# Optimizing vaccine design for Alzheimer's disease: Selective targeting of computationally-derived conformational B cell epitopes of soluble amyloid-beta toxic oligomers

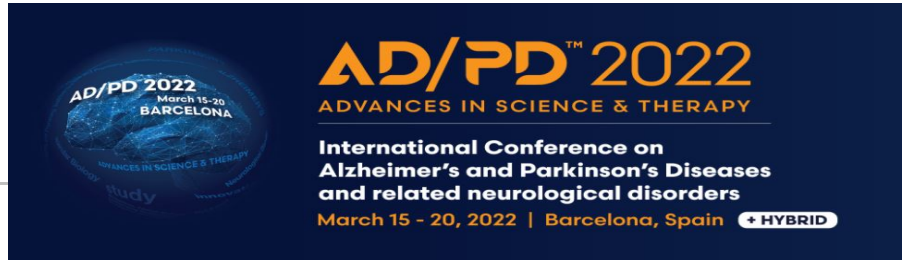
Johanne Kaplan, PhD
Chief Development Officer
ProMIS Neurosciences

ProMIS™ Neurosciences

Toronto Stock Exchange (TSX) ticker: PMN.TO
OTCQB ticker: ARFXF

March 20, 2022

# Disclosure




- Full time 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 vaccine from Elan consisting of aggregated human $A\beta_{1-42}$ + QS1 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
- ProMIS 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

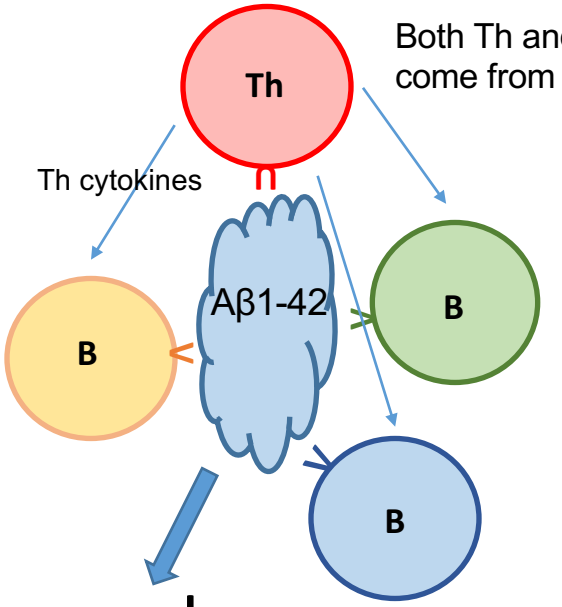
# Potential of the ProMIS platform for vaccine application

- 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 epitopes have demonstrated selectivity and protective activity against toxic AβO[1-3]
  - Monoclonal antibody PMN310 currently in IND-enabling studies for Alzheimer's disease (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
- Peptide-based vaccine tested in collaboration with VIDO – Vaccine and Infectious Disease Organization, University of Saskatchewan, Canada

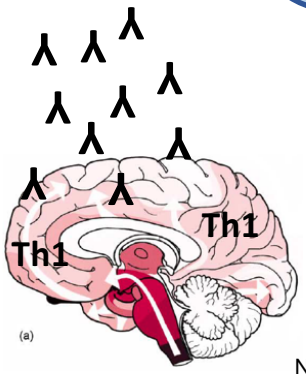
ProMIS™ Neurosciences

[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)



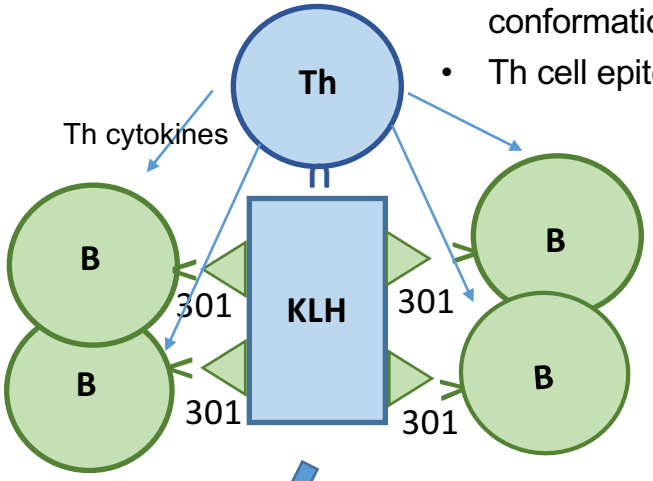

Both Th and B cell epitopes come from Aβ protein

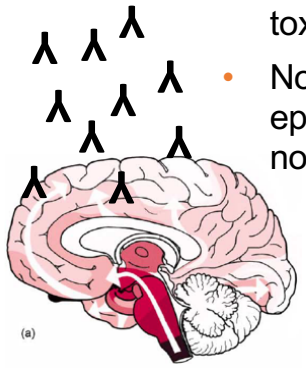



- Aβ B cell epitopes -> Non-selective antibody response to all forms of Aβ
- Aβ T helper epitopes -> Th1-driven meningoencephalitis upon recognition of epitope in the brain

## Second generation ProMIS Aβ vaccine

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

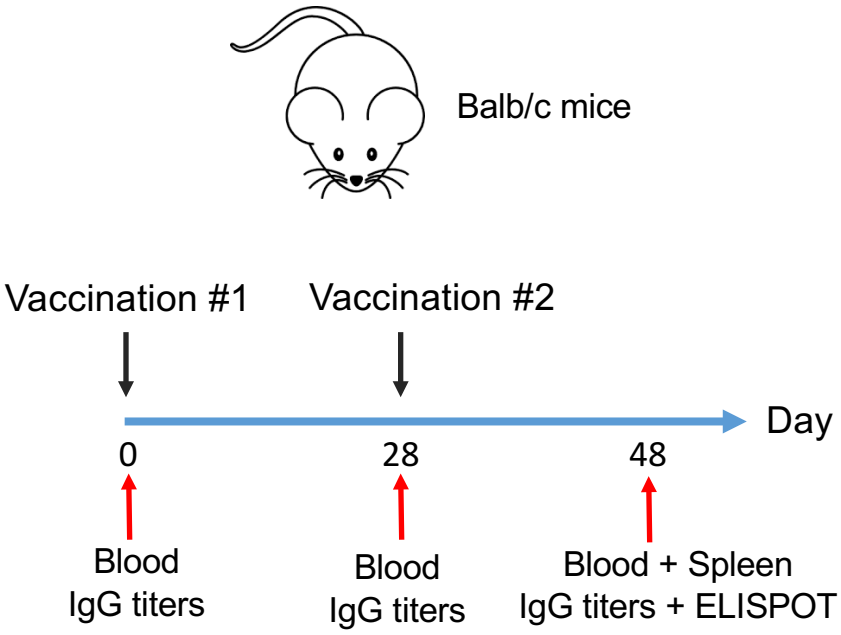


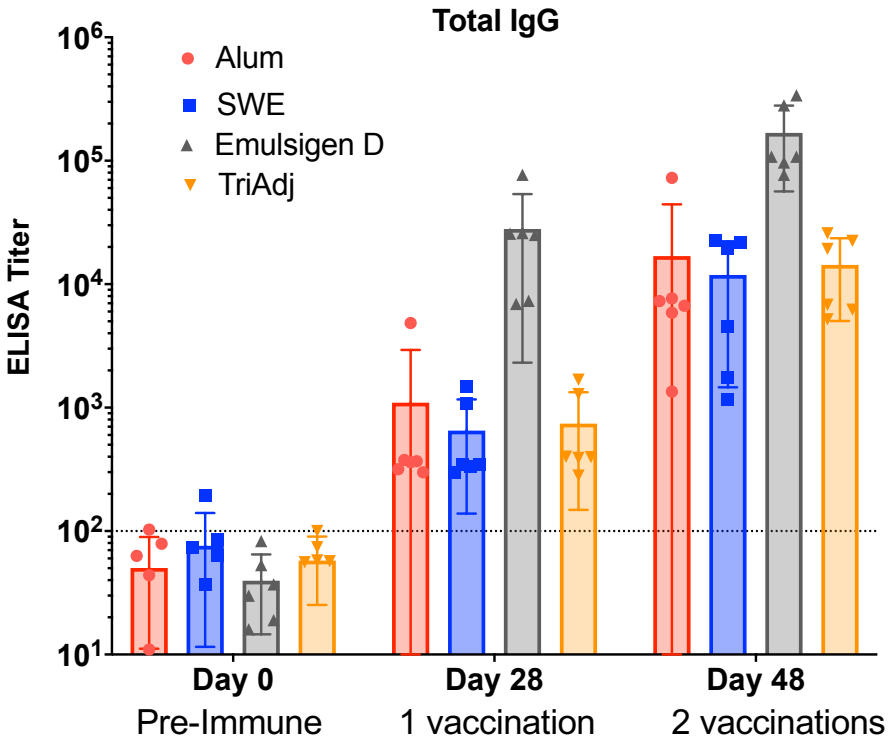




- Aβ conformational B cell epitope -> Antibody response selective for toxic Aβ oligomers
- No Aβ Th epitopes – KLH T helper epitopes not present in the brain, no meningoencephalitis

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 AβO conformational peptide epitope 301 conjugated to KLH and formulated with different adjuvants elicits a robust antibody response (ELISA)

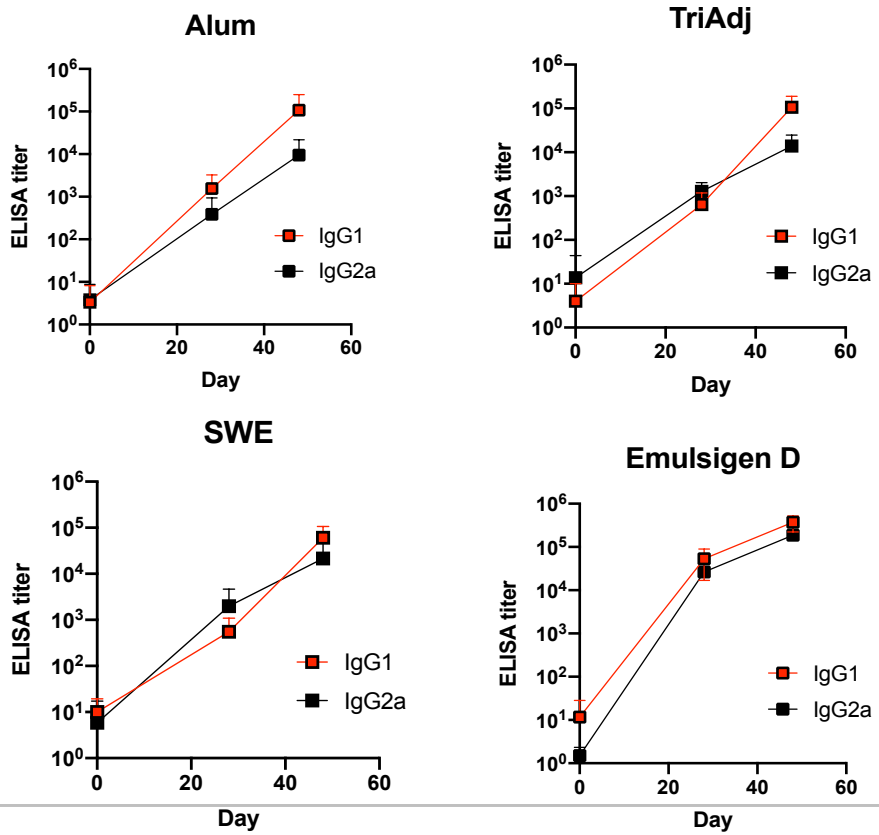



ProMIS™ Neurosciences

# Vaccination with different adjuvants elicits both IgG1 and IgG2a antibodies against the conformational peptide epitope (ELISA)

- All adjuvants induce both IgG1 and IgG2a antibody responses to the AβO conformational epitope
- Responses are skewed toward production of IgG1 antibodies (Th2-driven) vs IgG2a antibodies (Th1-driven) with alum and TriAdj
- SWE and Emulsigen D produce more comparable levels of IgG1 and IgG2a



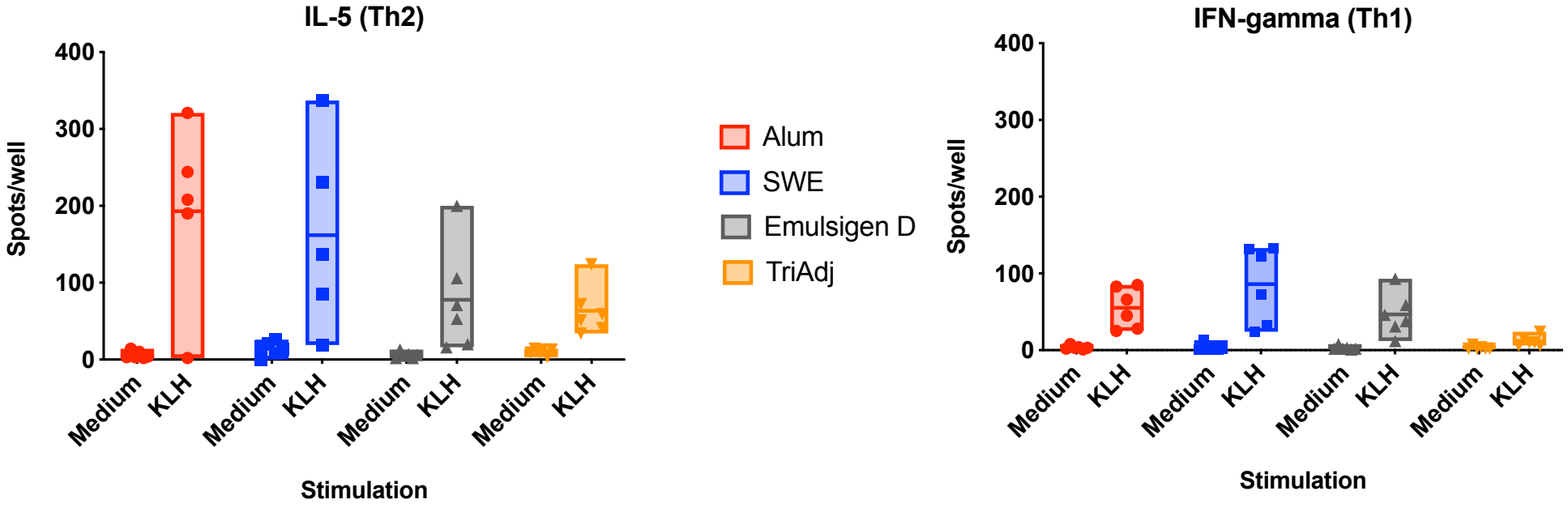

IgG1 > IgG2a
(Th2) (Th1)

IgG1 ≃ IgG2a
(Th2) (Th1)

ProMIS™ Neurosciences

# The KLH carrier elicits both Th1 (IFN-ɣ) and Th2 (IL-5) helper cytokines (ELISPOT) – 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**

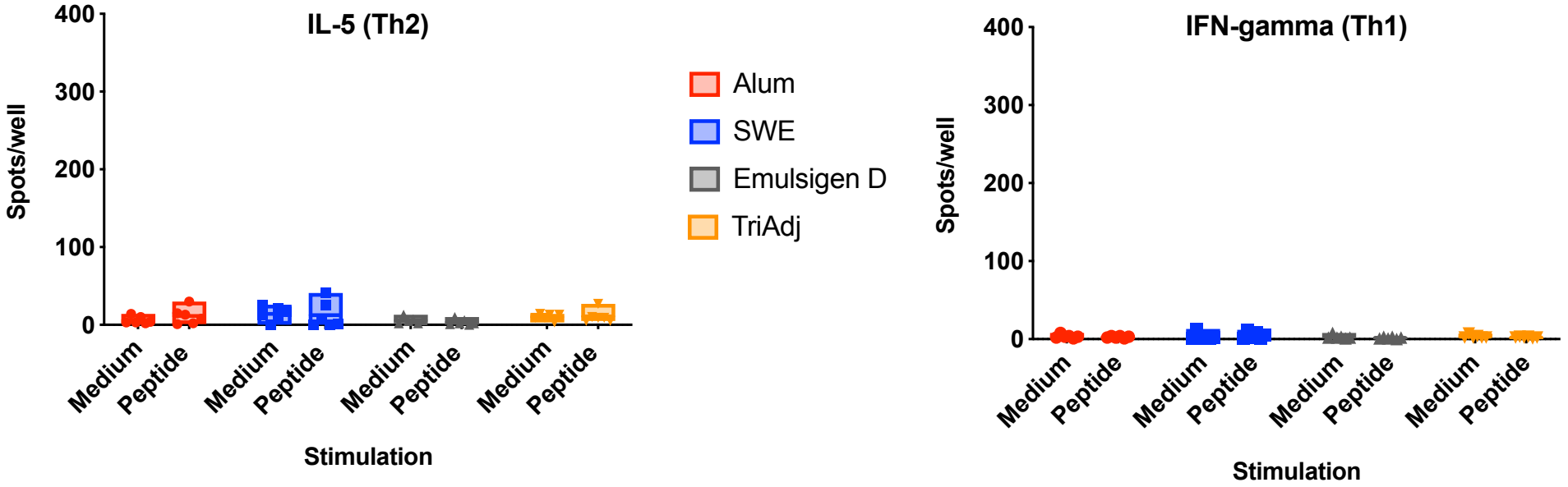



ProMIS™ Neurosciences

2 µg/ml KLH stimulation

# The conformational peptide epitope does not elicit Th cell cytokines (ELISPOT) – No detrimental inflammatory T cell response to Aβ

**The lack of T helper cytokine production in response to stimulation with 301 conformational peptide confirms that the peptide does not contain Th cell epitope(s), only a B cell epitope**

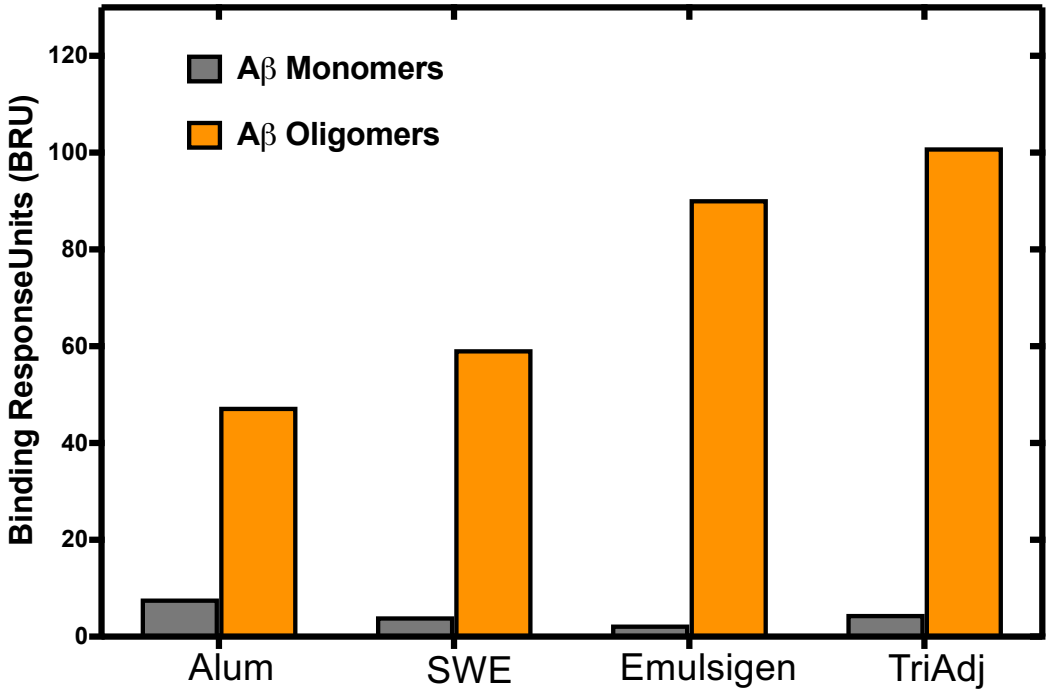



ProMIS™ Neurosciences

2 µg/ml 301-BSA stimulation

# Antibodies induced by vaccination are selective for Aβ oligomers vs monomers (SPR)

**Greater SPR binding response of immune sera to Aβ oligomers vs monomers with all adjuvants tested**

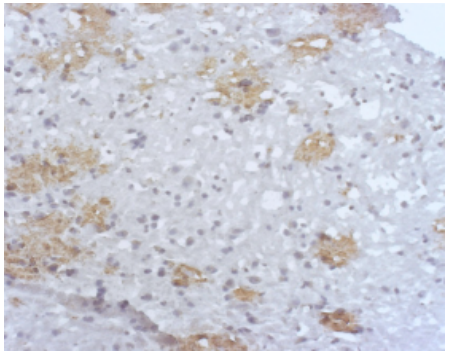



ProMIS™ Neurosciences

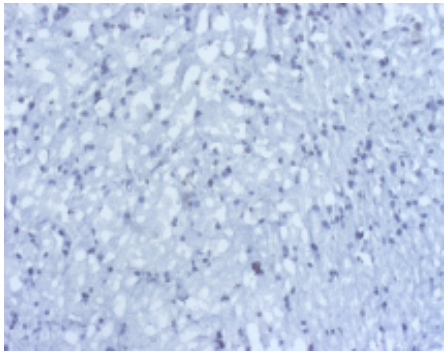
4% serum injected over immobilized monomers & oligomers
Pre-immune serum background subtracted

# Antibodies induced by vaccination do not bind plaque in AD brain –> Oligomer-selective antibody response with all adjuvants tested

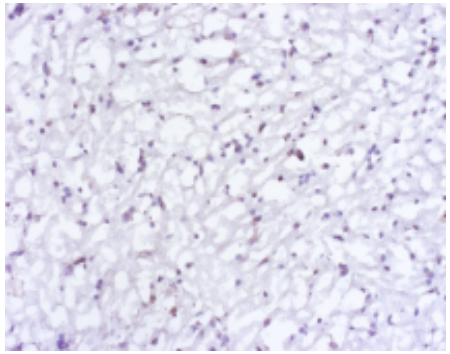
3D6 – Mouse bapineuzumab



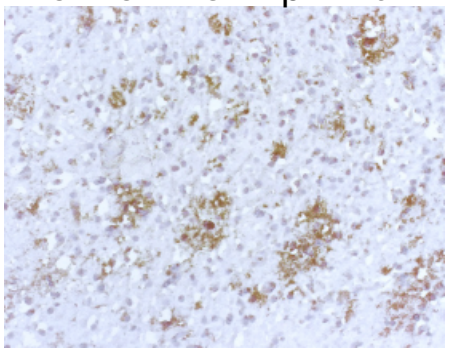
Alum



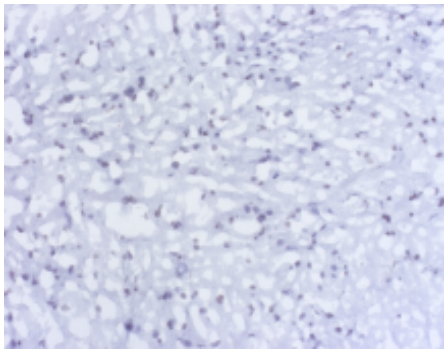
Emulsigen-D



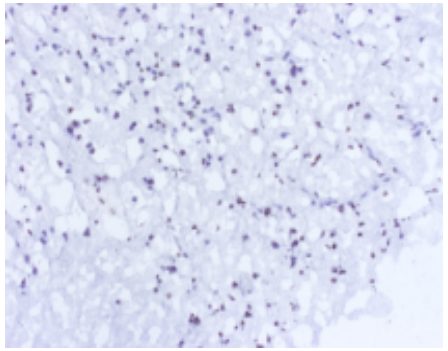
6E10 – Pan Aβ mAb



SWE



TriAdj



ProMIS™ Neurosciences

- 20X magnification
- No signal on normal, control brains

# Summary

- Initial results show robust induction of antibodies to conformational 301 peptide conjugated to KLH in the presence of various adjuvants, including alum approved for human use
- No potentially deleterious T helper responses to the 301 peptide epitope were detected. As expected, T helper responses developed against the carrier (KLH)
- The serum antibodies elicited are selective for AβO with little or no binding to monomers or plaque

❖ 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 and potentially reduces the risk of ARIA side-effects associated with binding to plaque and vascular deposits

# Acknowledgments


## University of British Columbia


Neil Cashman
Ebrima Gibbs
Juliane Coutts
Cheryl Wellington

## Vaccine and Infectious Disease Organization, University of Saskatchewan


Scott Napper
Erin Scruten