Optimized ACI-24, an amyloid beta (Abeta) vaccine that safely drives immunity to oligomers and Pyroglutamate Abeta, key pathological species of Alzheimer's disease (AD)

Emma Fiorini, PhD | AAIC 2022 | 2 August

AC Immune

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Disclosures

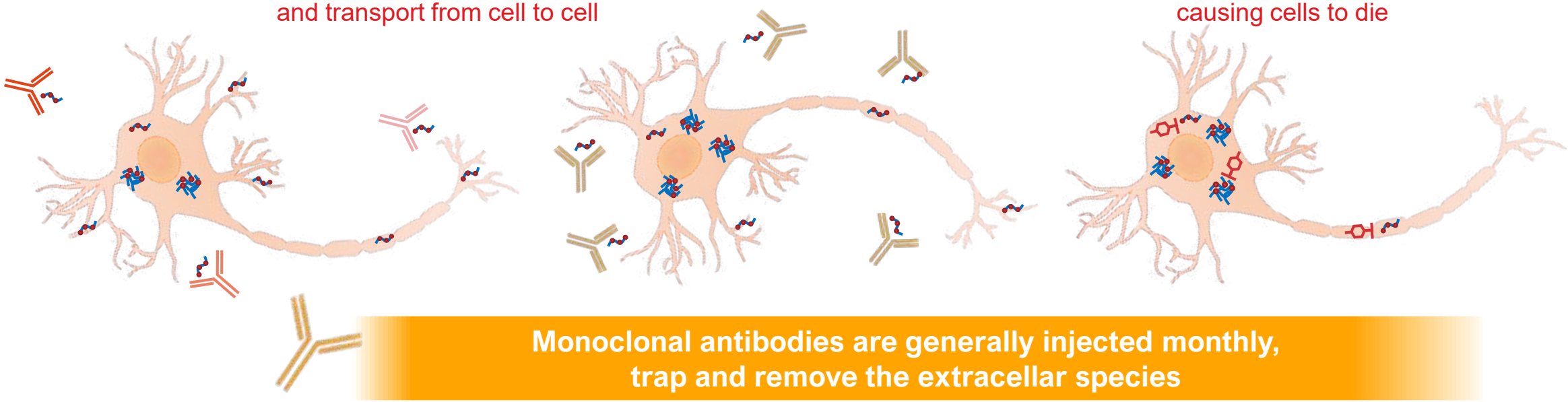
Emma Fiorini is an employee of AC Immune entitled to stock options

Different modalities for mono- or combination-therapeutic options

In Alzheimer's and Parkinson's diseases, pathology exists outside and inside the neuron

Extracellular pathology with local inflammation and transport from cell to cell

Intracellular aggregation and misfolding causing cells to die



Monoclonal antibodies are generally injected monthly, trap and remove the extracellar species

Small molecules can be taken daily orally, will enter cells and stop the toxic substance from forming

Vaccines are generally given 1-2 times per year to create our own antibodies that can be used to prevent or treat disease

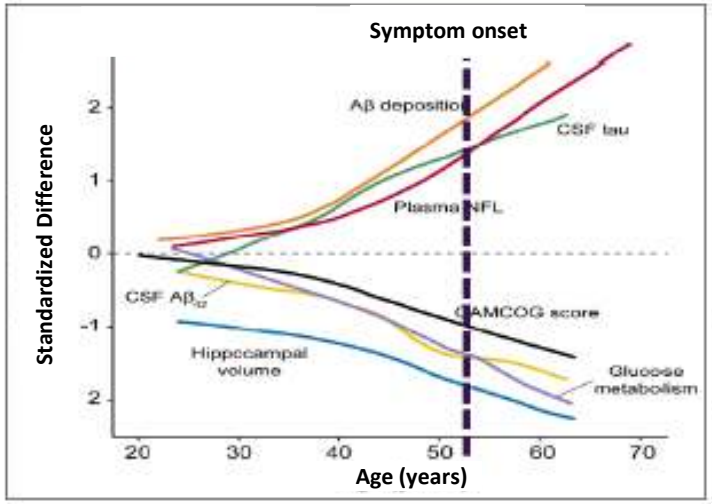
The rationale for anti Abeta vaccination in Alzheimer's disease (AD) and AD in Down syndrome (DS)

Unique possibility for treatment and prevention of AD[1] in a more homogeneous genetic population

Factors supporting a vaccine approach in DS

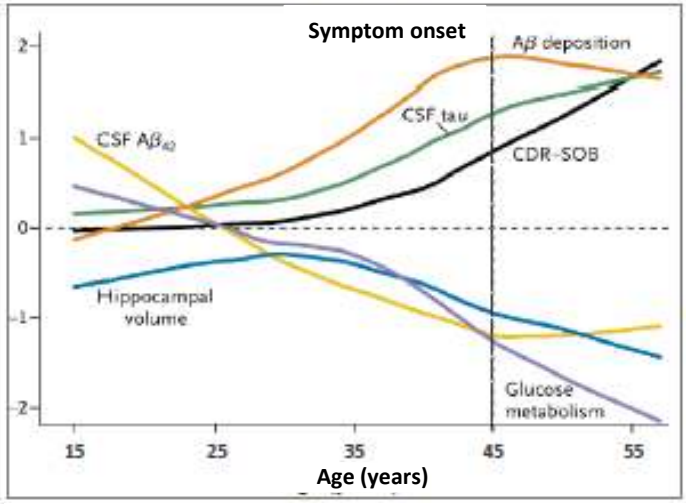
- Amyloid-beta precursor protein (APP) encoded by the *APP* gene generates amyloid beta
- Located on chromosome 21, the extra copy of the APP gene may cause increased risk of developing AD– like symptoms
- DS population is the largest population with early onset AD; 75–100% of people with DS have AD-like symptoms by age 60[1]
- Similar pathophysiology and biomarkers in DS and ADAD[2]

Alzheimer's disease in Down syndrome



Ref: Fortea, AAIC 2019

Autosomal dominant Alzheimer's disease (ADAD)



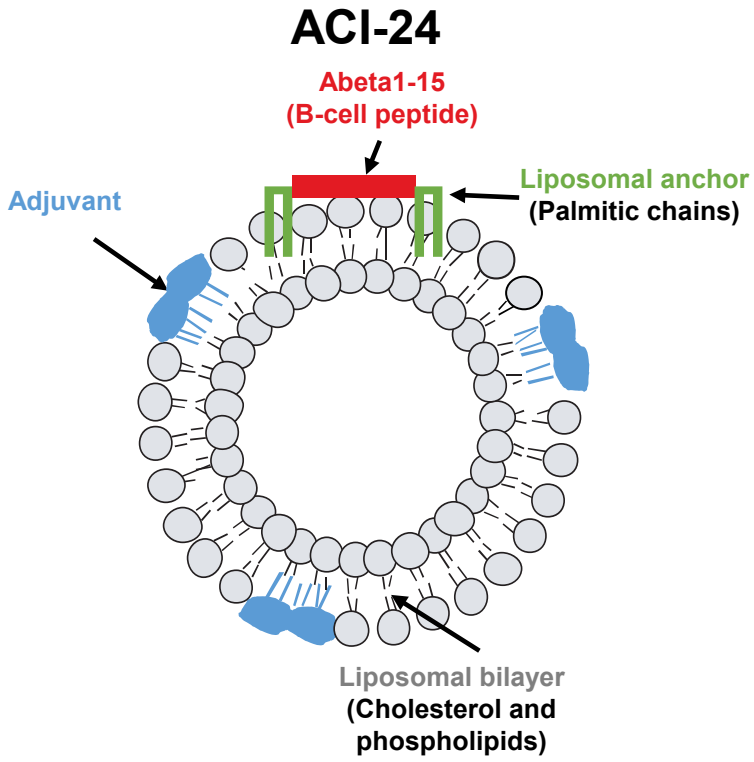
Ref: adapted from Bateman, NEJM 2012

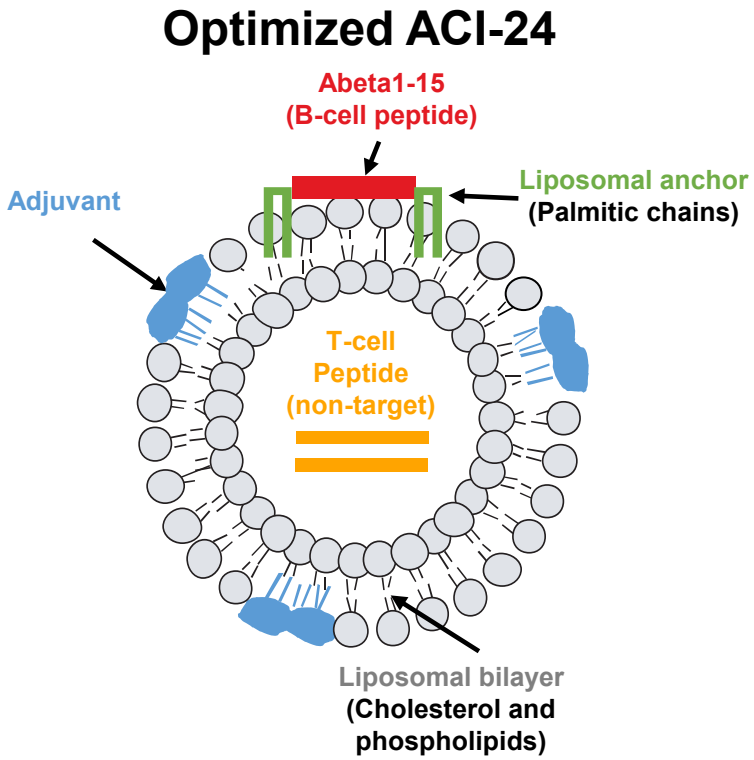
- Our anti-Abeta vaccine addresses a high unmet medical need of AD in DS
- Prevention of AD in DS may translate into a broader application in sporadic AD

(1) Strydom *et al.*, Alzheimer's Dement (NY). 2018; (2) Autosomal dominant Alzheimer's disease

Optimized ACI-24: a vaccine targeting Abeta 1-15

Includes bystander T-cell help



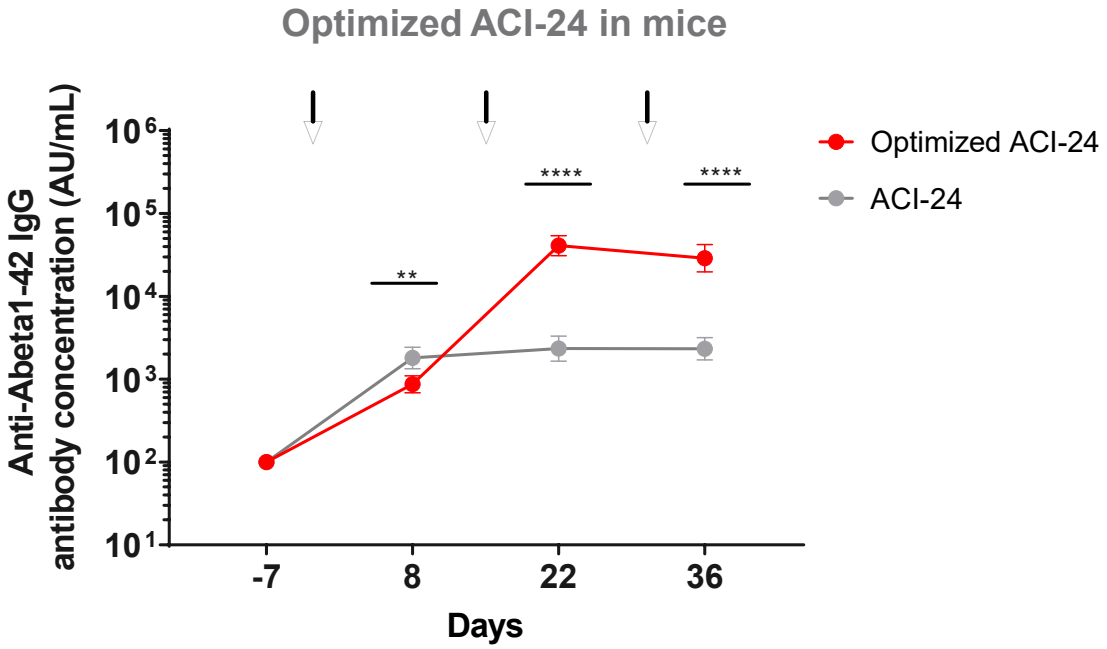


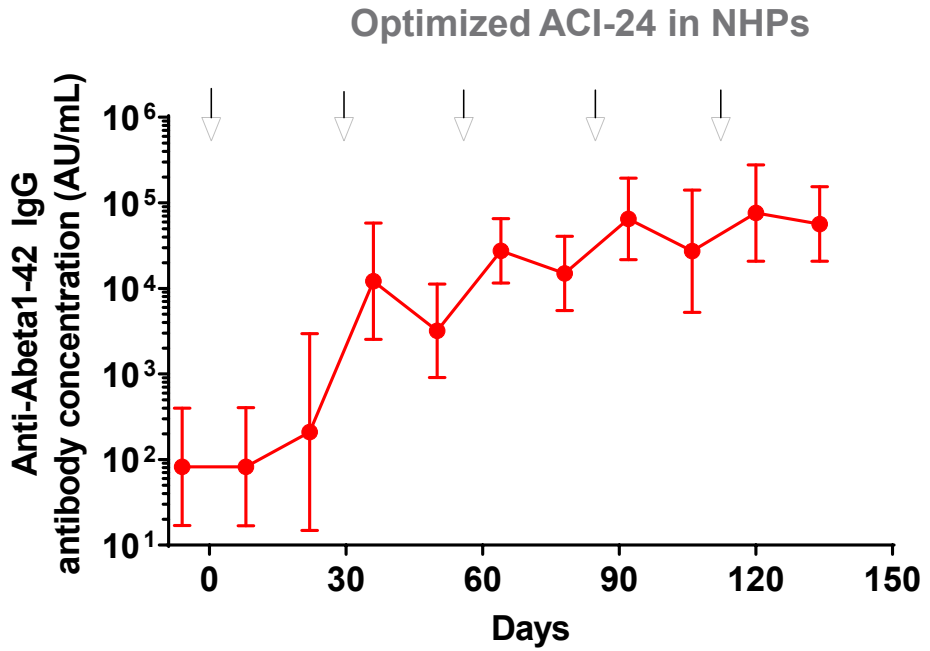
SupraAntigen® liposomal platform

- Target antigen presented on liposome optimally stimulates B cell receptors
- Safely stimulate non-Abeta T-cells to enhance and maintain anti-Abeta specific antibody responses via harnessing a bystander helper effect

Increased and prolonged immunogenicity with optimized ACI-24

Anti-Abeta1-42 IgG titers in mice and non-human primates (NHPs)





**=p<0.01
****= p<0.0001

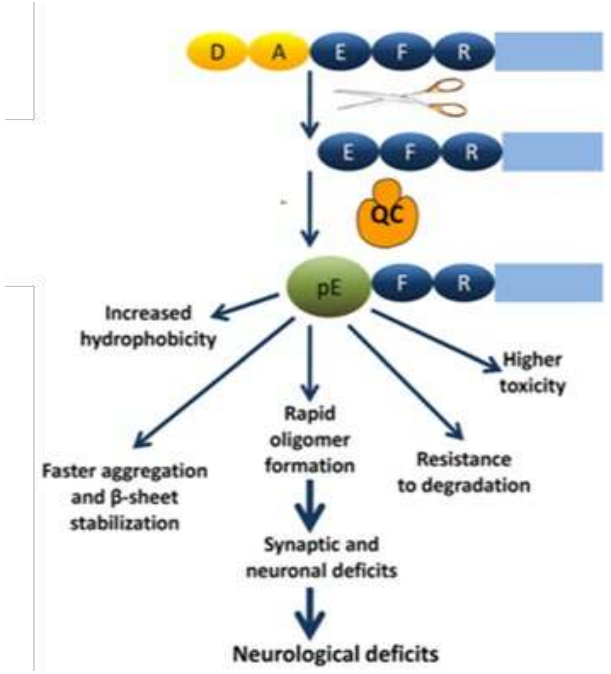
Ref.: AC Immune; Global Down Syndrome Forum 2021

01 Optimized ACI-24 induces significantly higher anti-Abeta1-42 IgG titers than ACI-24

02 Optimized ACI-24 induces boostable anti-Abeta1-42 IgG in NHPs

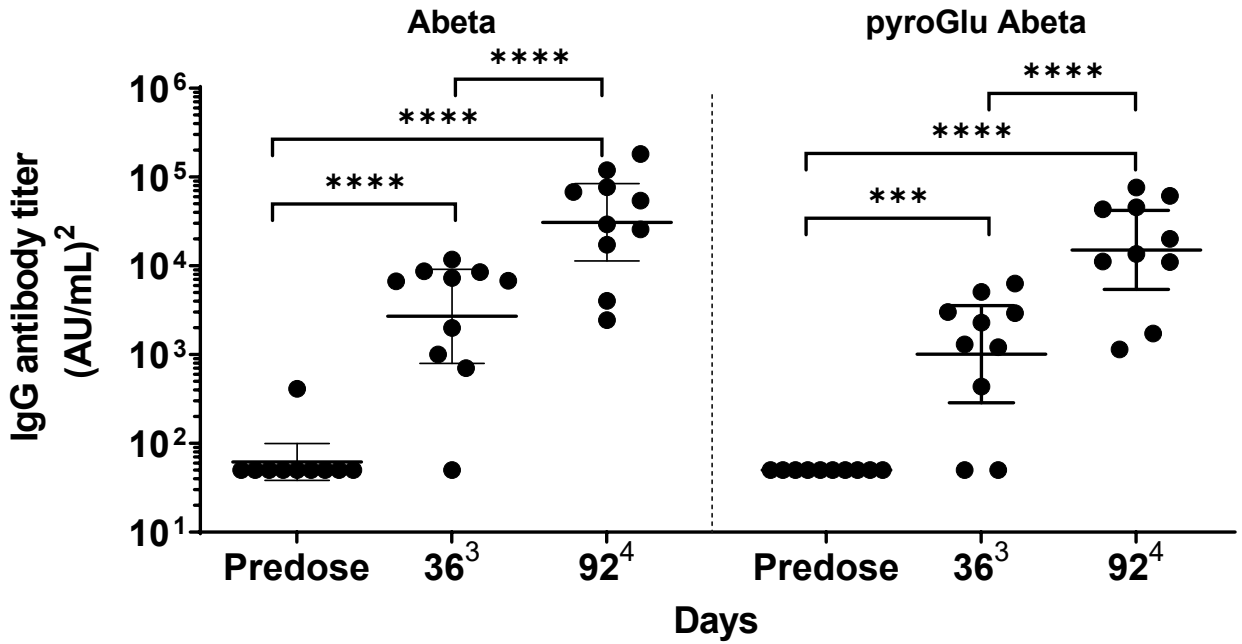
Targets multiple Abeta species

Response against Abeta1-42 and pyroGlu Abeta[1] in NHPs



Ref.: Jawhar S et al,; J of Biol Chem 2011

Optimized ACI-24 in NHPs



***=p<0.001, ***= p<0.0001

01 PyroGlu Abeta is a highly pathological truncated form of Abeta present in plaques of AD brains

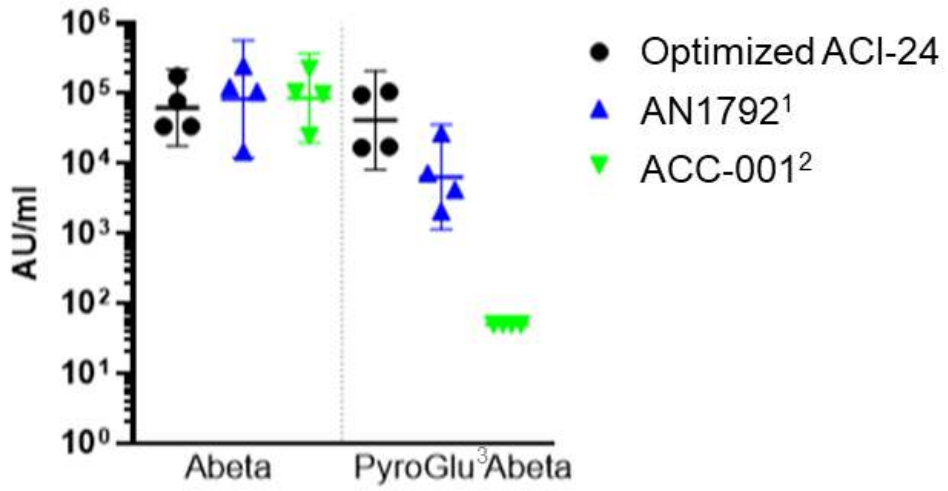
02 Sustained and enhanced IgG response that binds Abeta1-42 and pyroGlu Abeta

(1) pyroglutamate Abeta 3-42; (2) AU/mL=Arbitrary units; (3) Day 36,1 week after the 2nd injection; (4) Day 92, 1 week after the 4th injection

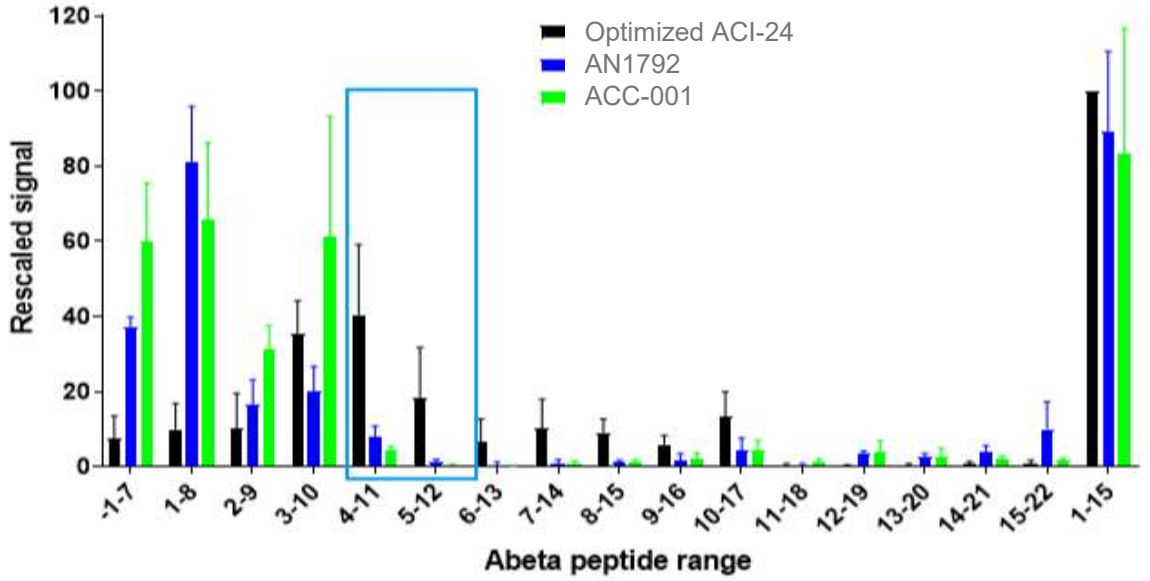
Unique antibody profile versus other Abeta vaccines

Superior pyroGlu Abeta recognition and epitope coverage in NHPs

Optimized ACI-24 generates high antibody titers against pyroGlu Abeta



Optimized ACI-24-induced antibodies recognize a broad range of N-terminal Abeta epitopes



Ref.: M. Vukicevic, et al., Brain Comm, 2022

01 Optimized ACI-24 represents a potential breakthrough compared to previous anti-Abeta vaccines

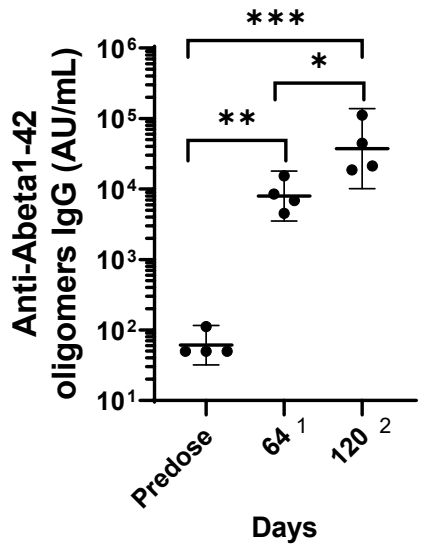
02 Superior binding to truncated pyroGlu Abeta that may result in amyloid plaque clearance and neuroprotection

(1) synthetic full-length Aβ peptide with QS-21 adjuvant; (2) vanutide cridificar (an investigational anti-Abeta therapeutic vaccine); (3) pyroGlu= pyroglutamate Abeta 3-42

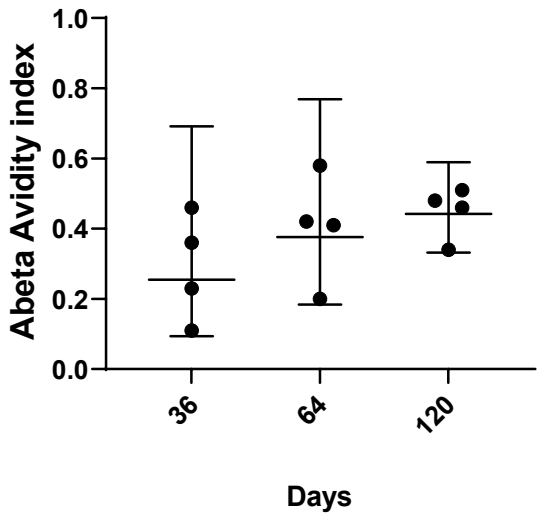
Targets oligomers, induces antibody maturation and binds Abeta

Further characterization post immunization of NHPs

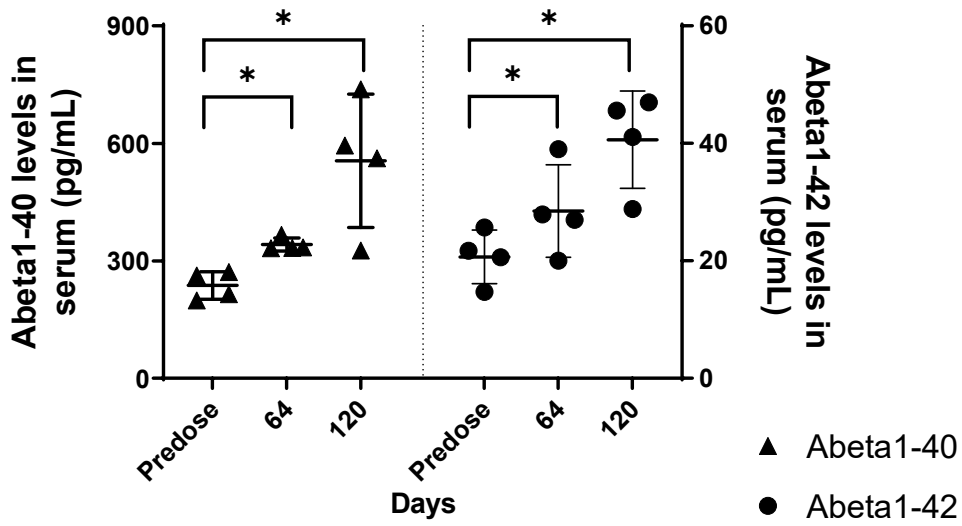
IgGs titers against oligomers



Avidity index



Abeta 1-40 and 1-42 protein level



*= p<0.05, **=p<0.01 ***=p<0.001

01 Strong and boostable response to Abeta oligomers with a maturation of the antibody response over time

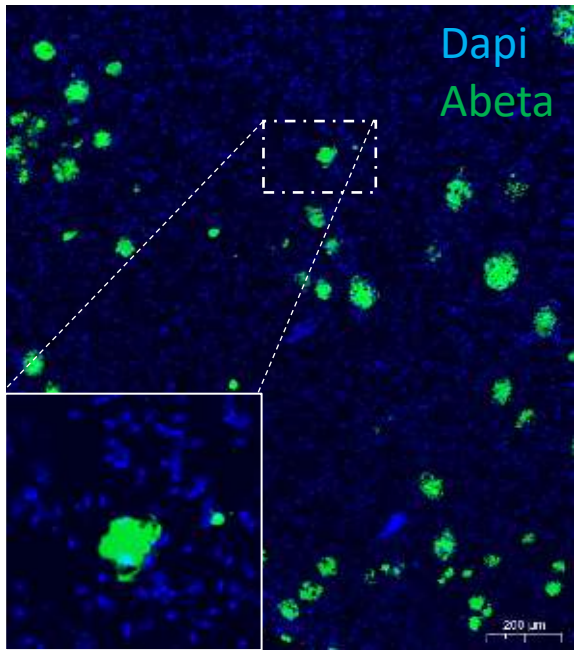
02 Vaccine-induced anti-Abeta IgGs engage Abeta1-40 and 1-42 in serum of NHPs

(1) Day 64, 1 week after the 3rd immunization; (2) Day 120, 1 week after the 5th immunization

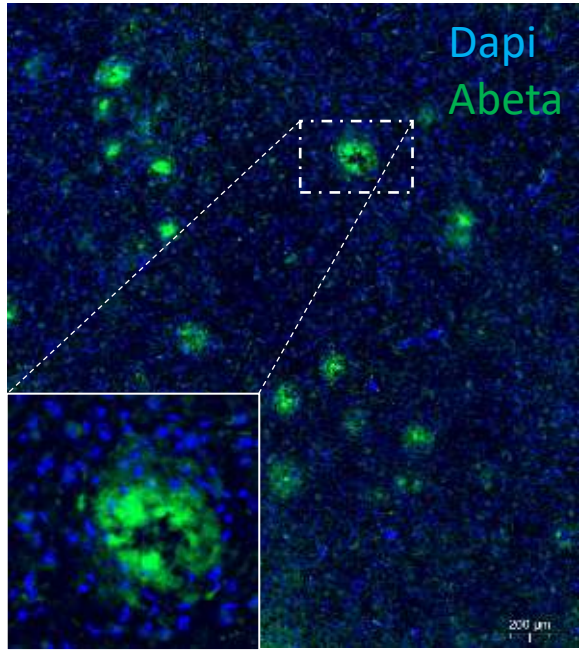
Produces antibodies that bind Abeta in human plaques

Using AD patient-derived brain tissue sections

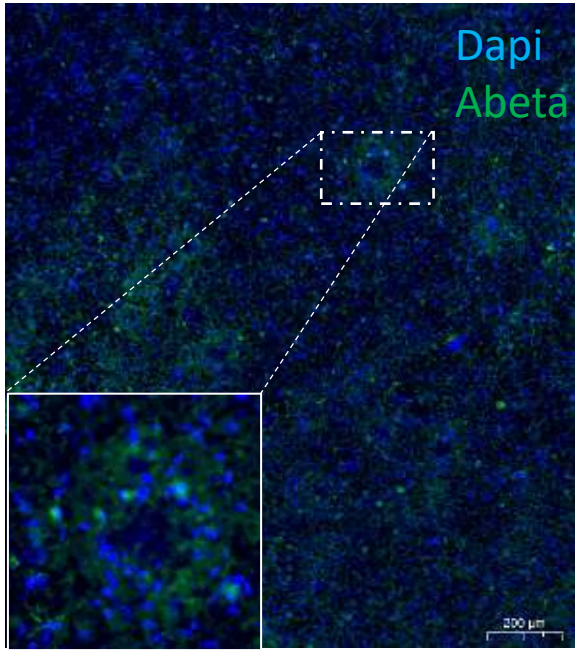
Positive control mAb 4G8



NHP serum, Day 64[1]



NHP serum, before immunization



Ref.: AC Immune; Global Down Syndrome Forum 2021

- Antibodies generated in NHPs post-vaccination with optimized ACI-24 bind to Abeta plaques on AD patient-derived brain tissue sections

(1) Day 64, 1 week after the 3rd immunization

Summary

- Optimized ACI-24, in addition to the Abeta1-15 peptide presented on the surface of the liposome to cross-link the BCR, has a non-Abeta T-cell peptide to enhance and maintain anti-Abeta-specific antibody responses
- Optimized ACI-24 induces strong and sustained IgG titers against key pathological Abeta species (oligomers and pyroglutamate)
- Optimized ACI-24 induces antibodies able to bind their targets in vivo and in human AD brain sections
- Optimized ACI-24 represents a potential breakthrough compared to previous Abeta vaccines, due to its unique induction of antibodies that recognize multiple pathological Abeta species
- The safety and efficacy of the vaccine is currently being evaluated in the biomarker-based ABATE clinical trial for the treatment and prevention of Alzheimer's disease and AD in DS (Refer to poster, P1-040)

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AC Immune

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