A New Vaccine Platform for Neurodegenerative disease: Epitope-Specific Nanoparticles

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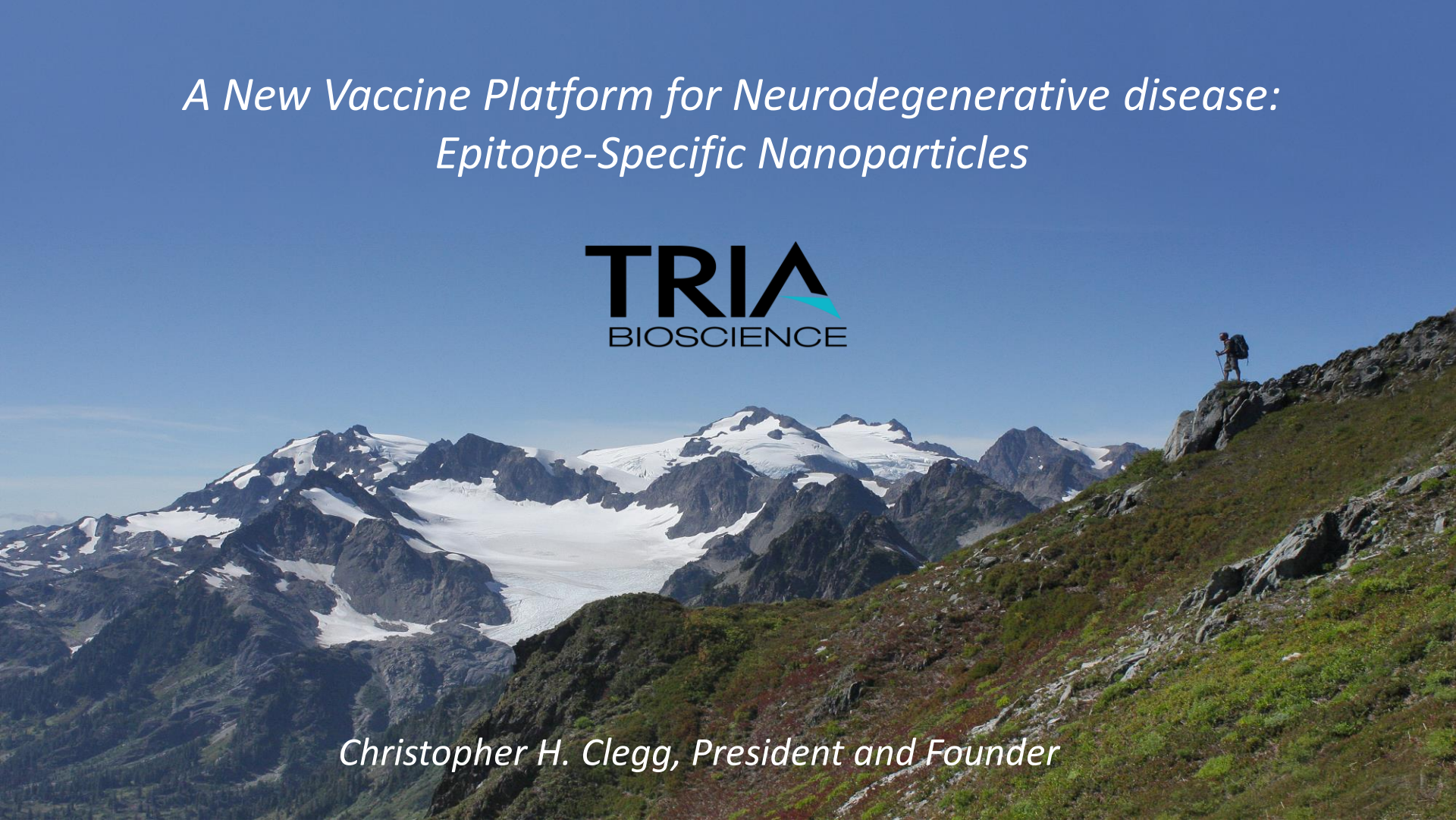


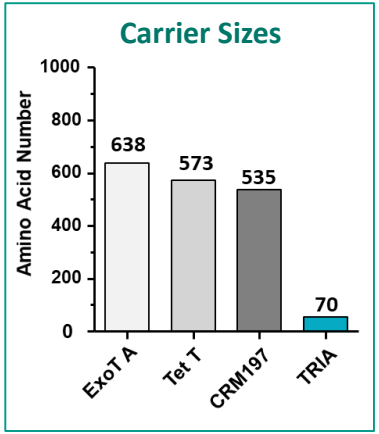
Christopher H. Clegg, President and Founder

Outline

- Technology overview
- Attributes for neurodegenerative disease

Conjugate vaccines

- Stimulating strong antibody responses to weak antigens requires their chemical conjugation to a recombinant protein carrier that mediates T cell help.
- Conjugate vaccines containing bacterial polysaccharides are among the most successful vaccines developed to date with combined sales of nearly $10B per year.
- However, these vaccines are expensive to manufacture and attempts to target other weak antigens including small molecule drugs, hormones and short peptides have generally failed.
- TRIA has modernized this technology by:
  - Miniaturizing the carrier down to 70 amino acids in size.
  - Manufacturing the carrier and target antigen simultaneously by solid-phase peptide synthesis.



TRIA's precision vaccine platform

Epitope-Specific Nanoparticles (ESnP)

- A patented approach for stimulating high titer, high affinity antibody responses to highly-specific antigens.
- Optimized for targeting synthetic chemicals, hormones and short peptides.
- Functional antibody responses induced in mice, rats, and non-human primates with >15 different antigens.
- Applications for this technology have been published using preclinical models of addiction, infection, asthma, and animal health.

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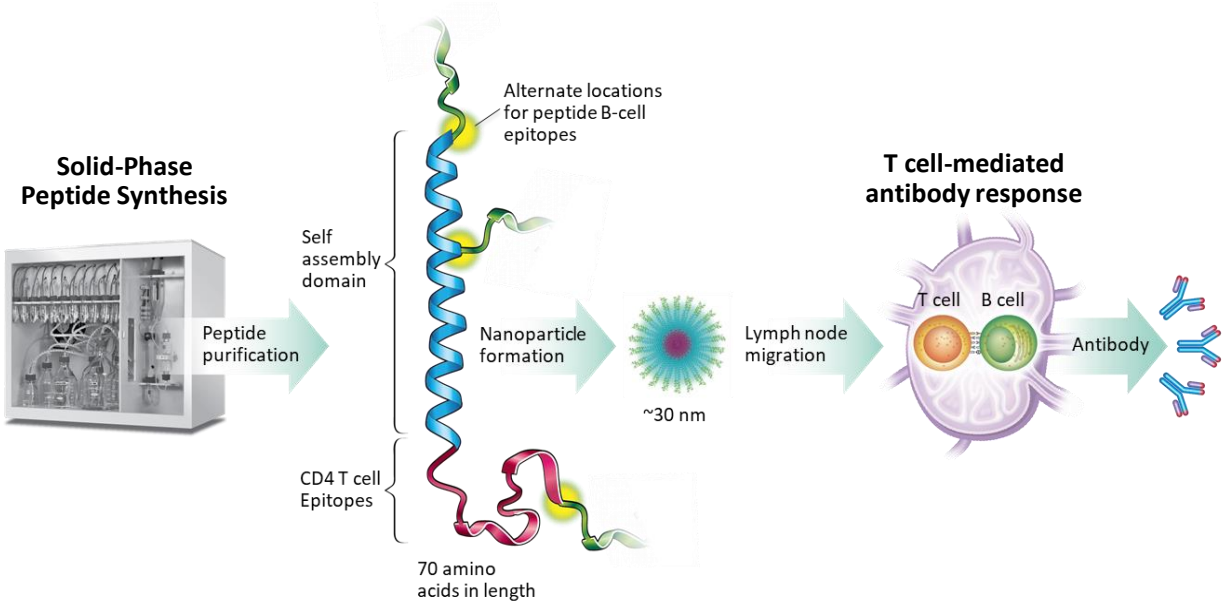
Epitope-specific nanoparticles

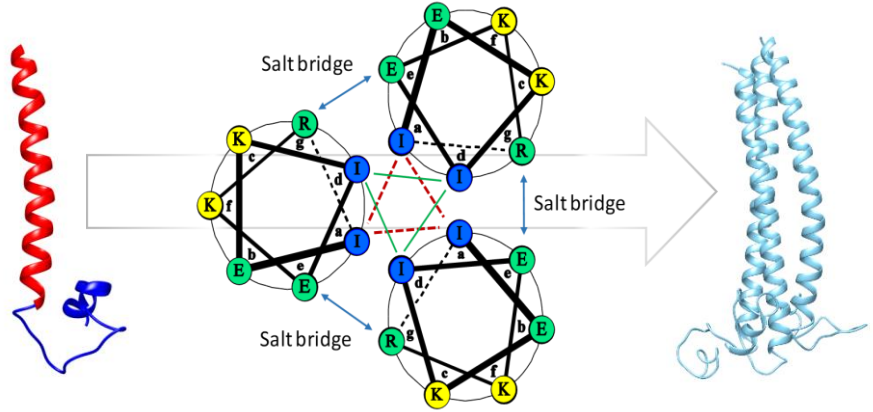
- Solid-phase synthesis generates a 70 amino acid carrier containing 3 functional domains *(Miller et al, PLOS One, 2014)*.
  - A self-assembly domain (blue) mediates nanoparticle formation and antigen presentation *(Zeigler et al, NPJ Vaccines, 2019)*.
  - Two universal CD4 T cell epitopes (red) stimulate durable antibody responses across populations *(Zeigler et al, Vaccine, 2019)*.
  - Target antigens are incorporated at alternative locations to ensure optimal B-cell activation *(Zeigler et al, Vaccine, 2019)*.



Domain 1: Peptide self-assembly and nanoparticle formation

Nanoparticle vaccines mimic structural features of microbial pathogens that stimulate adaptive immunity.

- Four repeating amphipathic sequences (IKKIEKR) mediate coiled-coil formation.
- Isoleucines interdigitate into a hydrophobic core.
- Lysines mediate solubility.
- Salt bridges between Glu and Arg stabilize the assembly.
- Nanoparticles are 20-30 nm in diameter and heat stable.



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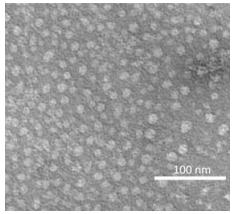
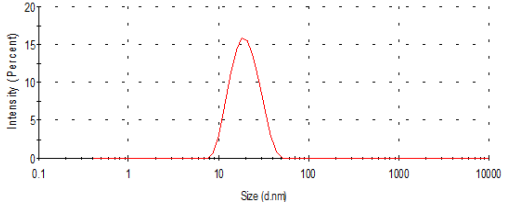


Dynamic Light Scattering



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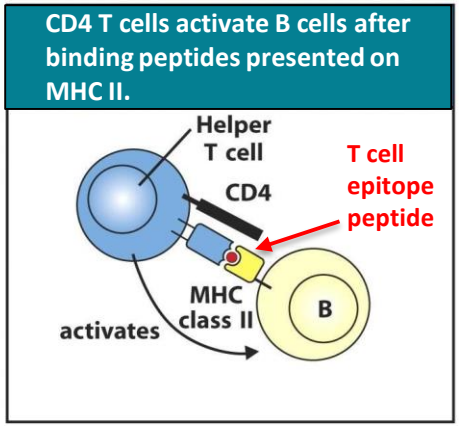
Domain 2: Universal CD4 T cell epitopes

Conjugate vaccine carriers play a critical role in stimulating T cell-mediated antibody responses.

- These carriers contain short peptide sequences (~15 AA) that are bound by MHC Class II receptors and presented to T cells.
- MHC II alleles are highly polymorphic and an individual's haplotype determines T cell epitope binding and antibody activation following vaccination.
- To ensure broad population coverage, our carriers are synthesized with two "universal" T cell epitopes that promiscuously bind most MHC II molecules.
- Experimentally, these epitopes induce strong antibody responses across specifies including mice, rats and cynomolgus macaques and are predicted to bind MHC alleles expressed in most humans.



Domain 3: Target B cell epitopes

Solid-phase synthesis is an ideal tool for optimizing antigen design

- Controls epitope location and valency critical for B cell receptor activation.
- Creates an identical homogenous vaccine product for uniform high affinity binding.
- Produces epitopes with constrained conformational structures, post-translational modifications and D-amino acid substitutions.
- Published experiments for stimulating functional antibodies against;
  - Small molecule drugs;
    - Nicotine
  - Linear and conformational peptide epitopes;
    - Gonadotropin-releasing hormone
    - IgE
    - Alzheimer's associated proteins; amyloid-β and tau
    - Influenza virus proteins: Hemagglutinin, Neuraminidase, M2 ectodomain
- Ideal for stimulating antibody responses to;
    - Bacterial carbohydrates
    - Drugs of abuse (cocaine, opioids, ect)
    - Organic compounds (natural toxins, pesticides, chemical weapons)

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Our advantage vs conjugate vaccines

- Superior activity.
  - Attaching epitopes to identical locations by solid-phase synthesis improves antibody responses relative to stochastic chemical conjugation reactions. (Zeigler et al, Vaccine, 2019)
  - The elimination of immunogenic sequences in recombinant carriers prevents epitope competition and eliminates induction of anti-carrier antibodies that suppress vaccine activity (Zeigler et al, Vaccine, 2019).
  - Preselected universal CD4 T cell epitopes enhance antibody production and reduce vaccine variability between subjects.
  - Amenable to peptide formulations that target multiple antigens simultaneously (Zeigler et al, 2019).
- Manufacturing is easy and fast.
  - Recombinant-free
  - Eliminates multistep production and purification requirements.
  - Simpler regulatory path, shorter development timelines, and lower COGs.

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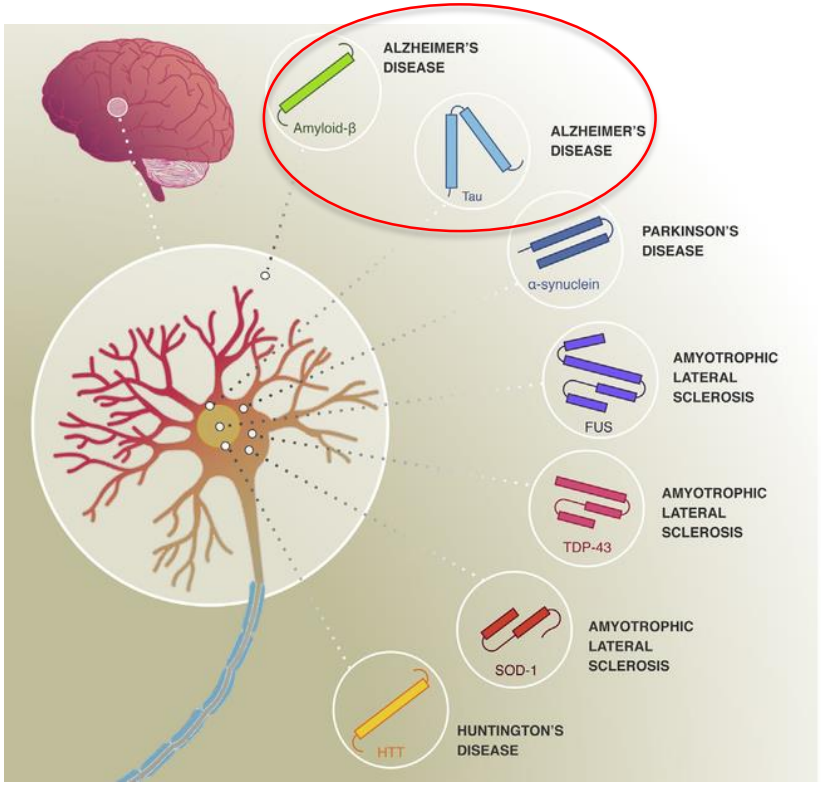
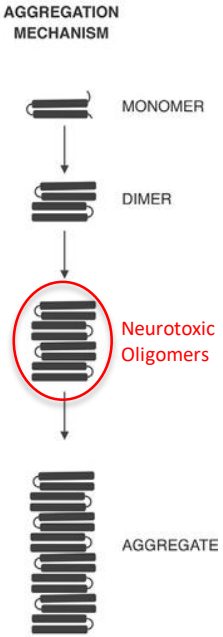
Aging-Related Neurodegenerative Diseases

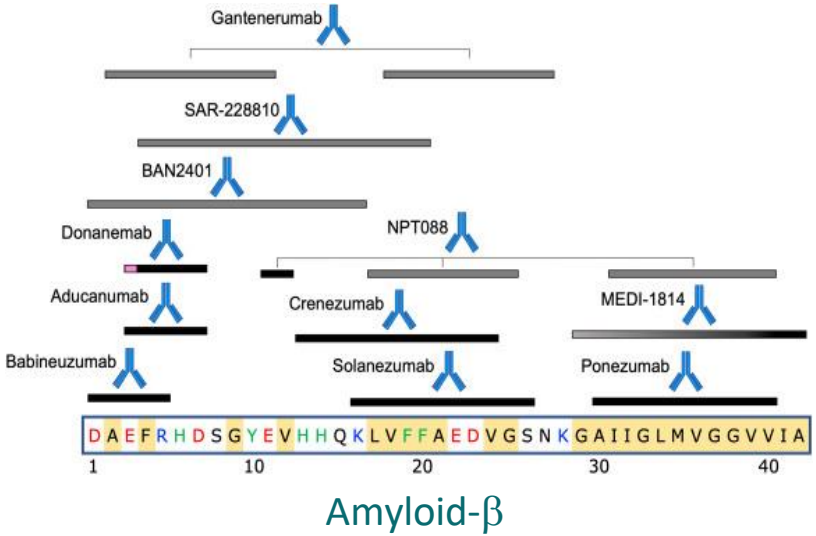
- The hallmark of neurodegenerative disease is the aggregation and deposition of misfolded proteins within the brain.
- Nearly 50 million people suffer from Alzheimer's worldwide, a number that is expected to triple over the next 30 yrs.
- The best method for preventing Alzheimer's in animal models uses monoclonal antibodies (MAbs) to clear pathogenic Amyloid β and tau proteins.





The promise of immunotherapy

- Multiple anti-amyloid β MAbs have been tested clinically that differ in epitope binding and mechanism of protein clearance.
- Aducanumab effectively removes plaque and improves cognition in early-stage patients and is poised for FDA approval.
- Key opinion leaders now advocate that therapy begin very early, possibly years, before symptom onset and that MAb combinations be used to improve protein clearance.
- This creates an opportunity for vaccines that are more convenient to use over time and much less expensive than MAbs.
- TRIA Bioscience has designed a best-in-class platform for leading this effort and is building vaccines that target clinically validated epitopes.

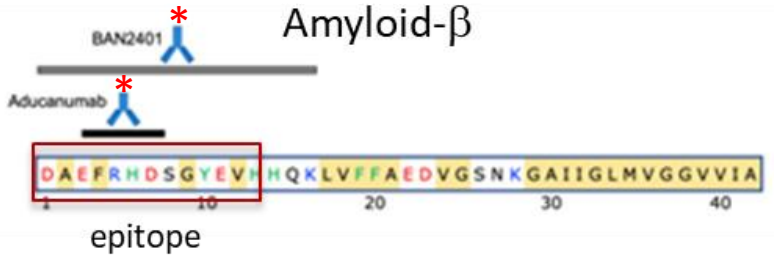


Amyloid-β

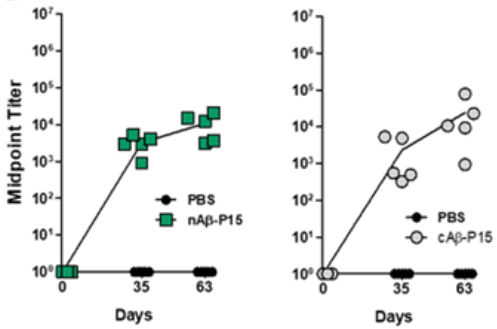
Taken from Plotkin SS, Cashman NR, Neurobiol Dis. 2020

Vaccine candidate for Alzheimer's disease

- Aducanumab binds a 5 amino acid epitope in the amino terminus of amyloid β.
- BAN2401, a second MAb that clears amyloid and improves cognition in patients, also binds the amino terminal end of the protein.
- A vaccine was synthesized with a 13 amino acid epitope (red box) that encompasses the Aducanumab and BAN2401 binding sites.
- Epitopes placed at either end of the peptide induced similar antibody titers.



Amyloid-β
(n-terminus)

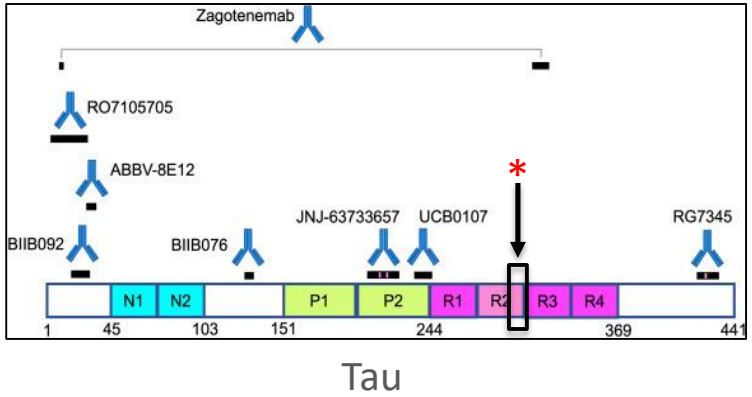


Amyloid-β
(c-terminus)

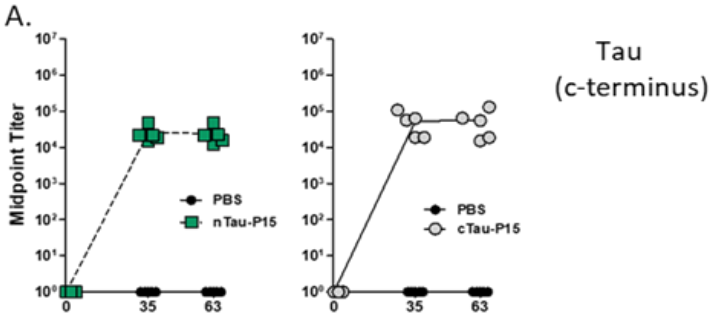
Male CD1 mice immunized 2x with 10 ug peptide + adjuvant

Inducing antibodies to tau

- Tau-specific MAbs are also being tested for Alzheimer's Disease and other tauopathies.
- MAbs that clear tau in patients bind the N-terminus (BII092, RO7105705) and a mid-region phosphorylation site (JNJ-63733657).
- A vaccine made with another clinical epitope (asterix) attached to the carrier's n- or c- terminus also induced a strong antibody response.
- This demonstrates the feasibility of building vaccines using validated amyloid *and* tau epitopes.



Tau (n-terminus)

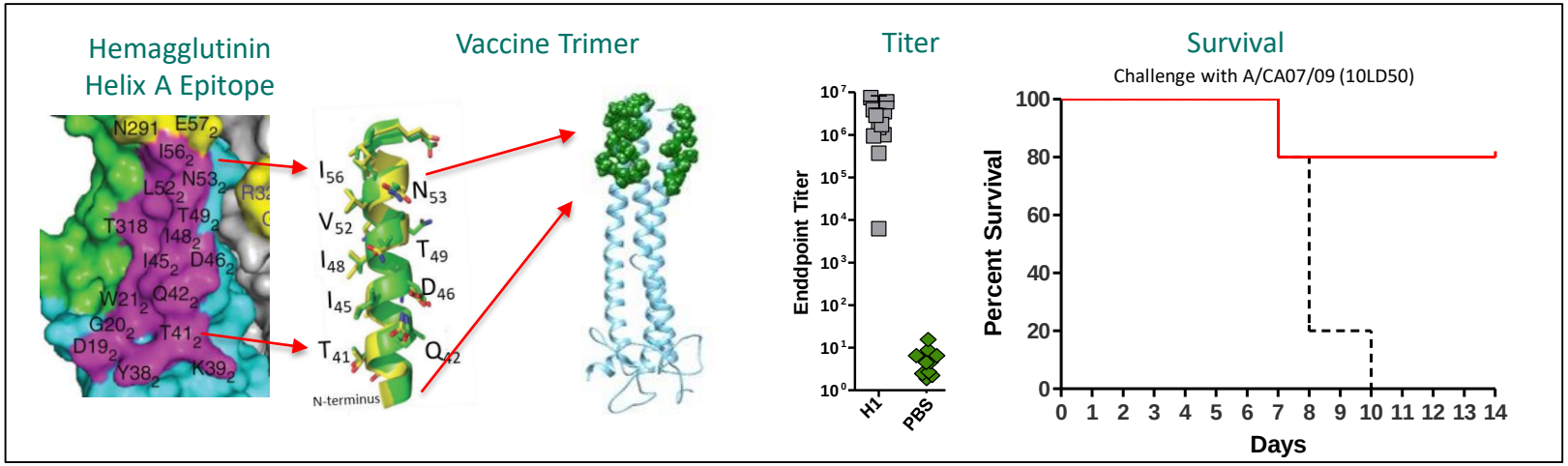


Tau (c-terminus)

Taken from Plotkin SS, Cashman NR, Neurobiol Dis. 2020

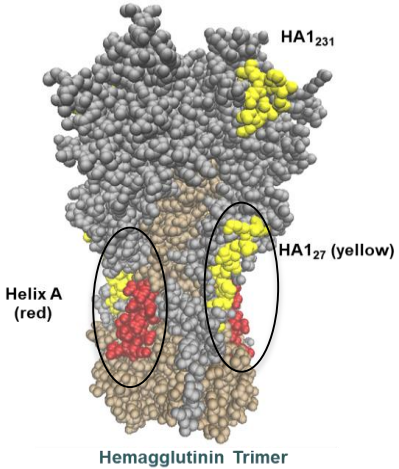
Targeting conformational epitopes

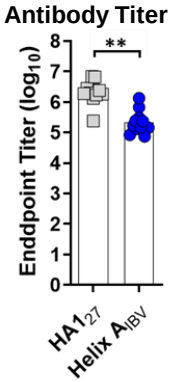
- Amyloid-β neurotoxicity is mediated by soluble oligomers rather than monomers, insoluble plaques or fibrils.
- Consequently, antibody selectivity may be improved by targeting conformational epitopes on oligomeric assemblies.
- TRIA builds antigens containing conformational epitopes using proprietary methods involving solid phase synthesis.
- In one example, antibodies recognizing the α-Helix A epitope in influenza hemagglutinin were induced using the carrier's α-helical domain to constrain the Helix A primary sequence to its native helical state. This vaccine protected mice effectively from virus.

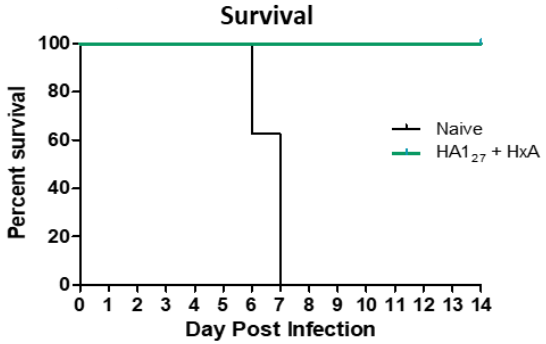


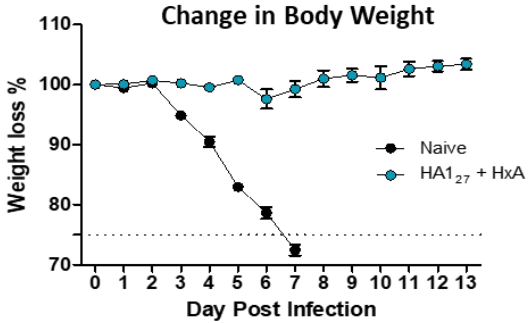
Targeting two epitopes simultaneously

- To improve efficacy, future immunotherapies may need to target multiple epitopes on the same protein.
- This concept is being tested using Gantenerumab and Solanezumab, two monoclonals that differ in amyloid binding epitope and mechanism of clearance.
- Vaccine formulations targeting 2 adjacent epitopes on the viral Hemagglutinin trimer induced equivalent antibody titers in mice and stimulated complete protection following virus challenge.



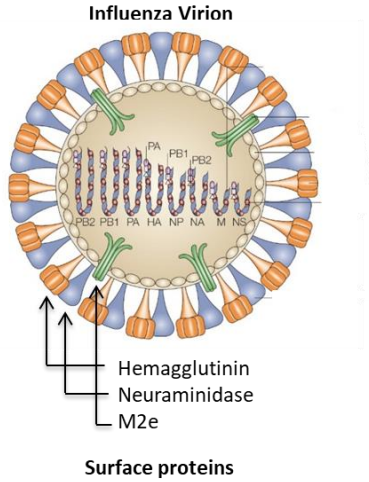


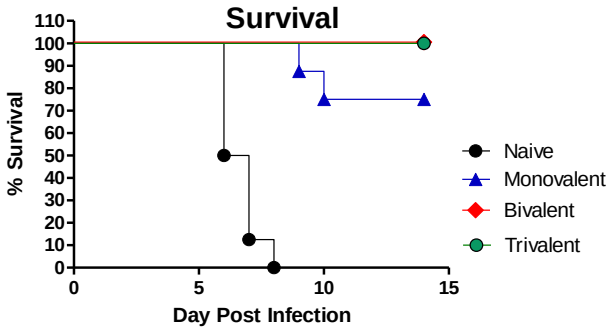


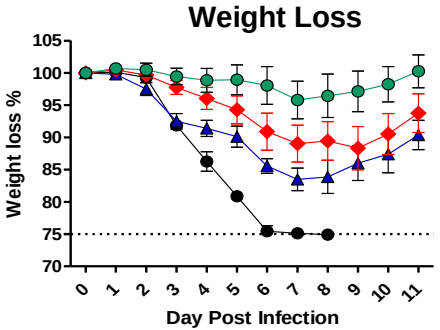


Targeting epitopes on multiple proteins

- Future immunotherapies may also need to clear both amyloid β and tau proteins.
- Vaccine formulations targeting three viral proteins (HA, NA, and M2e) improved protection against influenza A. Thus, demonstrating the technology's ability to induce functional antibodies to multiple proteins.

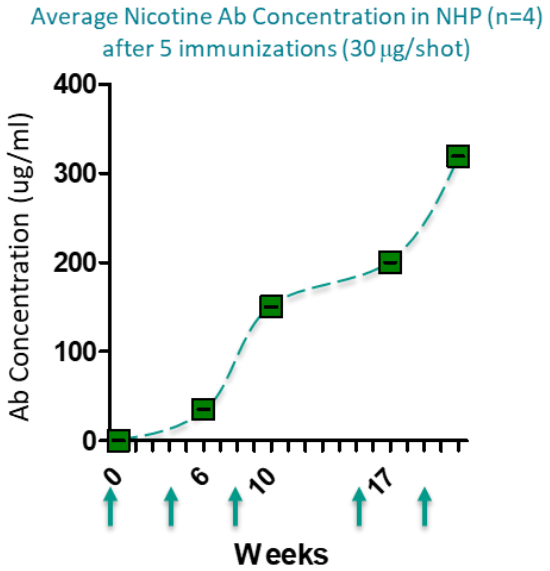






Robust antibody concentrations in non-human primates

- Alzheimer's vaccines will need to stimulate strong long-term antibody responses.
- TRIA can accomplish this as shown in an experiment using Cynomolgus macaques that were immunized 5 times with an anti-nicotine vaccine.
- Antibody concentrations continued to rise after 21 weeks and exceeded 300 μg/ml sera, a value that meets or exceeds aducanumab's steady-state levels [J. Ferrero et al. 2016 169-176].



Summary

- There is an unmet need for treatments that can slow the onset and progression of neurodegenerative disease.
- MAb-based therapies are beginning to show clinical benefit for Alzheimer's disease, thus validating a vaccine approach.
- TRIA has invented a precision vaccine platform with the attributes needed to:
  - Induce functional antibodies to validated epitopes on amyloid β, tau and pathogenic proteins in other neurodegenerative diseases.
  - Formulate vaccines that target multiple epitopes for additive or synergistic responses.
  - Induce long-term therapeutic antibody concentrations.
- TRIA's lead vaccine candidate targets the overlapping Aducanumab and BAN2401 epitopes and its clinical development will be guided by the comparison between the antibody concentrations induced during Phase 1 and those mediating MAb efficacy.
- TRIA is seeking collaboration/licensing opportunities that will support the development of this vaccine and vaccines for additional neurodegenerative diseases.

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