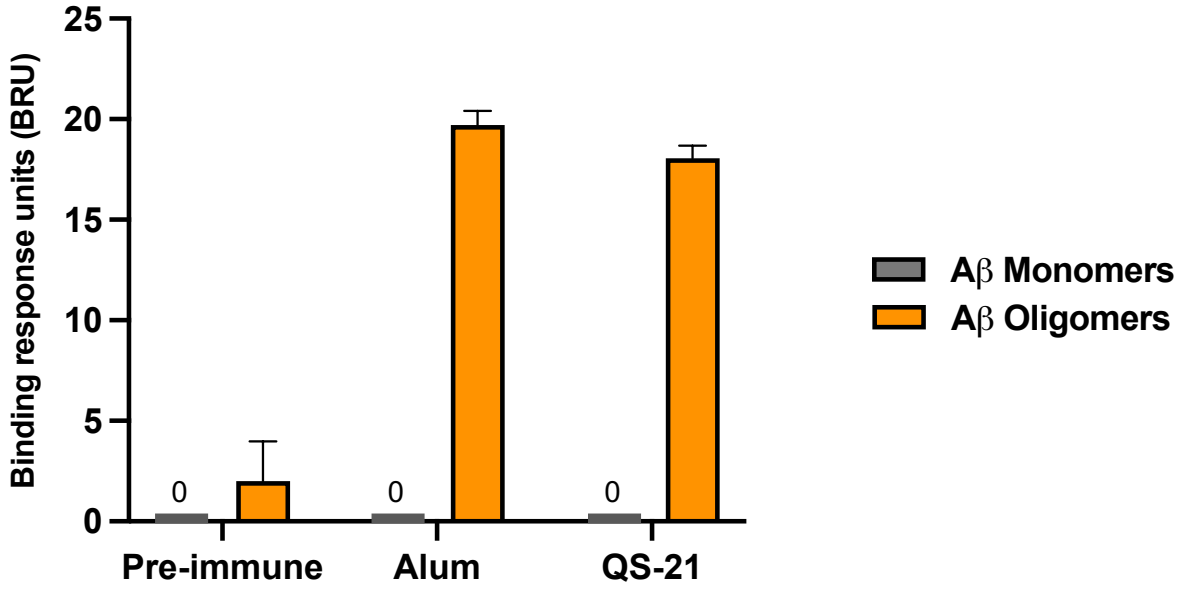
The KLH carrier elicits both Th1 (IFN-ɣ) and Th2 (IL-5) helper cytokines in ELISPOT assay – Source of T cell help



- The production of T helper cytokines in response to KLH stimulation confirms that KLH provides effective Th cell epitopes to support the anti-AβO peptide antibody response
- Alum: Response is skewed toward induction of IL-5 (Th2 cytokine) consistent with greater IgG1 (Th2-driven) vs IgG2a (Th1-driven) antibody production
- QS-21: Comparable induction of IL-5 (Th2) and IFN-γ (Th1) cytokines consistent with comparable levels of IgG1 and IgG2a antibody production

Spleens at 6 months post-vaccination

The antibodies induced by vaccination are selective for Aβ oligomers vs monomers

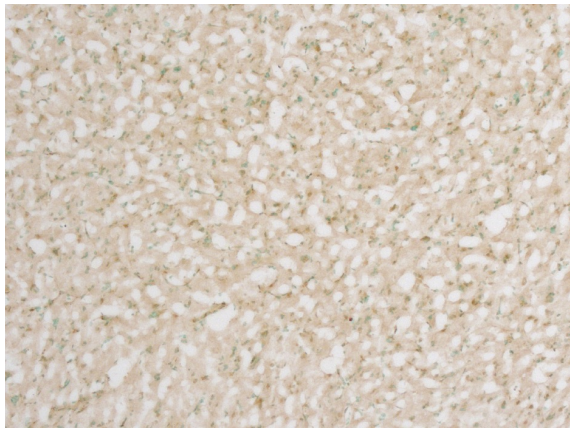


Antibodies in immune sera bind Aβ oligomers and not monomers (surface plasmon resonance - SPR)

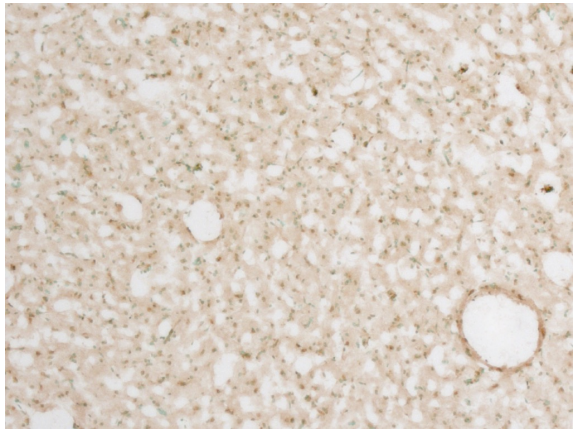
- Day 76 antisera
- 1.6% concentration injected over immobilized monomers & oligomers

Antibodies induced by vaccination do not bind plaque in AD brain –> Oligomer-selective antibody response

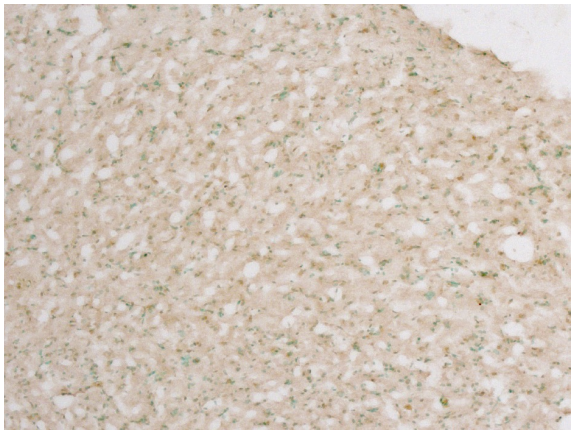
Alum



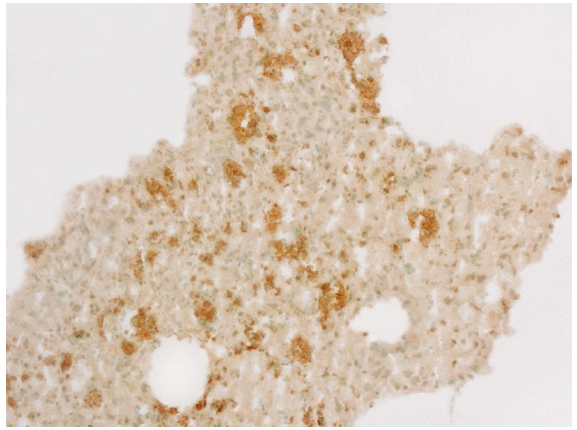
QS-21



Pre-immune



6E10 – Pan Aβ mAb



- Day 76 antisera
- 10X magnification
- No signal on normal, control brain

Summary

- Robust and sustained antibody response elicited by intramuscular vaccination with a conformational AβO peptide epitope conjugated to KLH and formulated with adjuvants approved for human use, alum and QS-21
- No potentially deleterious T helper responses to the conformational AβO peptide epitope detected. As expected, T helper responses developed against the carrier (KLH) -> Reduced risk of meningoencephalitis
- The serum antibodies elicited were selective for Aβ oligomers with no detectable binding to monomers or plaque -> Reduced risk of ARIA

❖ Immunization with a vaccine consisting of a conformational AβO B cell epitope conjugated to a carrier protein (KLH) appears to exhibit the desired characteristics

- Strong antibody response to Aβ with no measurable pro-inflammatory T cell response to Aβ
- Oligomer selectivity of the antibodies most efficiently focuses the response on the pathogenic species of Aβ

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