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

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Background

Amyloid-beta (Aβ) vaccines have the potential to protect against disease but also carry the risk of eliciting proinflammatory T cell responses causing meningoencephalitis, and plaque-reactive antibodies that can increase the risk of brain edema (ARIA-E). To circumvent these issues and induce an antibody response that selectively targets soluble toxic Aβ oligomers (AβO), without inducing potentially detrimental B or T cell responses against plaque or normal Aβ, we used our Collective Coordinates computational platform to design a vaccine consisting of a conformational epitope of AβO, coupled to keyhole limpet hemocyanin (KLH) as a carrier protein to provide T cell help and comparing 2 different adjuvants approved for human use (alum & QS-21).

Methods

Mice received 3 immunizations, 4 weeks apart, with vaccine conjugate in alum or QS-21 as adjuvants. Serum titers of total IgG, IgG1 and IgG2a antibodies to the peptide epitope were measured by ELISA. The selectivity of serum antibodies for toxic AβO versus monomers was evaluated by surface plasmon resonance, and plaque reactivity was assessed by immunohistochemistry on AD brain sections. T helper type 1 (Th1) and type 2 (Th2) responses to the peptide and to KLH were evaluated by ELISPOT analysis of splenic lymphocytes.

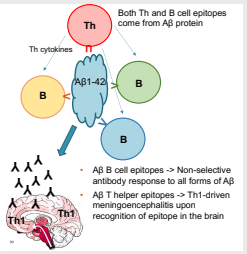
Results & Conclusions

- 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 -> Response focused on pathogenic AβO + Reduced risk of ARIA

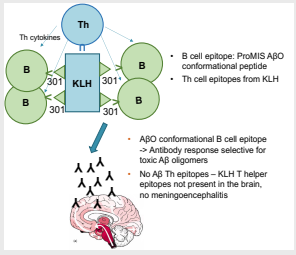
1. Designing an optimal Aβ vaccine

- **ProMIS approach:** Use our Collective Coordinates computational platform to design a vaccine consisting of a conformational B cell epitope of Aβ oligomers (AβO), coupled to keyhole limpet hemocyanin (KLH) as a carrier protein to provide T cell help.
- **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

2. First generation Aβ vaccine (Elan)

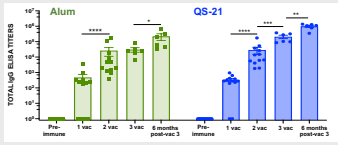


Second generation ProMIS Aβ vaccine

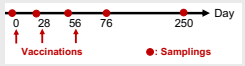


Note: T helper epitopes are presented on the surface of antigen-presenting cells in association with MHC Class II after uptake and processing of the vaccine. B cell epitopes in the vaccine are presented directly to B cells.

3. Vaccination with AβO conformational peptide epitope conjugated to KLH elicits a robust and sustained antibody response



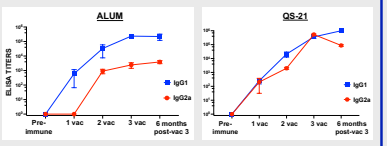
*p=0.0152, **p=0.0043, ***p=0.0008, ****p<0.0001, Vac = vaccination



Total IgG ELISA titers

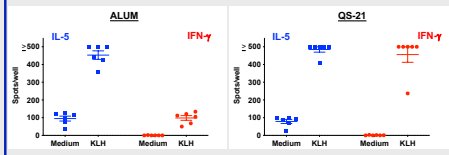
- Comparably high antibody titers achieved after 2 intramuscular vaccinations with either alum or QS-21 as the adjuvant
- Third vaccination provides further increase in titer with QS-21
- High titers sustained and increased out to 6 months after the last vaccination

4. Vaccination elicits both IgG1 and IgG2a antibodies against the conformational Aβ oligomer 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

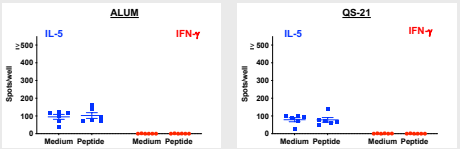
5. The KLH carrier elicits both Th1 (IFN-γ) and Th2 (IL-5) helper cytokines in ELISPOT assay – Source of T cell help



- 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

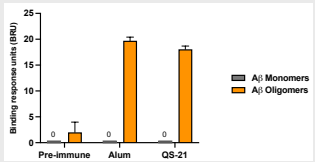
6. The conformational AβO epitope does not elicit Th cell cytokines in ELISPOT assay – No detrimental inflammatory T cell response to Aβ



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

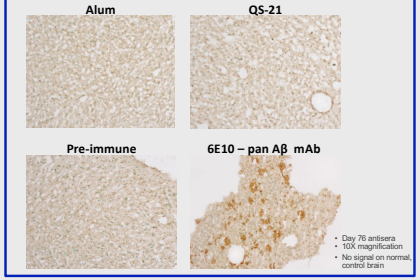
7. The antibodies induced by vaccination are selective for Aβ oligomers *vs* monomers



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

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



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

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