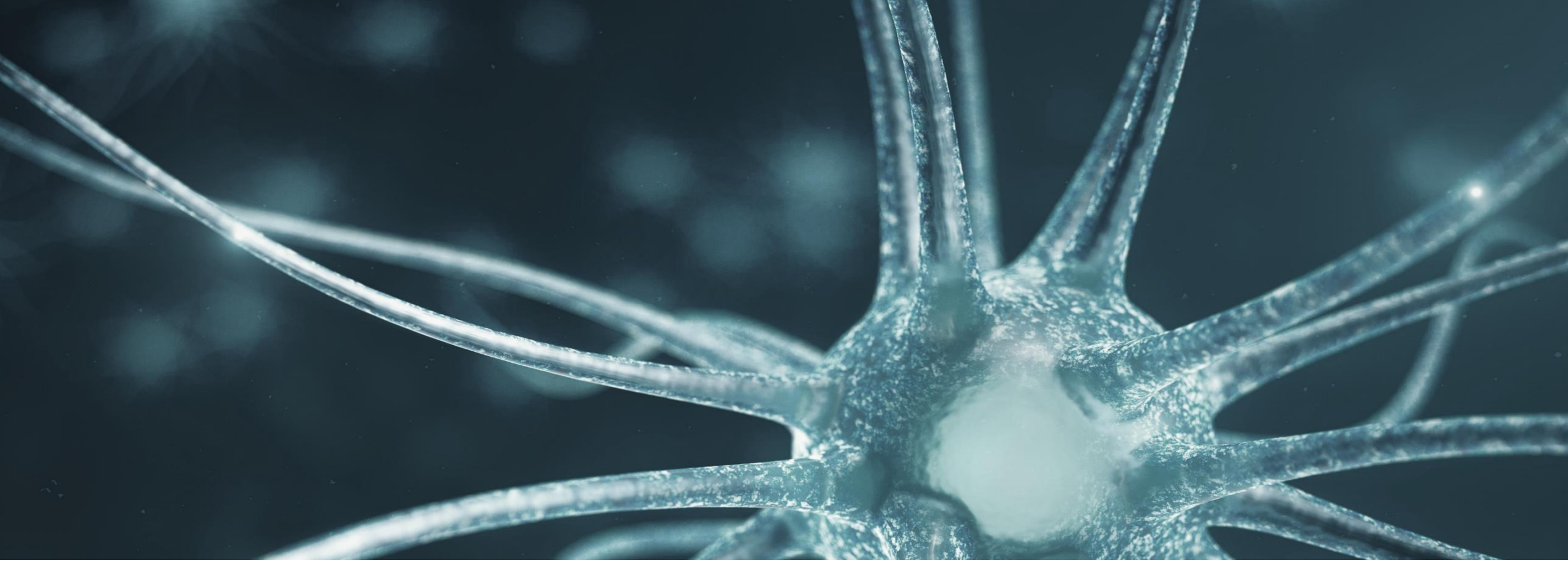

A novel anti-amyloid beta (Abeta) vaccine, a potent immunotherapy for the prevention and treatment of Alzheimer's disease in Down Syndrome

Emma Fiorini, PhD | ADPD, April 2023

AC Immune

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Conflict of interest disclosure

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

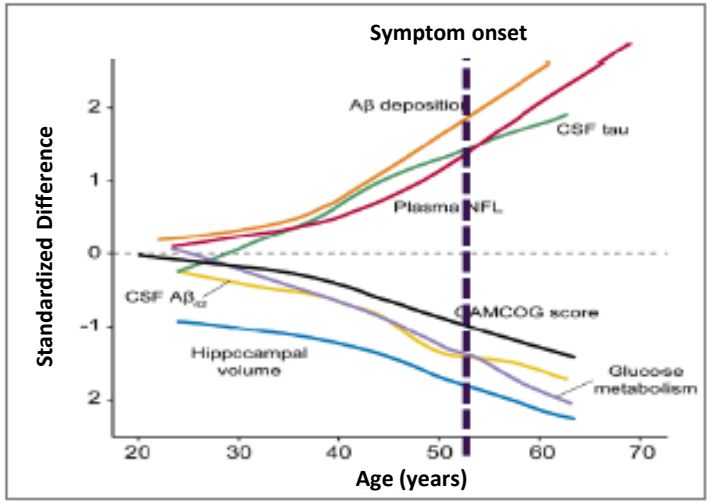
The rationale for anti Abeta vaccination in Alzheimer's disease (AD) and AD in Down syndrome (DS)

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

Factors supporting a vaccine approach in DS

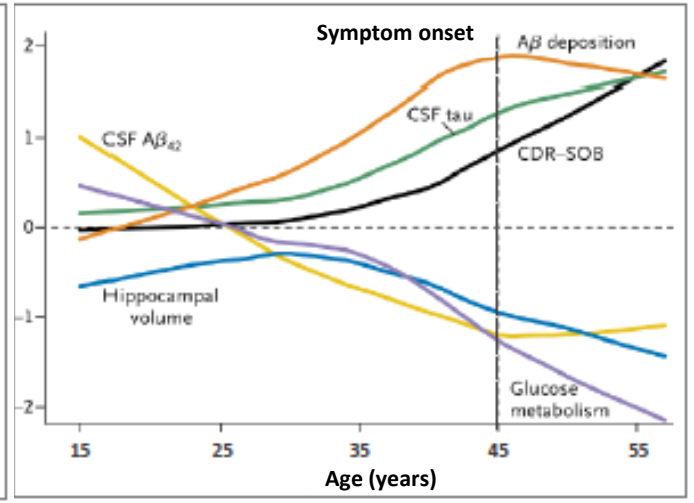
- Amyloid-beta precursor protein (APP) encoded by the *APP* gene generates amyloid beta
- Located on chromosome 21, the extra copy of the APP gene may cause increased risk of developing AD– like symptoms
- DS population is the largest population with early onset AD; 75–100% of people with DS have AD-like 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)



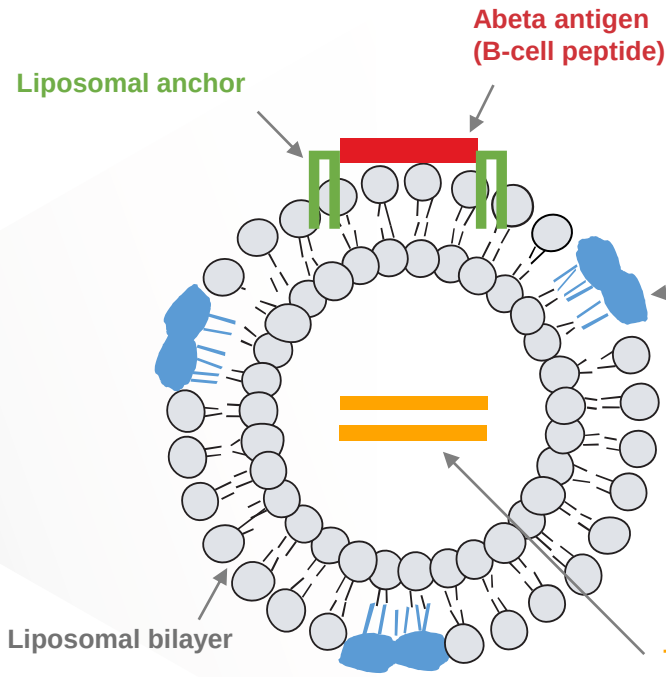
Ref: adapted from Bateman, NEJM 2012

- 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

Disruptive potential of SupraAntigen® platform

Optimized ACI-24 that deliver superior antibodies to fight neurodegenerative diseases



Target specificity
Conformation specificity

IgM → IgG
Immune memory
Maturation towards pathological species

Optimal immunogenicity

Boostable
Sustained responses
Avidity increase (binding potency)

- Carefully selected Abeta antigen embedded to drive a specific and conformational polyclonal response
- Non-Abeta specific T-helper peptide incorporated to optimize the antibody response

From ACI-24 to optimized ACI-24

Selection of optimal T-helper peptide: *in silico* immunogenicity evaluation

Single T-cell epitope	
Peptide name	**Immunogenicity score**
a	**-27**
b	**8**
c	**10**
d	**-2**
e	**17**
f	**6**
g	**23**
h	**1**
i	**32**
j	**12**

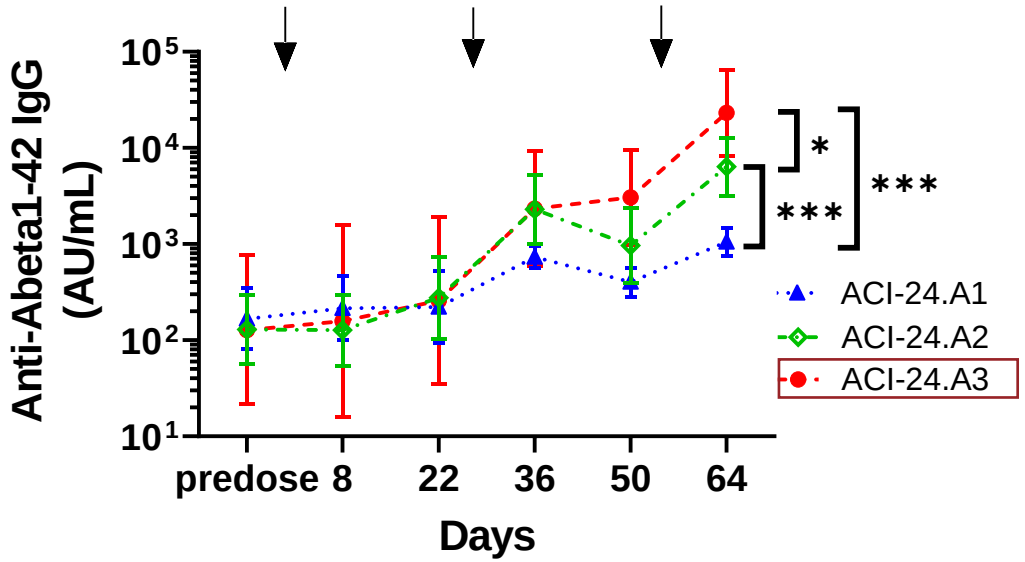
Concatenated T-helper epitopes		
Peptide number	**Number of peptides**	**Immunogenicity score**
1	2	**40**
2	2	**57**
3	4	**143**

- An initial *in silico* evaluation was performed to select the most promising T-helper epitopes
- Concatenated T-helper epitopes have higher *in silico* immunogenicity score than the individual T-helper peptides

From ACI-24 to optimized-ACI-24

Selection of optimal T-helper peptide: from *in silico* to *in vivo* immunogenicity validation

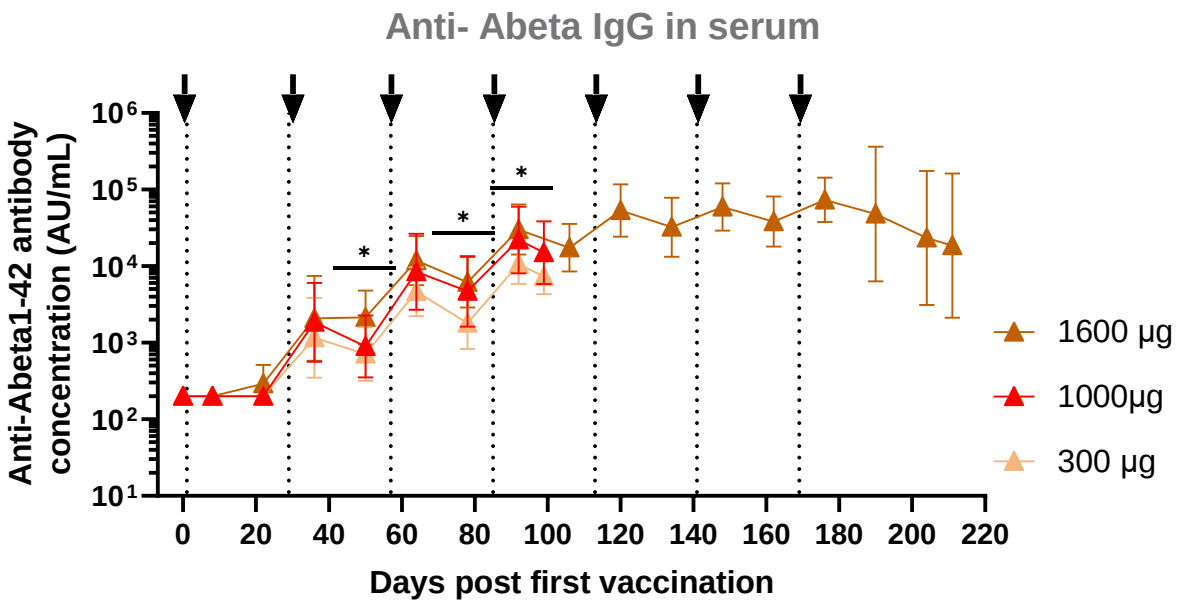
Concatenated T-helper epitopes		
Peptide number	**Immunogenicity score**	**Vaccine name**
1	40	ACI-24.A1
2	57	ACI-24.A2
3	143	ACI-24.A3

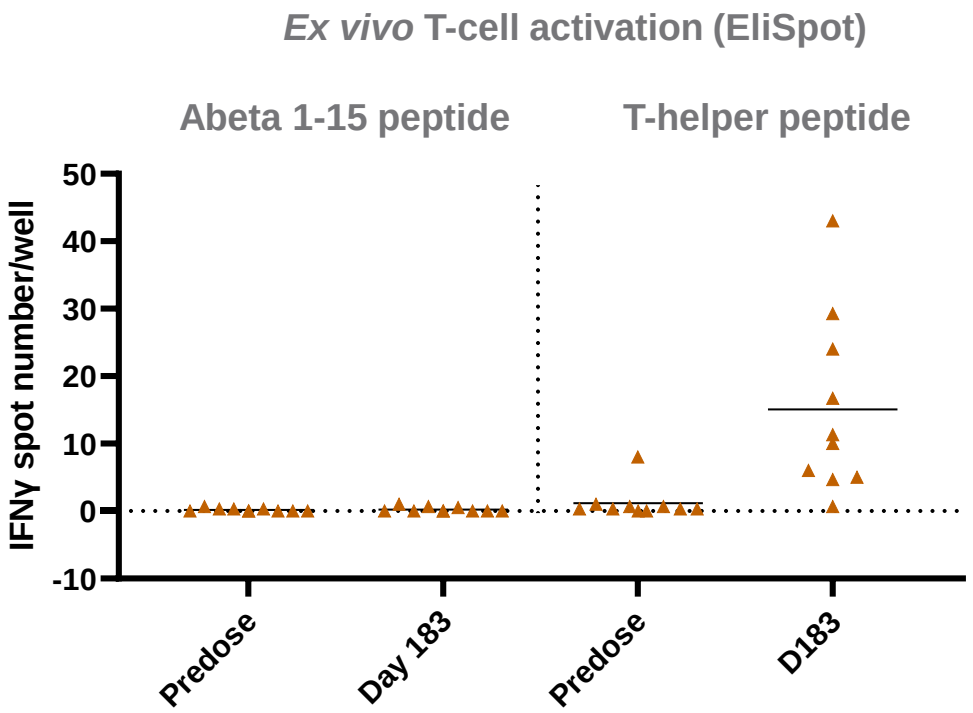


- Concatenated T-helper epitopes with the best *in silico* immunogenicity score were incorporated into ACI-24 vaccine and tested *in vivo* in Non-Human primates (NHPs)
- The ACI-24 with incorporated T-helper sequence #3 showed the best immunogenicity in NHPs

ACI-24.060: safe and strong anti-Abeta antibody response

Immunogenicity in non-human primates (NHPs)





Day 183: 2 wk post 7th immunization

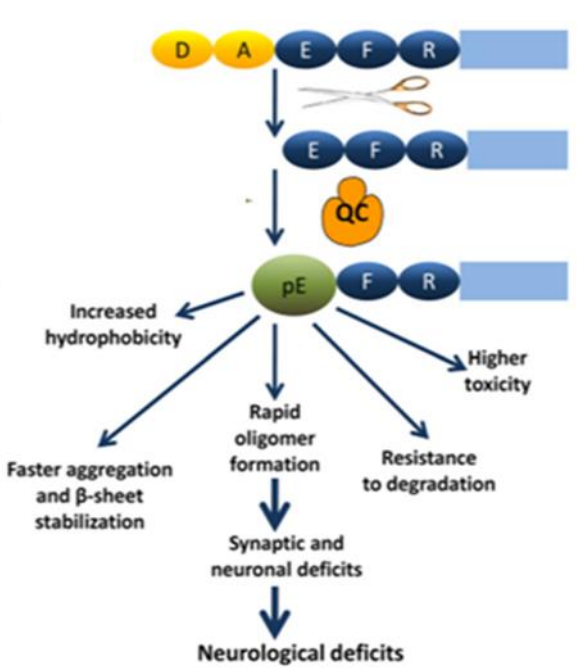
*: p-value < 0.05

NHP: non-human primates

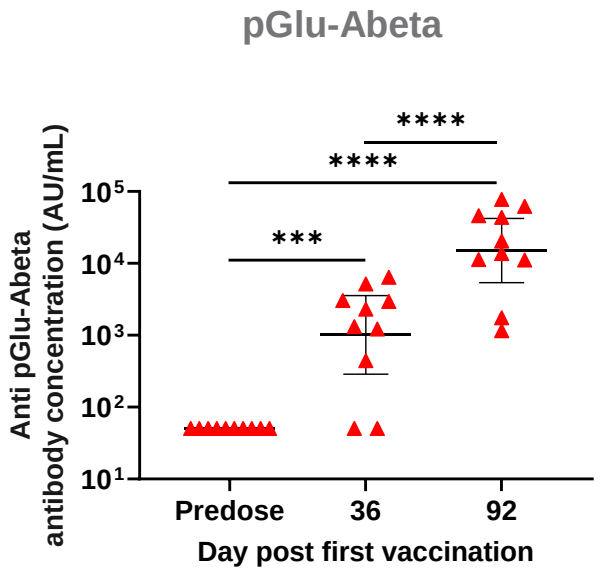
- Immunization with ACI-24.060 induces a strong, boostable, maintained and dose-dependent anti-Abeta IgG response in NHPs
- Immunization with ACI-24.060 **does not** induce Abeta specific T-cell activation

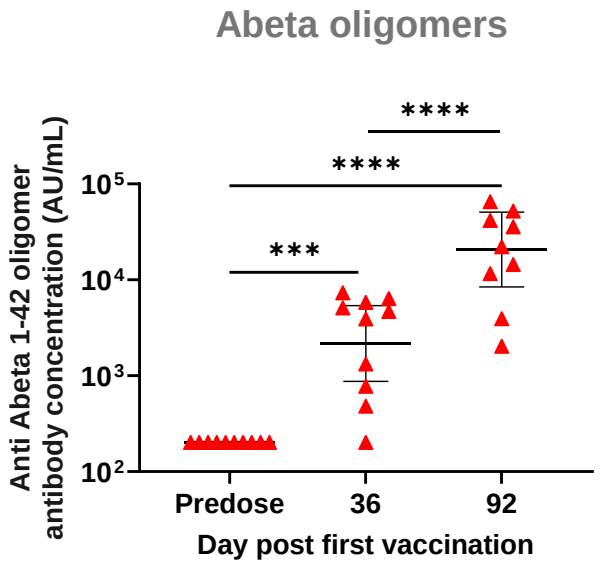
ACI-24.060: targets the highly toxic species of Abeta

Further characterization of immunogenicity in NHPs



Serum IgG levels binding to:





***: p-value < 0.001; ****: p-value < 0.0001

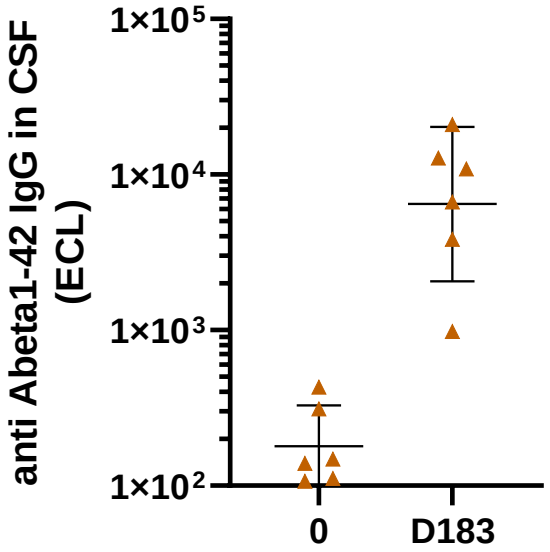
Day 36: 1 wk post 2nd immunization
Day 92: 1 wk post 4th immunization

- Vaccination of NHPs induces generation of antibodies that bind Abeta oligomers as well as the truncated pyroglutamate Abeta species

ACI-24.060: presence of vaccine-induced antibodies in NHP CSF and target engagement on human AD brains

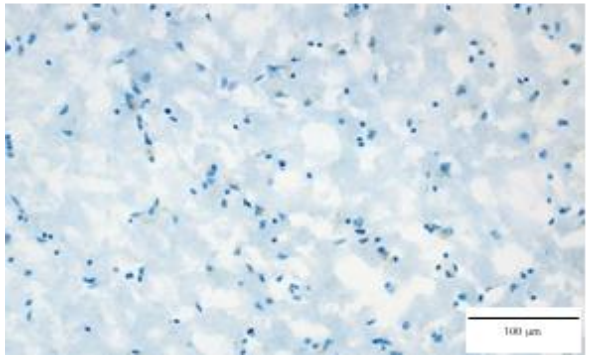
:

Anti-Abeta IgG in NHP CSF

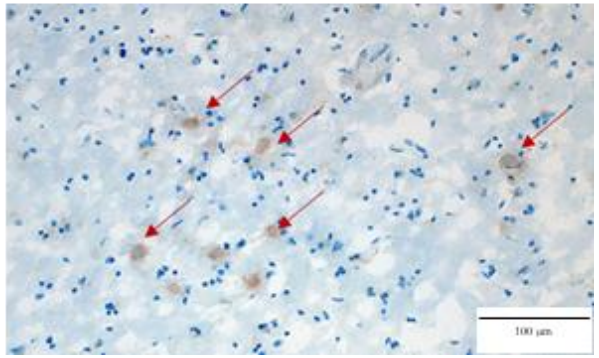


Immunolabelling in AD brain sections

Pool of monkey sera at predose



Pool of monkey sera at Day 92

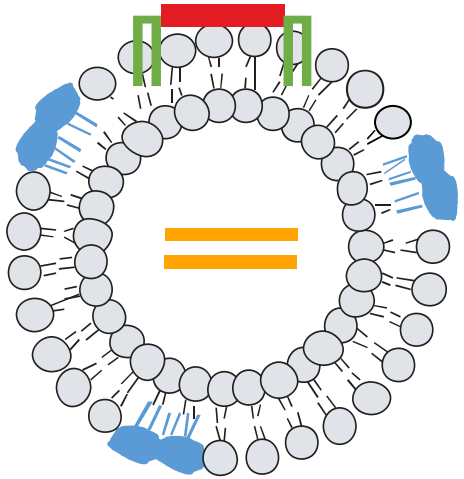


- Anti-Abeta antibodies are present in CSF of NHPs after vaccination with ACI-24.060
- Antibodies generated in NHPs post-vaccination with ACI-24.060 bind to Abeta plaques on AD patient-derived brain tissue sections

Summary of ACI-24.060

ACI-24.060 delivering superior immunogenicity in pre-clinical studies

ACI-24.060



Generates target-specific antibody response

Safely engages Abeta-unrelated T-cells to enhance & maintain immune response

Preclinical Performances

Immunogenicity against Abeta	++++[1]
Boosting	++++
Immunogenicity against Abeta pathological species	++++
Non-Abeta T-helper activation	+++
Anti-Abeta IgG in CSF	+++
Target engagement on human AD brains	+++

- The excellent pre-clinical results led to Phase 1b/2 ABATE clinical trial in AD, where ACI-24.060 showed positive initial ad-interim safety and immunogenicity results

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We continue to shape the future of neurodegeneration by discovering and developing breakthrough therapies through pioneering science and precision medicine

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