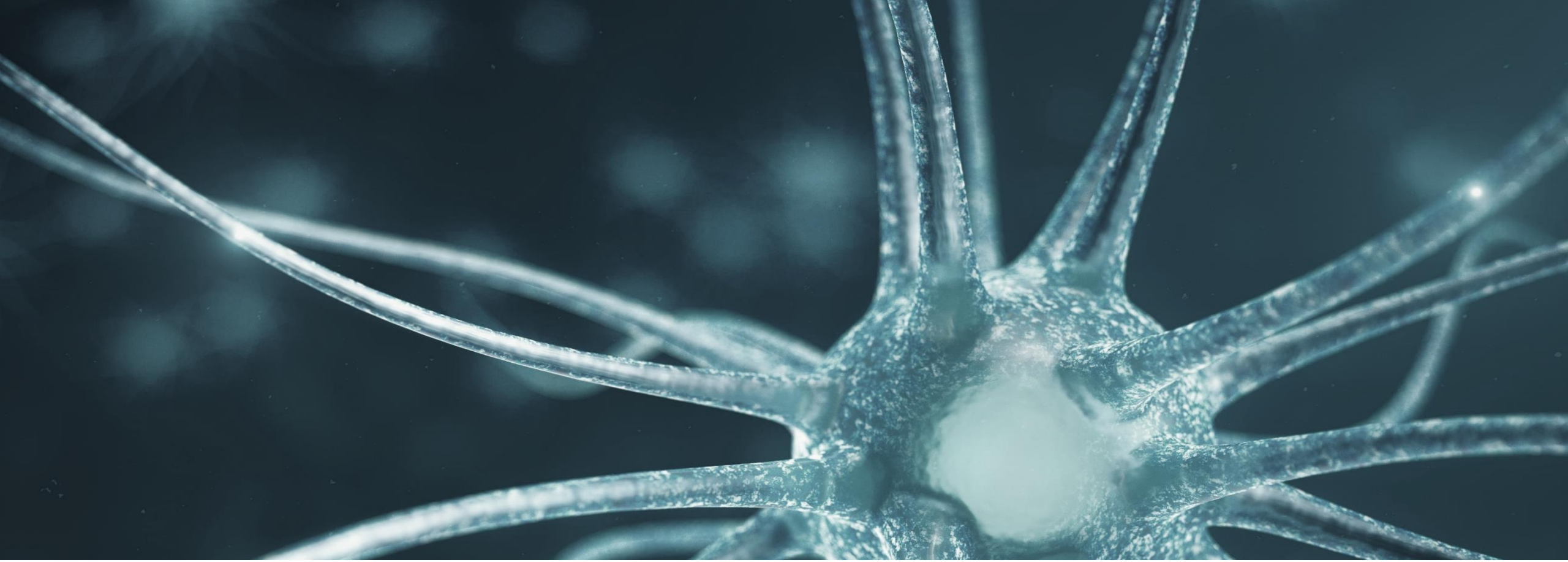

An optimized Amyloid beta (Abeta) vaccine that safely drives immunity to the key pathological species of Alzheimer's disease (AD)

Marija Vukicevic, PhD | AD/PD™ 2022 | 18 March

AC Immune

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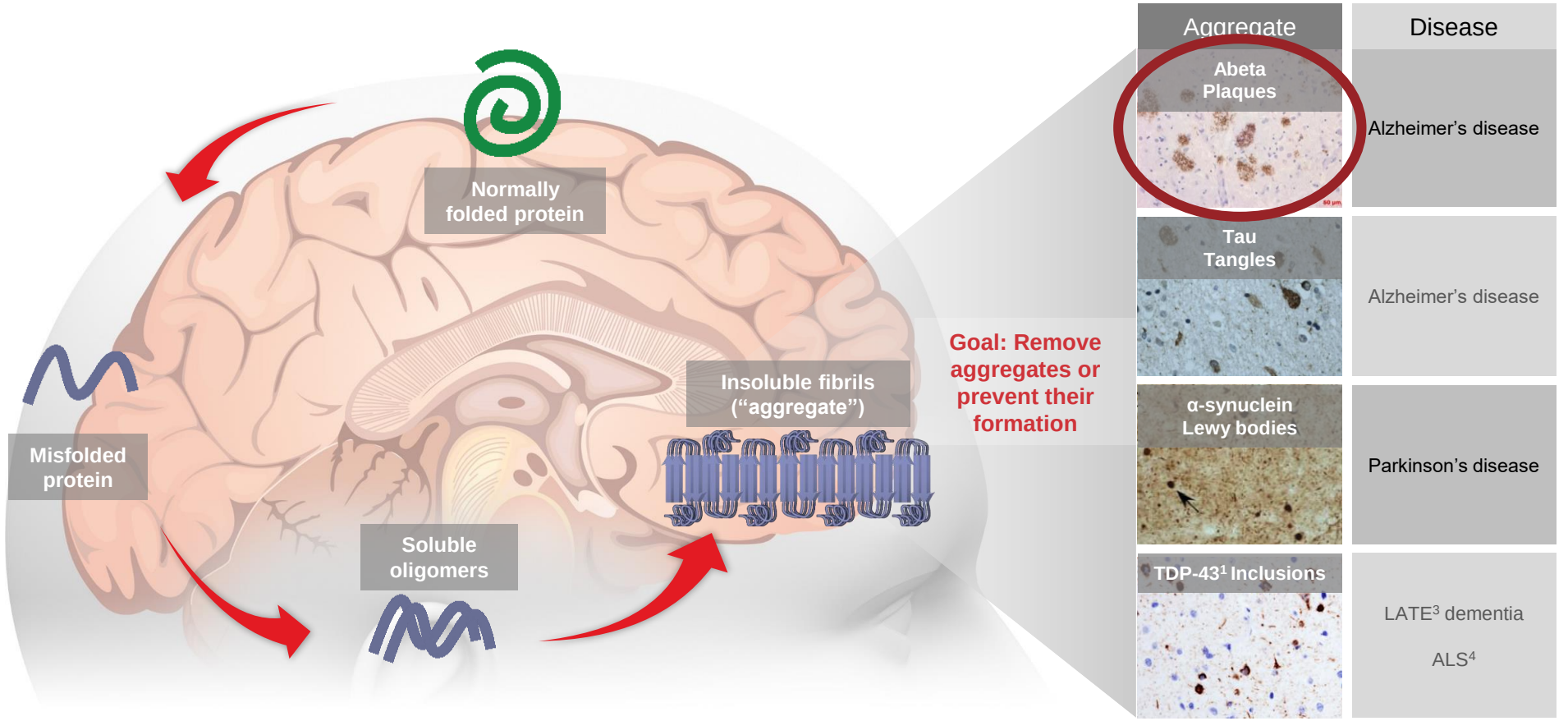
Misfolded proteins: Leading causes of neurodegenerative diseases

Abeta, Tau, a-synuclein, and TDP-43[1] are important NDD[2] drug targets



Refs: Soto 2003, http://www.alz.org/brain; Nag *et al.* Acta Neuropathologica Communications (2018) 6:33;
(1) TAR DNA-binding protein 43; (2) Neurodegenerative disease; (3) Limbic-predominant age-related TDP-43 encephalopathy; (4) Amyotrophic lateral sclerosis

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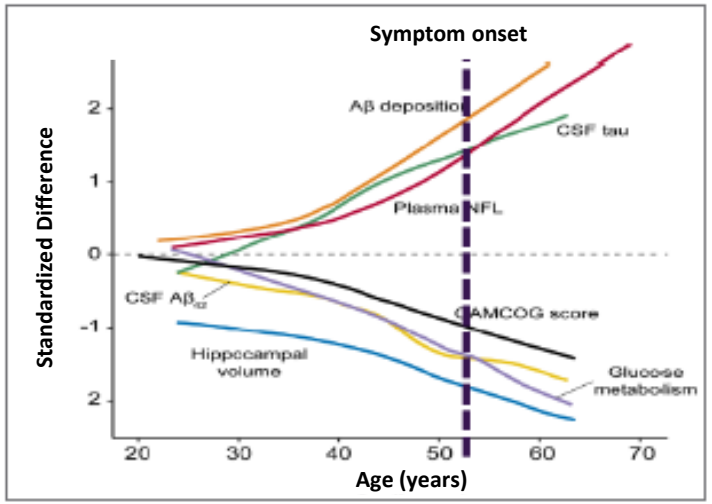
The rationale for vaccination in Alzheimer's disease (AD) and AD in Down syndrome (DS)

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

Factors supporting a vaccine approach in DS

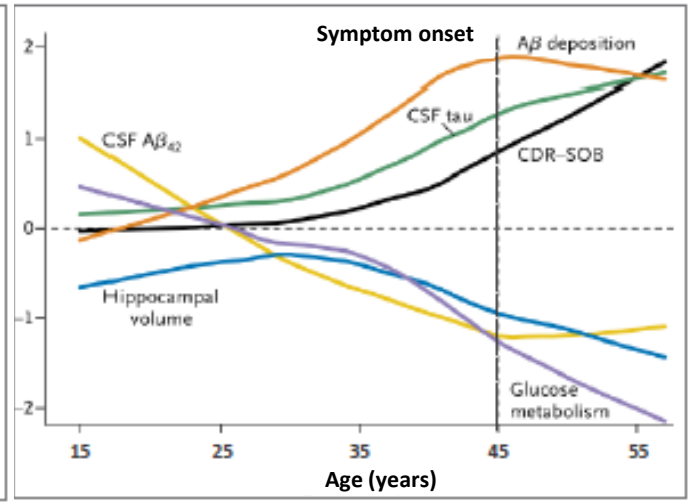
- Amyloid-beta precursor protein (APP) encoded by the *APP* gene generates amyloid beta
- Located on chromosome 21, the extra copy of the APP gene may cause increased risk of developing AD– like symptoms
- DS population is the largest population with early onset AD; 75–100% of people with DS have AD-like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

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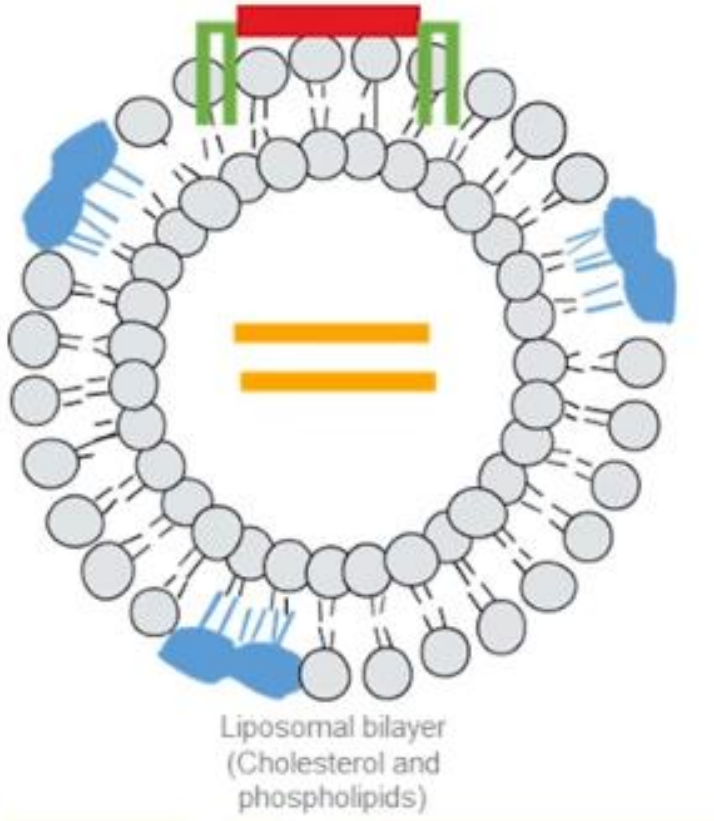
Optimized ACI-24 formulation: Building on safety and initial efficacy

Adding bystander T-cell help



Optimized ACI-24 includes the original:

- B-cell peptide: ACI-24 (Pal1-15)
- Adjuvant: MPLA[1]
- Anchored into the liposomal bilayer

Adds:

- Non-Abeta T-helper cell epitope peptides:
  - Epitopes derived from different origins, for example, tetanus
  - To provide bystander T-cell help

- Safely stimulate non Abeta T-cells to enhance and maintain anti-Abeta specific antibody titers via harnessing a bystander helper effect

(1) Synthetic Monophosphoryl Lipid A

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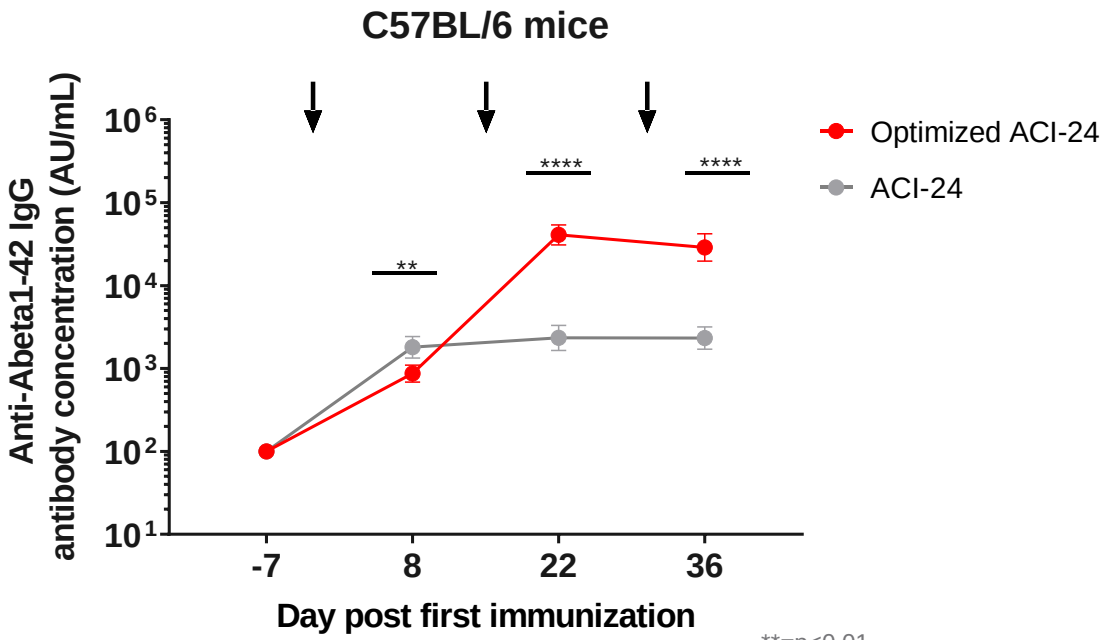
Optimized ACI-24: Immunogenicity in animals

Anti-Abeta1-42 IgG titers in mice and nonhuman primates



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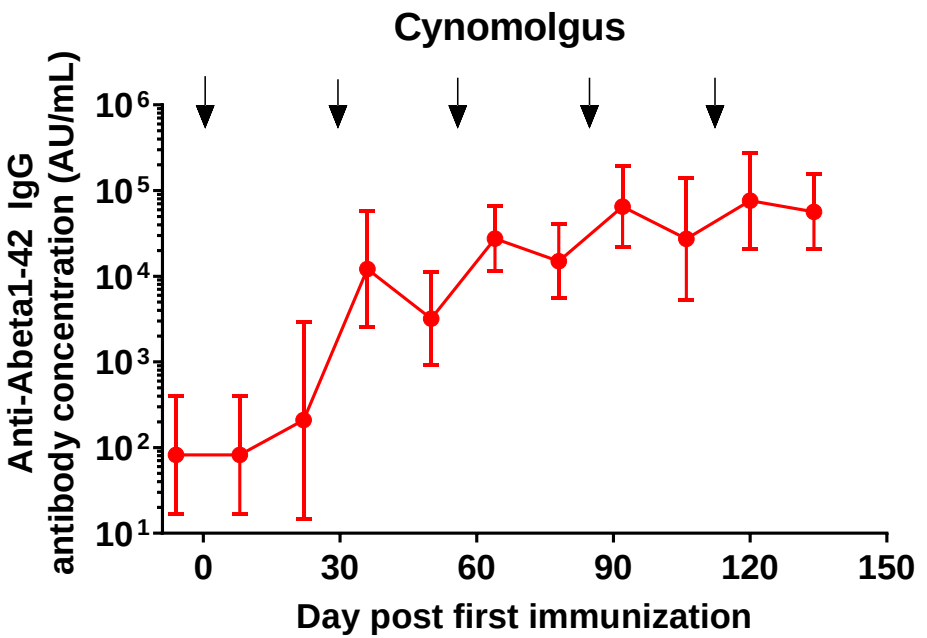

Ref.: AC Immune; Global Down Syndrome Forum 2021

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

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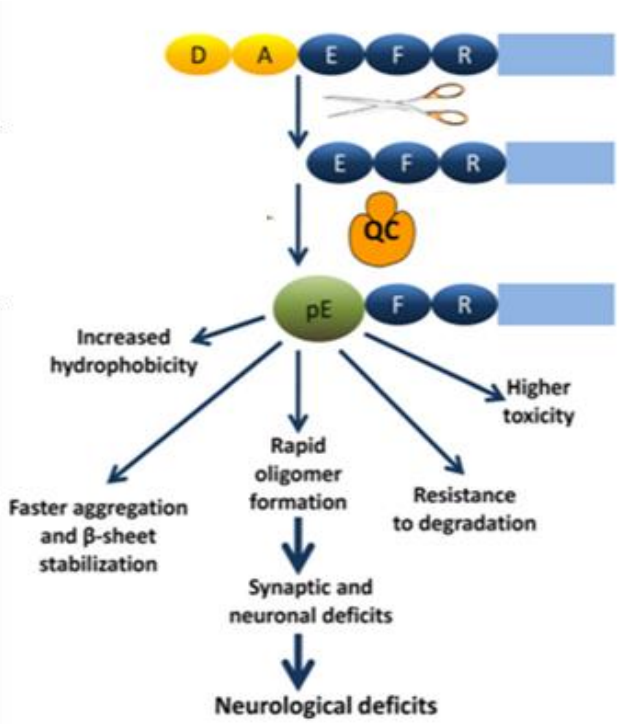
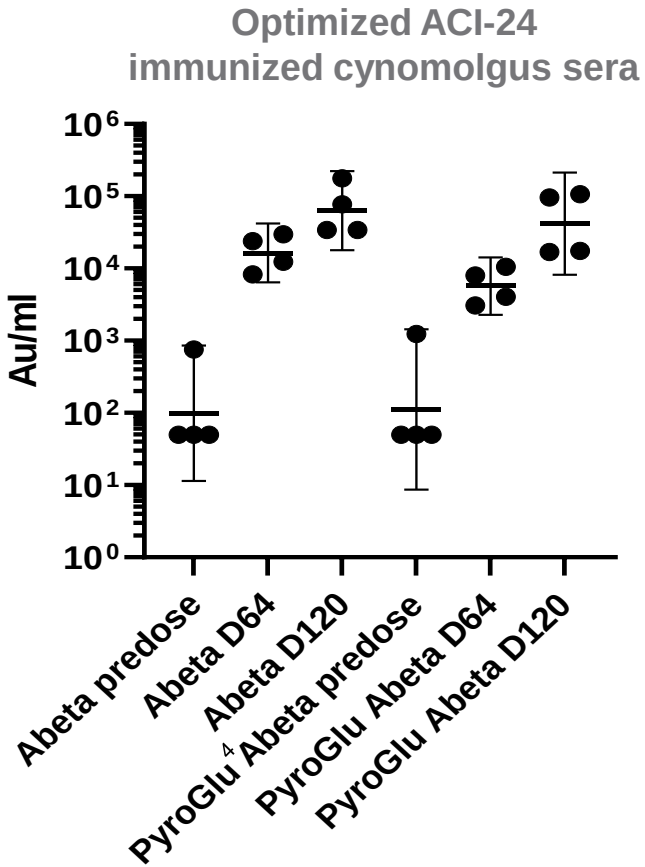
Optimized ACI-24: Induces a strong antibody response

To Abeta1-42 and PyroGlu Abeta in nonhuman primates



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



Sample	Abeta(1-42) binding (geo mean; AU[1]/ml)	PyroGlu Abeta binding (geo mean; AU/ml)
Predose	99	112
Day 64[2]	16,389	5,689
Day 120[3]	63,096	41,810

Ref.: AC Immune; Global Down Syndrome Forum 2021

- Sustained and enhanced IgG response that binds Abeta(1-42) and pyroglutamate Abeta, the truncated, highly pathological form of Abeta

(1) Arbitrary units; (2) Results obtained 1 week after the 3rd injection; (3) Results obtained 1 week after the 5th injection; (4) Pyroglutamate

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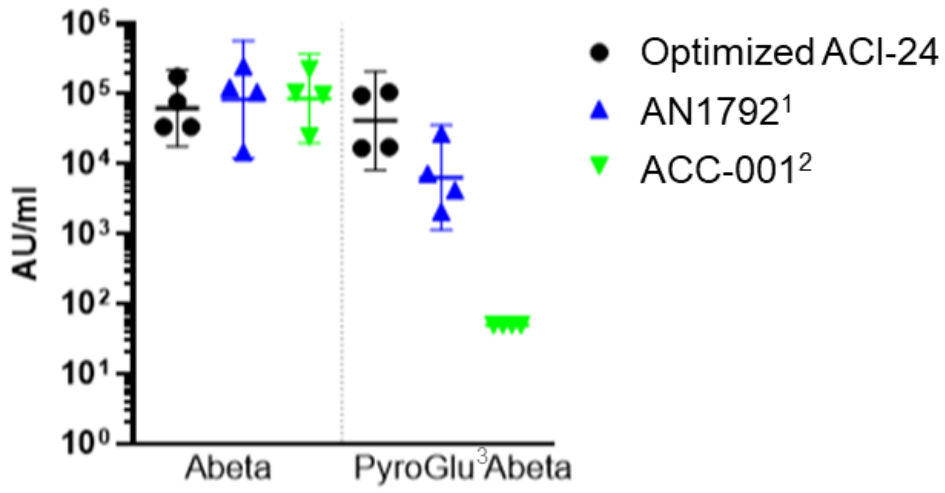
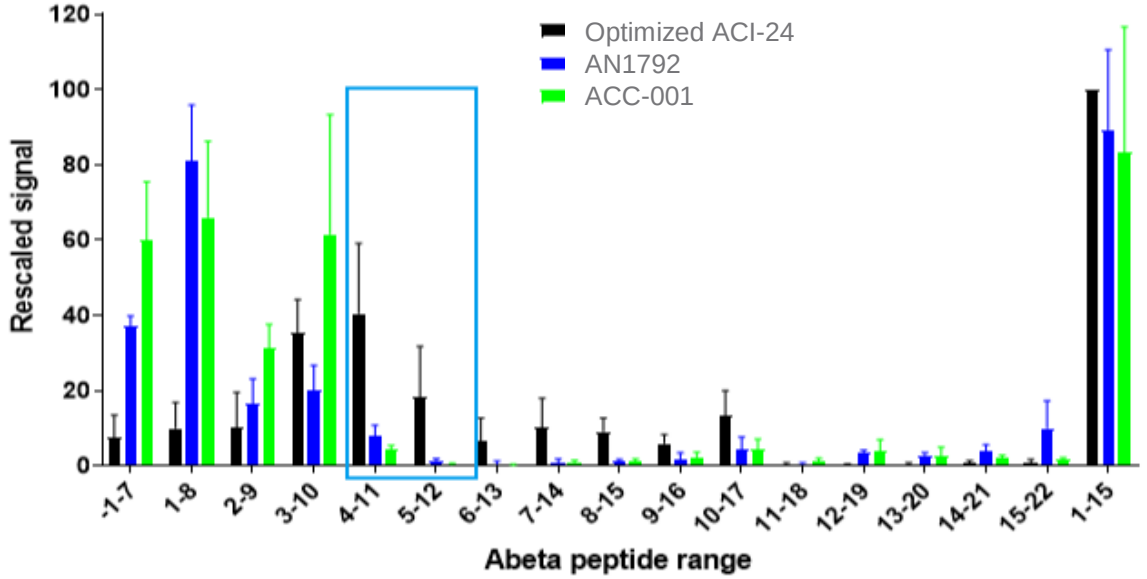
Optimized ACI-24: Antibody profile versus other Abeta vaccines

Illustrates a superior coverage of epitopes including for truncated pyroGlu Abeta

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 high levels of 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) Pyroglutamate

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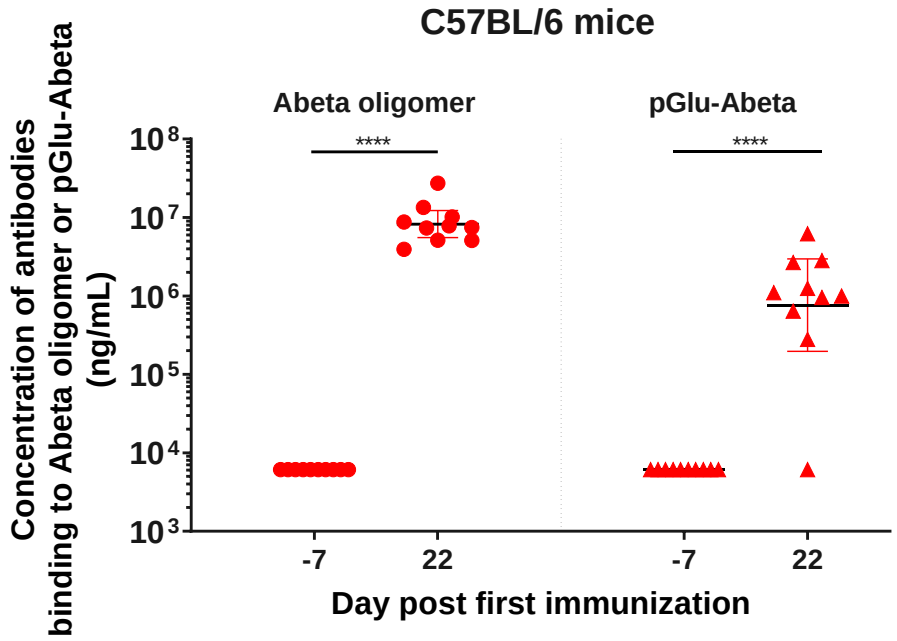
Optimized ACI-24: Immunogenicity in animals

Antibodies against oligomeric and pGlu Abeta pathological species in mice and nonhuman primates



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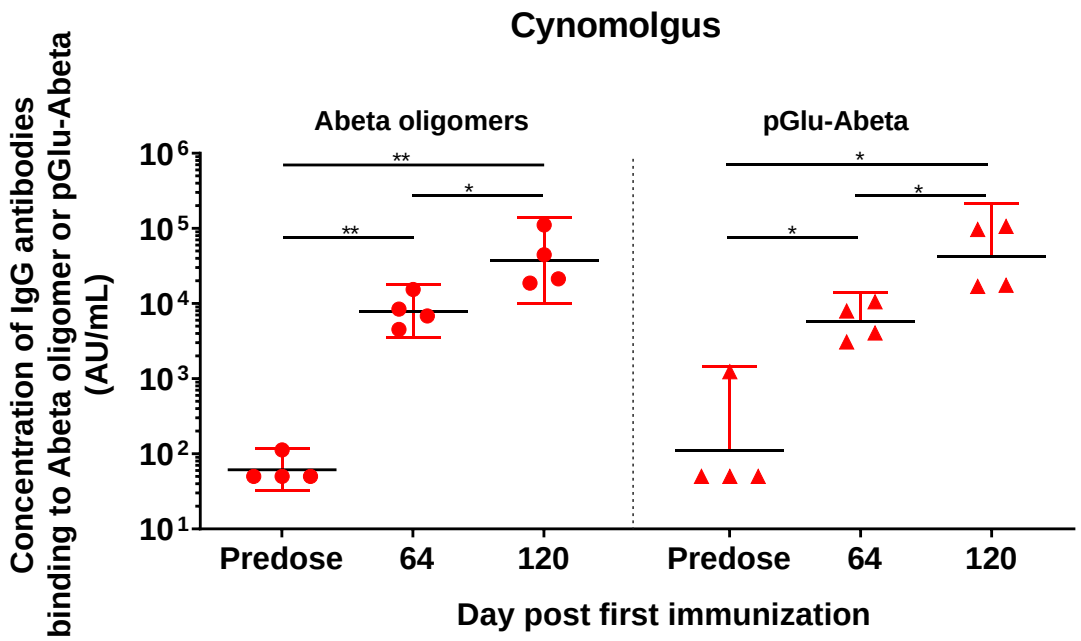

*= p<0.05, **=p<0.01

Ref.: Global Down Syndrome Forum 2021; M. Vukicevic, et al., Brain Comm, 2022

C57BL/6 mice: Day -7, predose; Day 22, results obtained 1 week after the 2nd immunization
Cynomolgus monkeys: Day 64, results obtained 1 week after the 3rd immunization; Day 120, results obtained 1 week after the 5th immunization

- Optimized ACI-24 generates antibodies able to recognize pathological Abeta species in mice and NHPs: toxic oligomers and pyroglutamate

(1) Pyroglutamate Abeta 3-42

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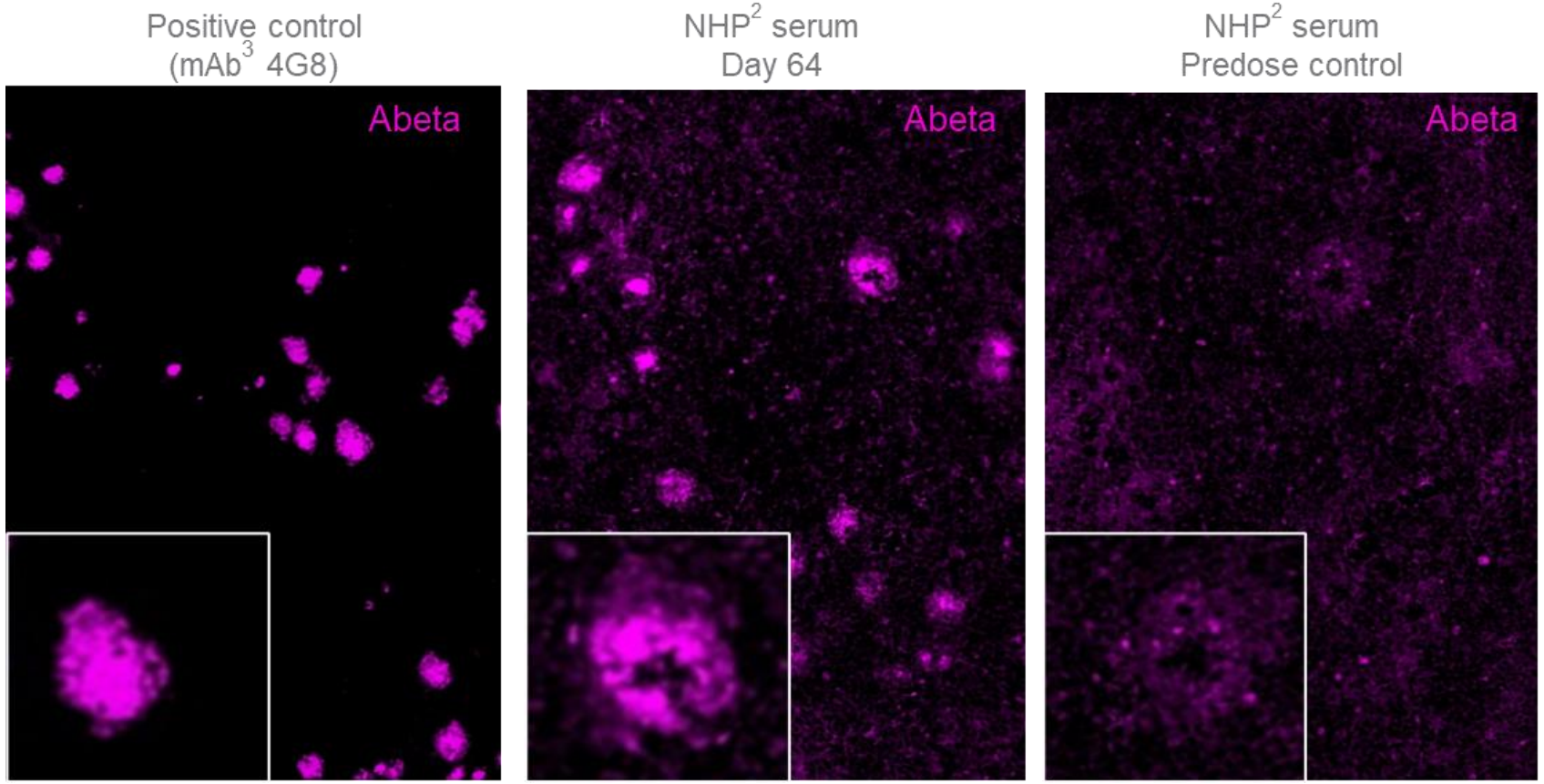
Optimized ACI-24: Target engagement

Binding to Abeta plaques on AD[1] patient-derived brain tissue sections



Ref.: AC Immune; Global Down Syndrome Forum 2021

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

(1) Alzheimer's disease; (2) Non-human primates; (3) Monoclonal antibody

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Summary

- ACI-24 is a safe and active immunotherapy targeting Abeta generated on AC Immune's proprietary SupraAntigen® liposomal platform
- Optimized ACI-24, in addition to the Abeta1-15 peptide, has a non-Abeta T-cell peptide to enhance and maintain anti-Abeta-specific antibody responses
- Optimized ACI-24 induces strong and maintained IgG titers against key pathological Abeta species (oligomers and pyroglutamate) in mice and non-human primates
- Optimized ACI-24 represents a potential breakthrough compared to previous Abeta vaccines, due to its unique binding profile to pathological Abeta species
- Optimized ACI-24 has a broad potential across Abeta-driven diseases, including DS-related, genetic and sporadic AD

AC Immune is dedicated to addressing the high unmet medical need of the AD and DS community via our safe and potent vaccination approach

AD: Alzheimer's disease; DS: Down syndrome

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