# Advantages of next generation SupraAntigen® liposomal vaccine platform to immunize against pathological targets of Alzheimer's disease (AD)

Marie Kosco-Vilbois, PhD | CTAD, Dec 2022

AC Immune

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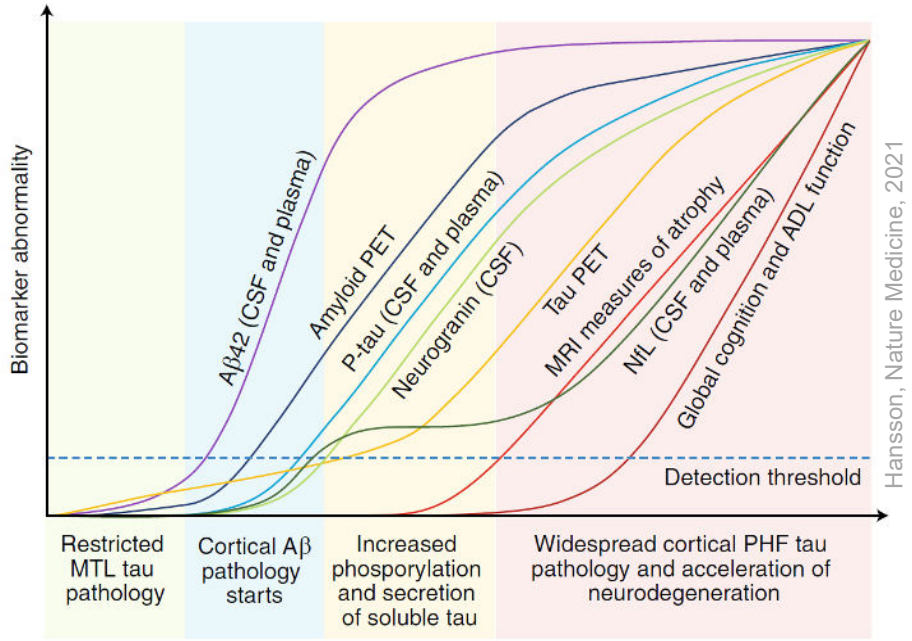
## Conflict of interest disclosure

*Marie Kosco-Vilbois is an employee of AC Immune entitled to stock options.*

# Pathological Abeta and Tau: promising targets for early intervention in AD

## Two predictive biomarkers in sporadic AD and genetic forms of dementia

### CSF[1], plasma and PET[2] biomarkers




Hansson, Nature Medicine, 2021

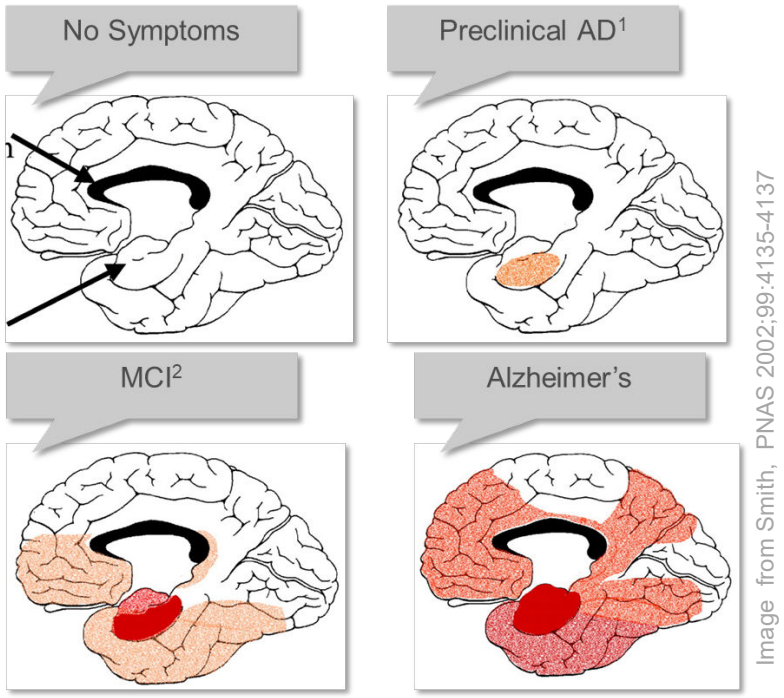


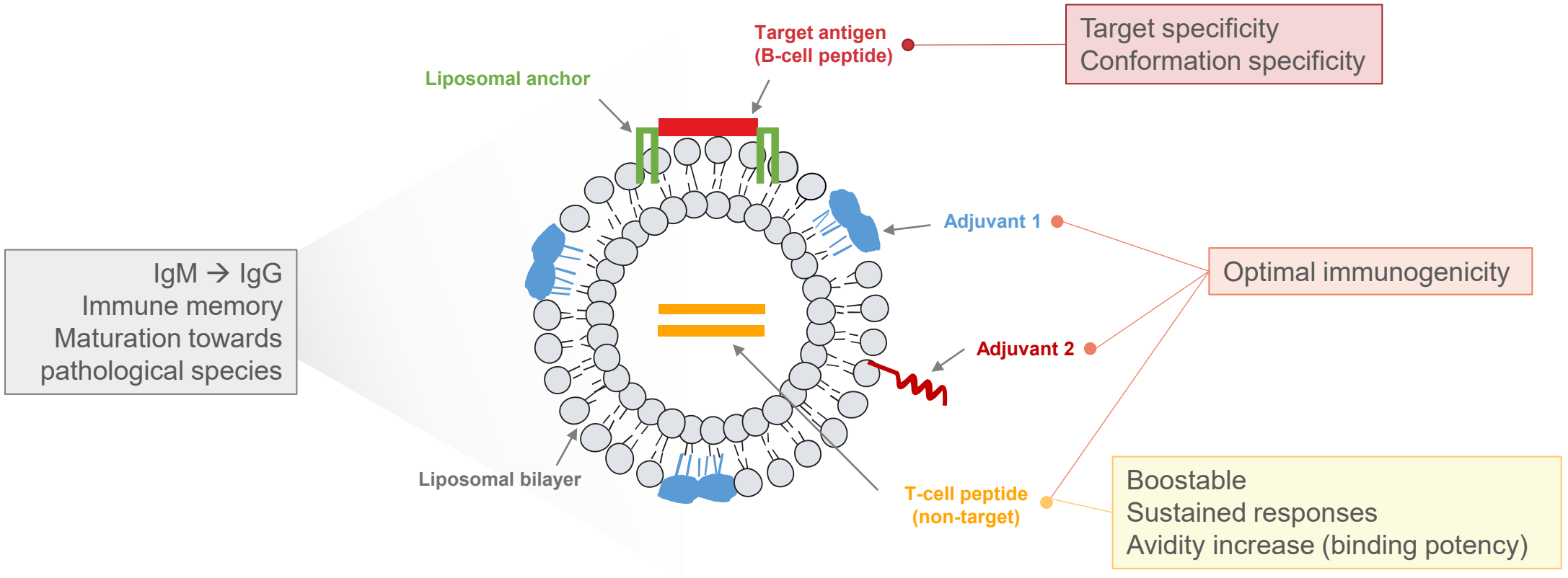

Image from Smith, PNAS 2002;99:4135-4137

- Abeta and Tau are clinically validated targets and already start to accumulate during preclinical stages of AD, before symptoms appear
- Thus, a vaccination approach to clear pathological Abeta and Tau early or even before disease symptom onset is a highly attractive immunotherapy approach

(1) Cerebrospinal fluid; (2) Positron emission tomography

# Disruptive potential of SupraAntigen® platform

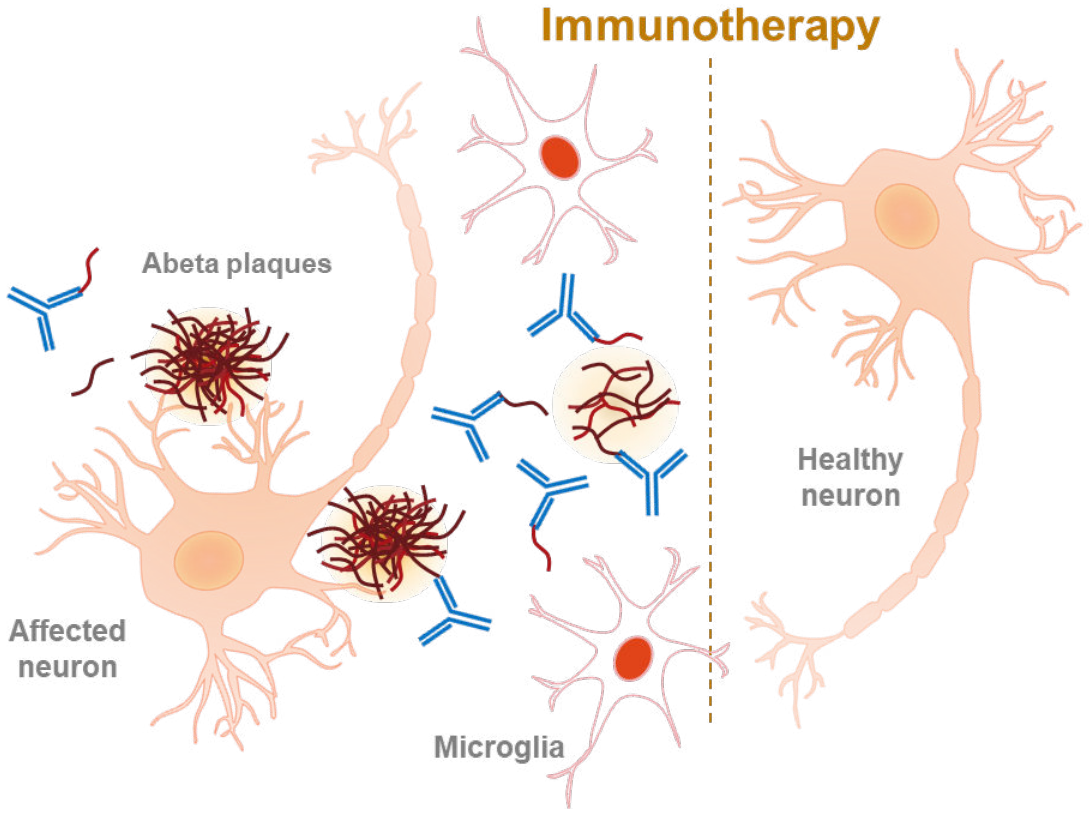
## Optimized vaccines that deliver superior antibodies to fight neurodegenerative diseases




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

# Active immunization for early intervention in Alzheimer's Disease

Targeting pathological species of Abeta offers a viable opportunity for prevention and treatment




- Abeta is a clinically validated target that accumulates during preclinical stages of AD
- Abeta vaccines are formulated to induce target-specific lasting and boostable polyclonal antibody responses targeted to the pathological species

# Optimized ACI-24: ACI's anti-Abeta vaccine

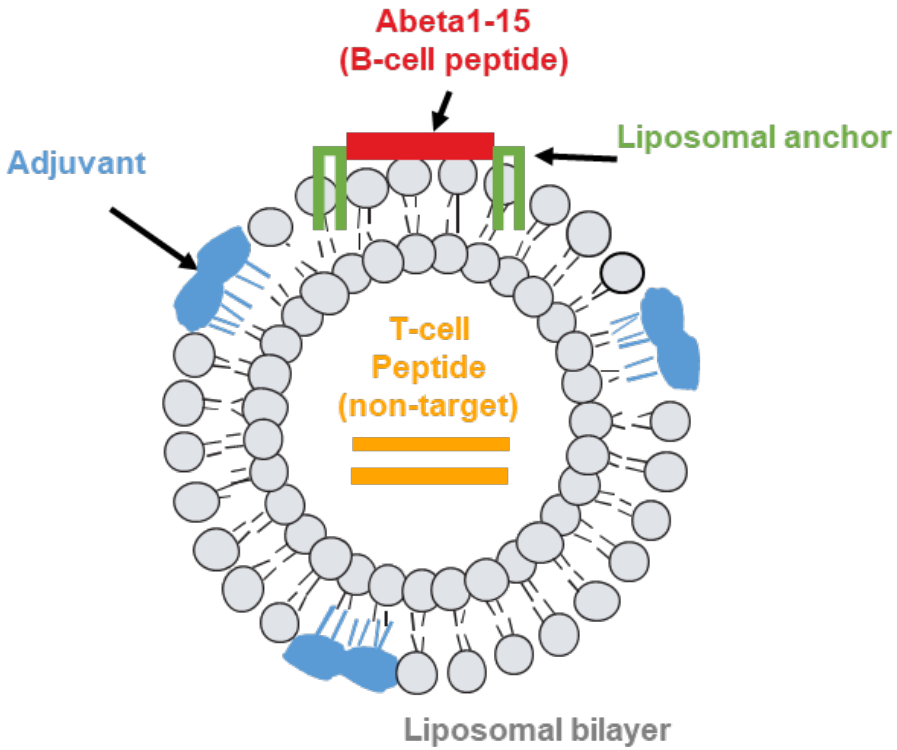
## Key differentiating advantages

**1** **Broad epitope coverage of oligomeric and pyro-Glu Abeta** (i.e., the targets of lecanemab and donanemab)

**2** **Safe and well tolerated** - no ARIA-E observed as antibody response progressively builds in the body

**3** **Long-lasting antibody responses** that allows 1-2x doses per year for ease of maintenance therapy

**4** **Attractive storage and handling conditions**
4°C / 40°F for 3 years and room temp for 2 years




**Optimized ACI-24 vaccine**

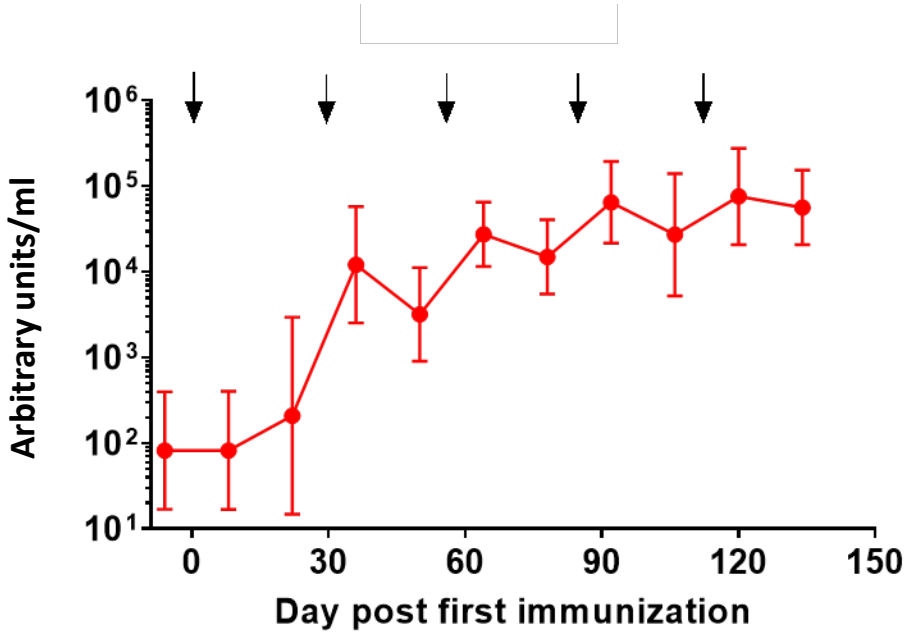
(1) In all primary and secondary endpoints

# Optimized ACI-24: Targets the highly toxic species of Abeta

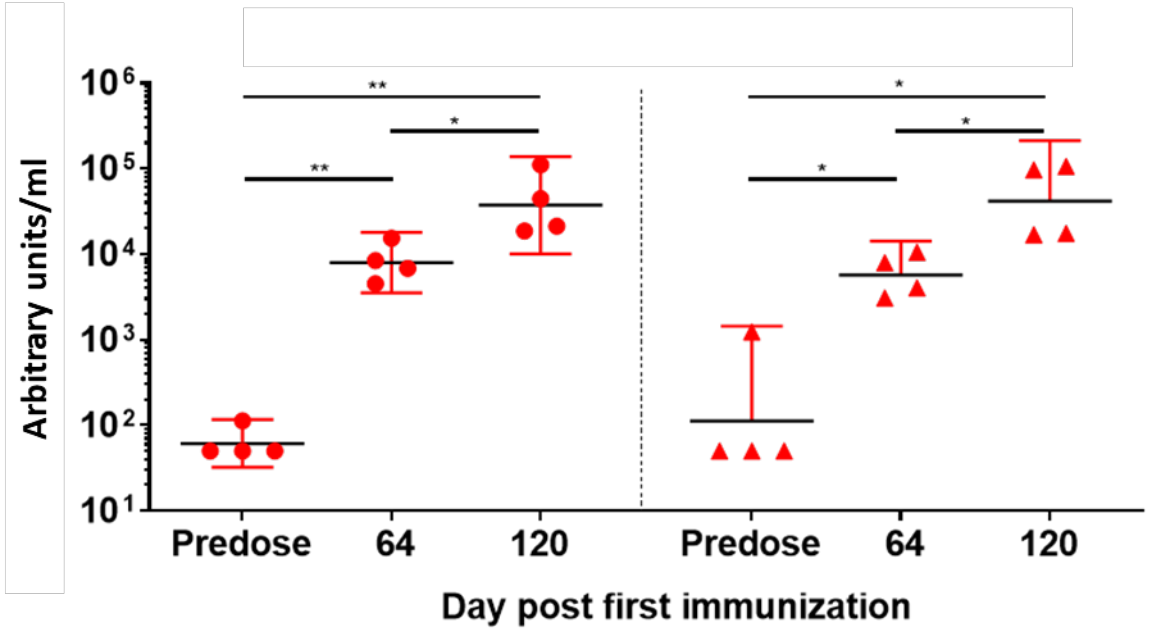
## Strong, boostable, homogeneous IgG titers in non-human primates

Ref.: AC Immune; Global Down Syndrome Forum 2021

**Serum IgG levels binding to Abeta1-42**




**Serum IgG levels binding to:**
**Abeta oligomers** **pGlu-Abeta**




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

Day 64: 1 wk post 3rd immunization
Day 120: 1 wk post 5th immunization

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

NHP: non-human primates

- Vaccination of NHPs induces a strong anti-Abeta 1-42 response, generation of confirmation antibodies that bind Abeta oligomers as well as the truncated pyroglutamate species of Abeta

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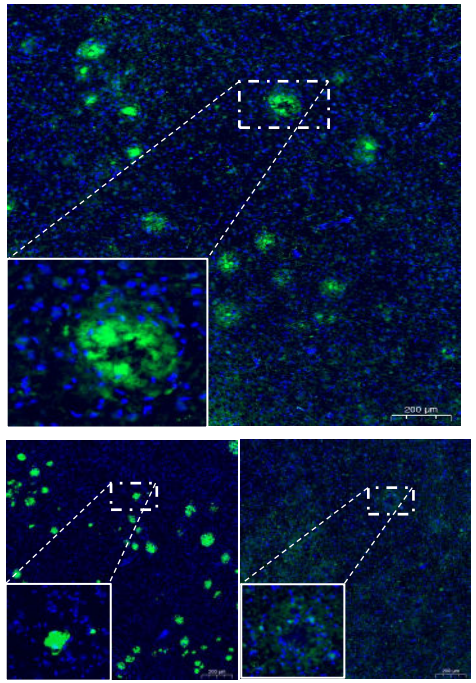
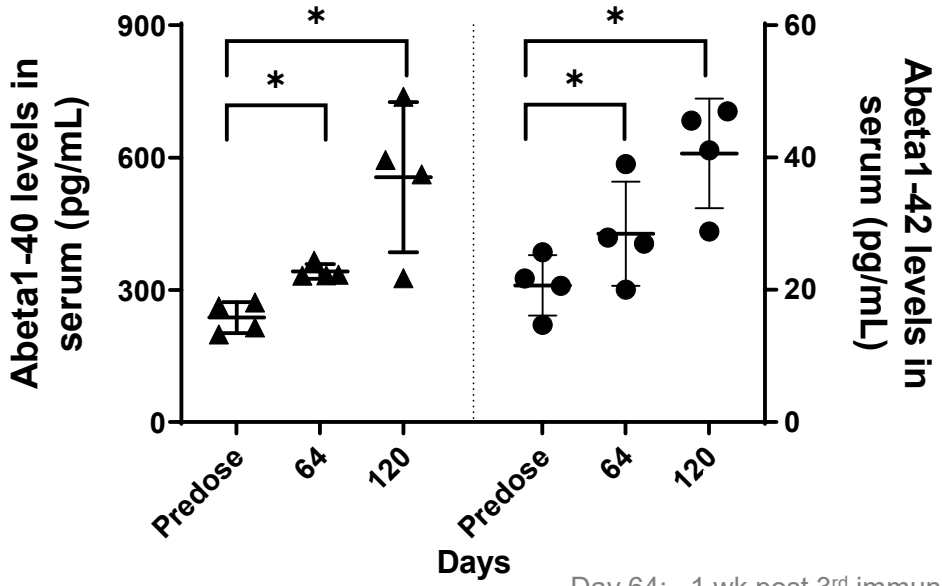
# Optimized ACI-24: Vaccination drives production of more effective antibodies

## Target engagement observed in AD brain sections and NHP sera levels of Abeta 1-40 and 1-42

**Abeta plaque labeling (Immunohistology)**




**Serum protein levels**




Day 64: 1 wk post 3rd immunization
Day 120: 1 wk post 5th immunization

*= p<0.05

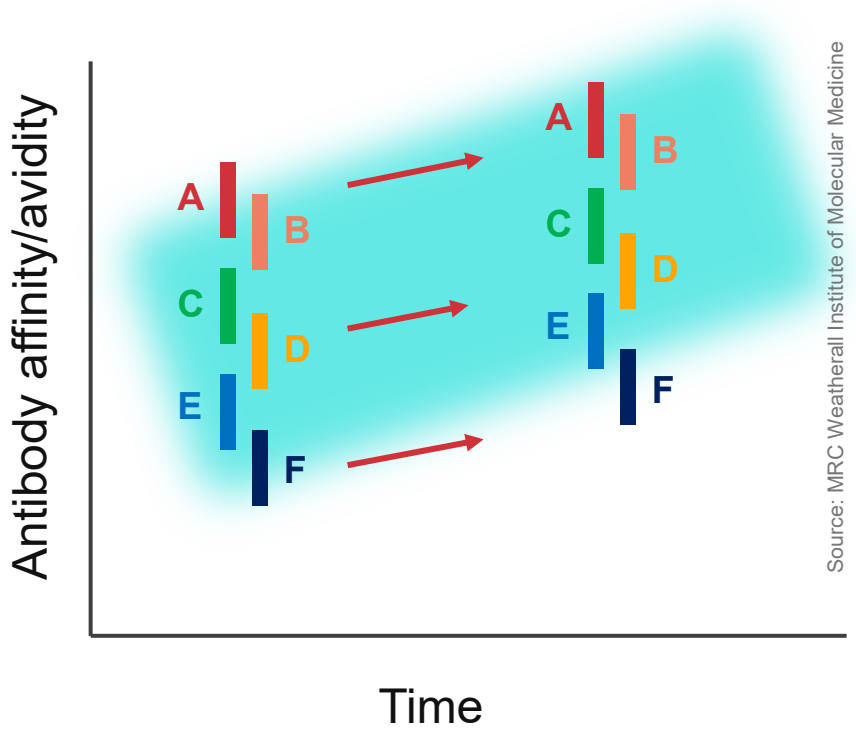
NHP: non-human primates

- Antibodies generated with optimized ACI-24 post vaccination of NHPs:
  - Bind to Abeta plaques on Alzheimer's disease brain sections
  - Engage the target, i.e., Abeta1-40 and 1-42, in the blood of NHPs (pharmacodynamic marker)

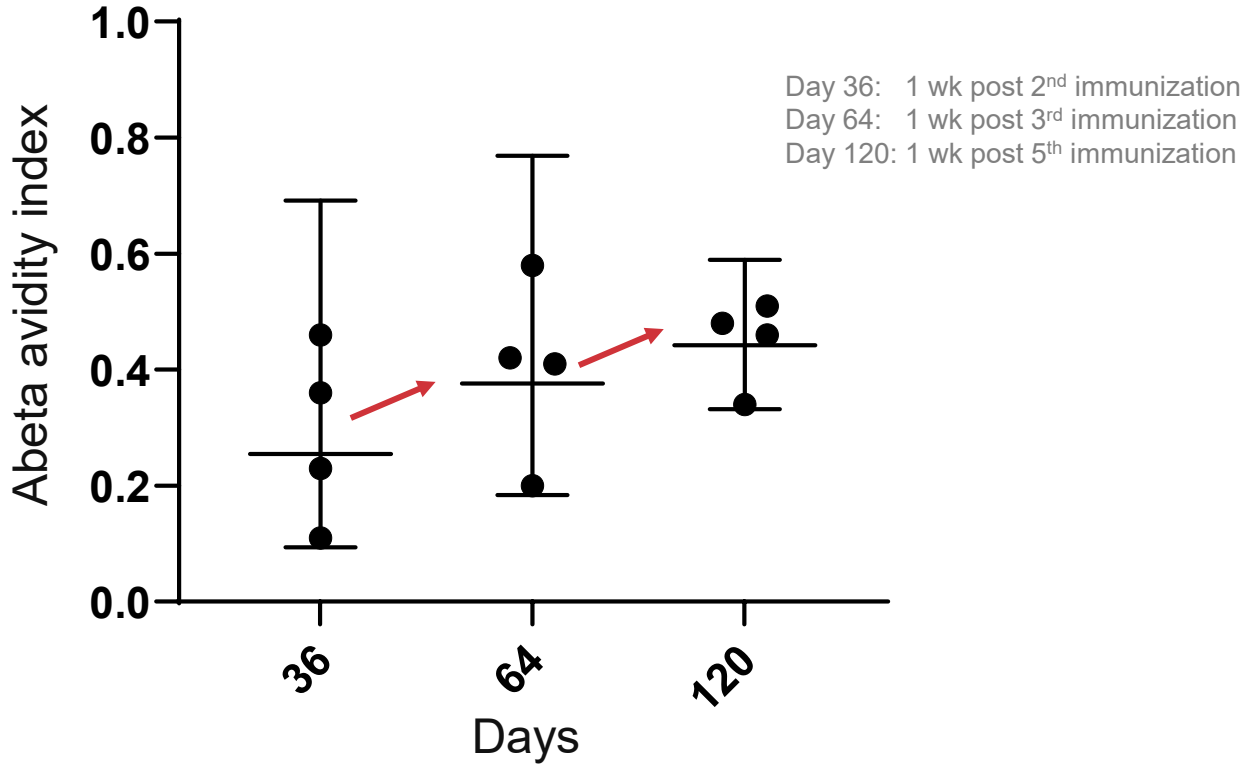
# Optimized ACI-24: Vaccination drives maturation of the antibodies

## Increase in affinity for Abeta over time in NHPs

**Kinetics of optimal antibody responses**




**Abeta binding capacity post multiple vaccinations**

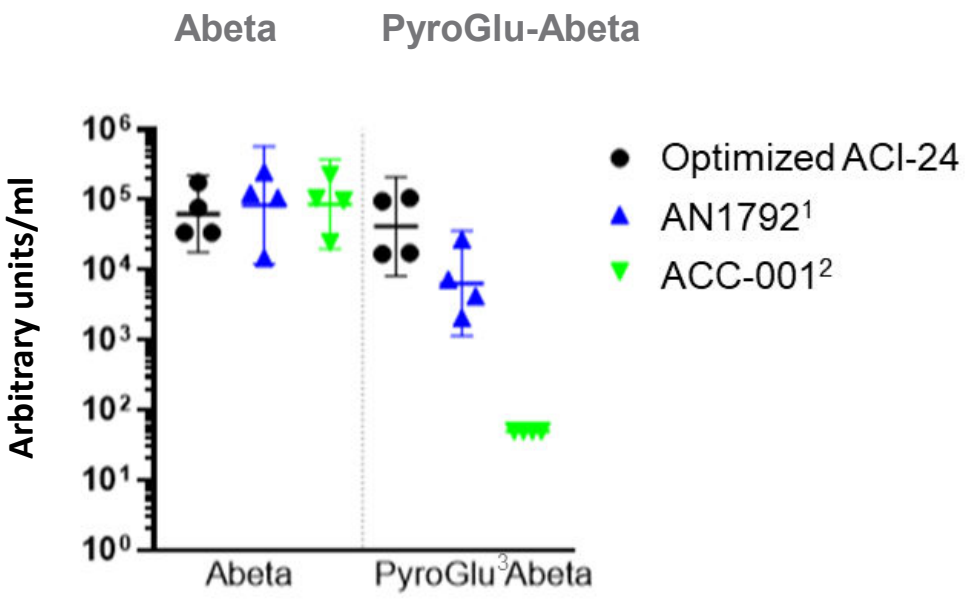



NHP: non-human primates

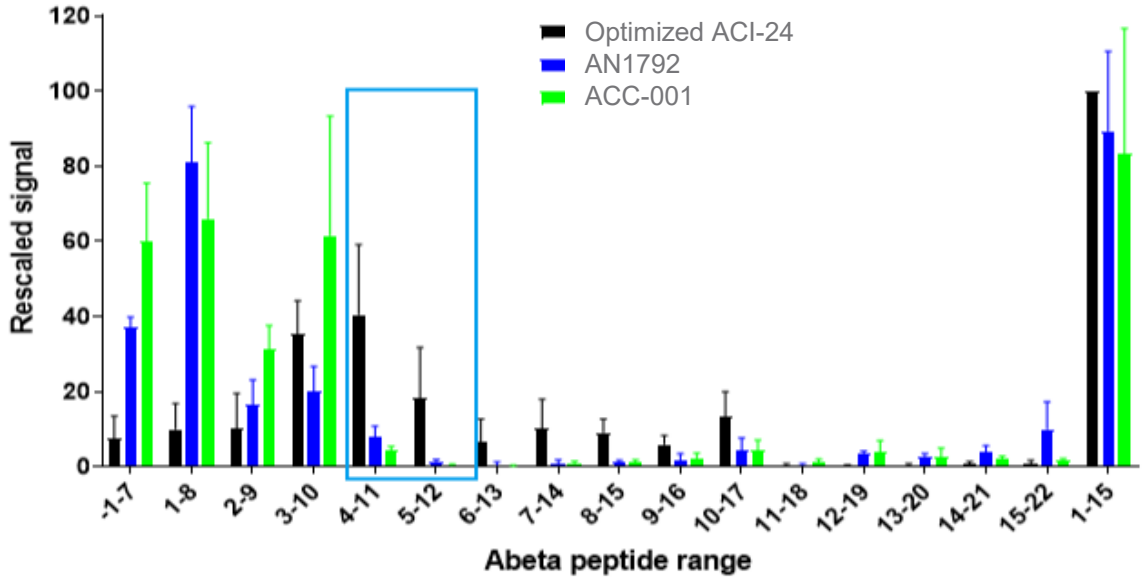
- Vaccination with optimized ACI-24 of NHPs produces stronger antibody binders with time reflecting affinity maturation of the polyclonal response

# Optimized ACI-24: Unique polyclonal Ab profile as compared to other clinically tested Abeta vaccines post vaccination of NHPs

**Serum IgG levels binding to:**




**Epitope mapping**



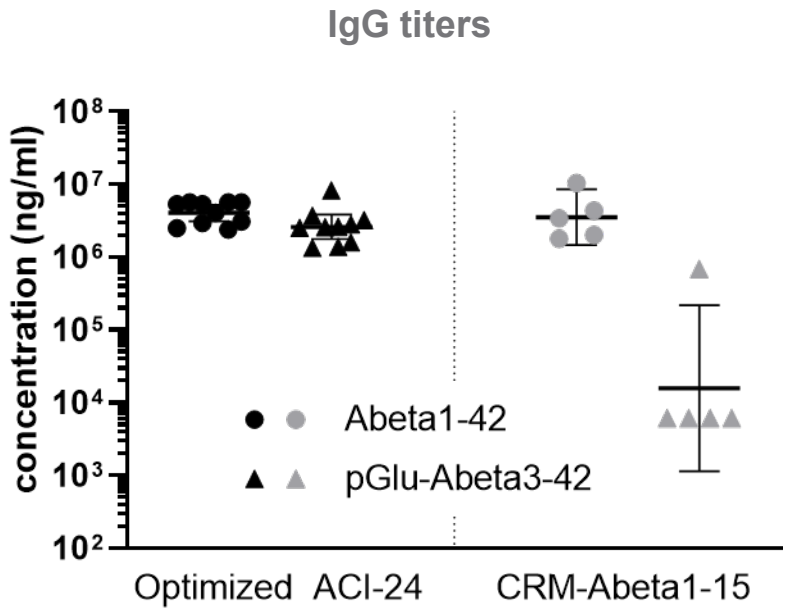

Ref.: M. Vukicevic, et al., Brain Comm, 2022

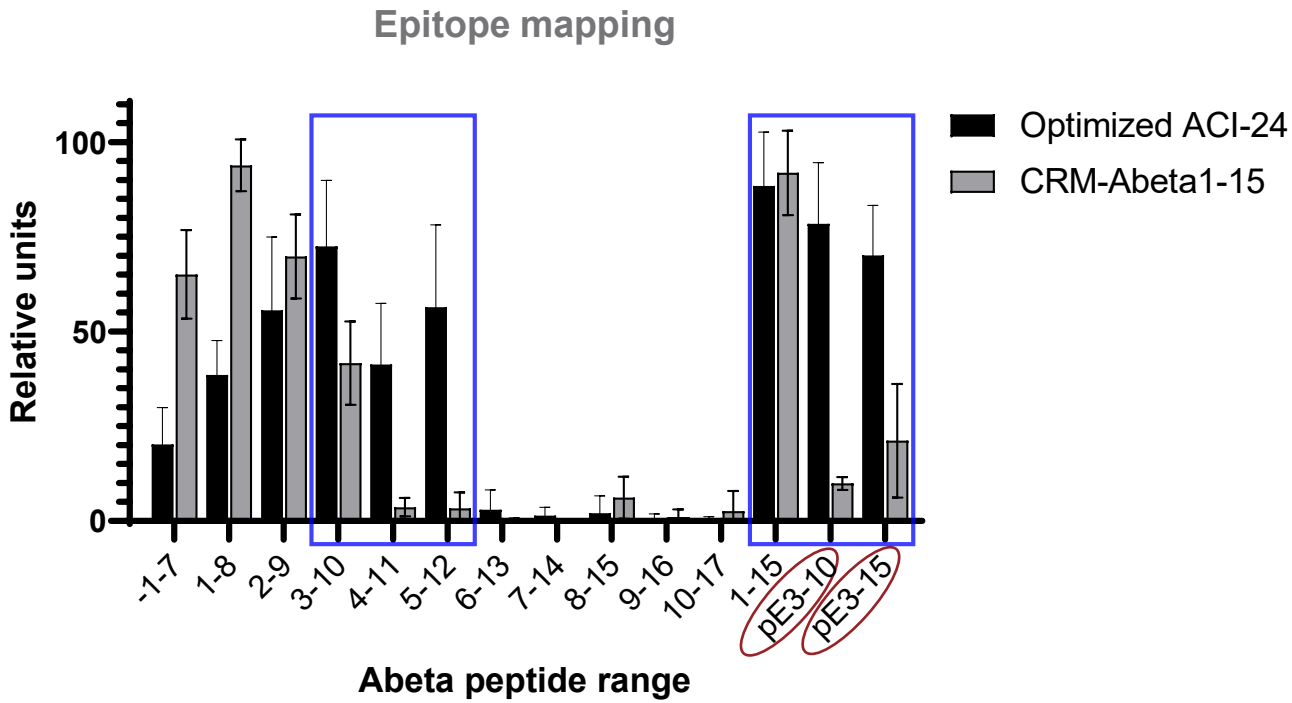
- Optimized ACI-24-induced antibodies recognize a broad range of N-terminal Abeta epitopes
- Superior binding to truncated pyroGlu Abeta that may result in amyloid plaque clearance and neuroprotection

(1) synthetic full-length Aβ peptide with QS-21 adjuvant; (2) vanutide cridificar (an investigational anti-Abeta therapeutic vaccine); (3) Pyroglutamate; NHP: non-human primates

# Presentation of Abeta 1-15 by liposome vs CRM formulations

## Superior coverage of epitopes including for pyroGlu Abeta by optimized ACI-24



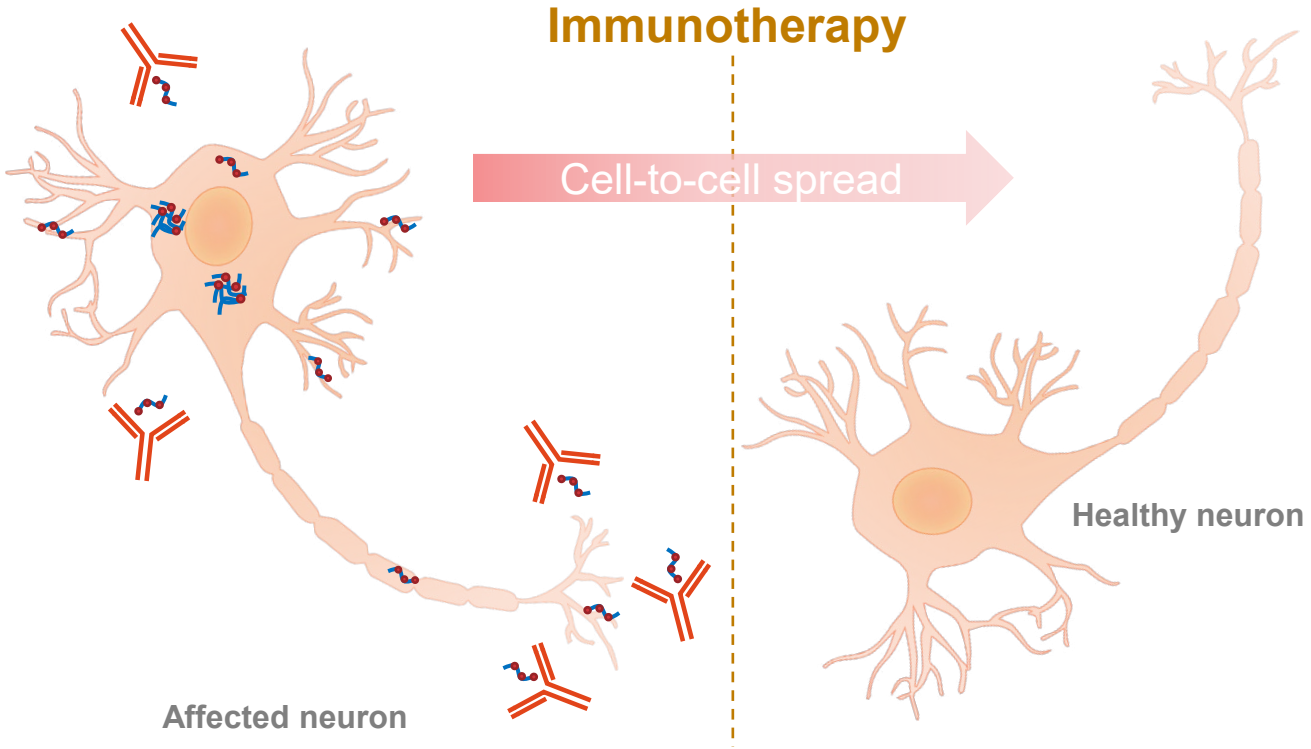




Study performed in C57Bl/l6 mice; CRM, cross-reactive material from mutated form of diptheria toxin

- Both the liposomal and CRM carriers able to present the Abeta 1-15 peptide to induce anti-Abeta IgG titers
- However, presentation of the Abeta 1-15 peptide on the liposome formulation generates a strong and homogeneous response to pGlu-Abeta

# Active immunization for early intervention in Alzheimer's Disease

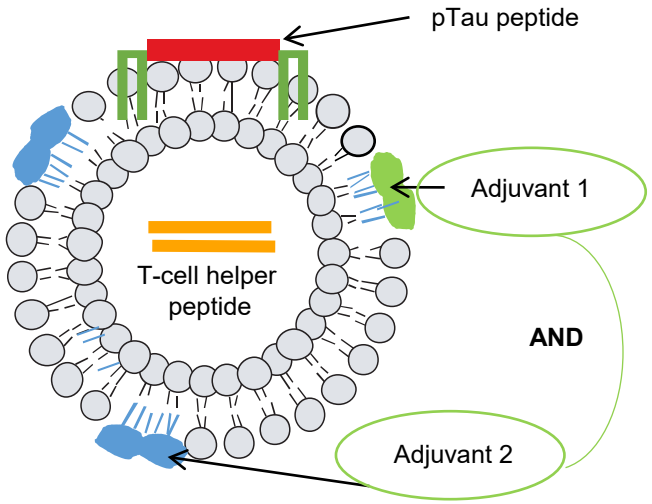
## Priming the immune system to prevent aggregation and accumulation of Tau

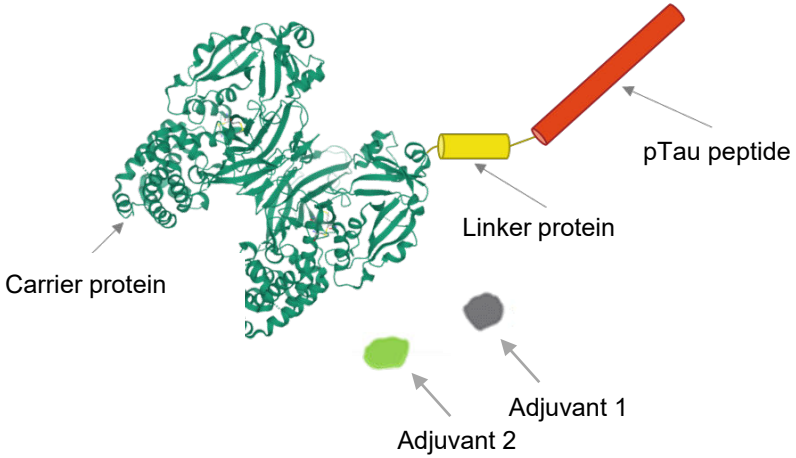



- Antibodies selectively bind, trap and remove pathological Tau to prevent cell-to-cell spread
- Vaccines induce a target-specific, lasting and boostable polyclonal antibody response

# Next generation anti-phospho Tau (pTau) peptide vaccines

## Liposomal ACI-35.030 and conjugate JACI-35.054 vaccines



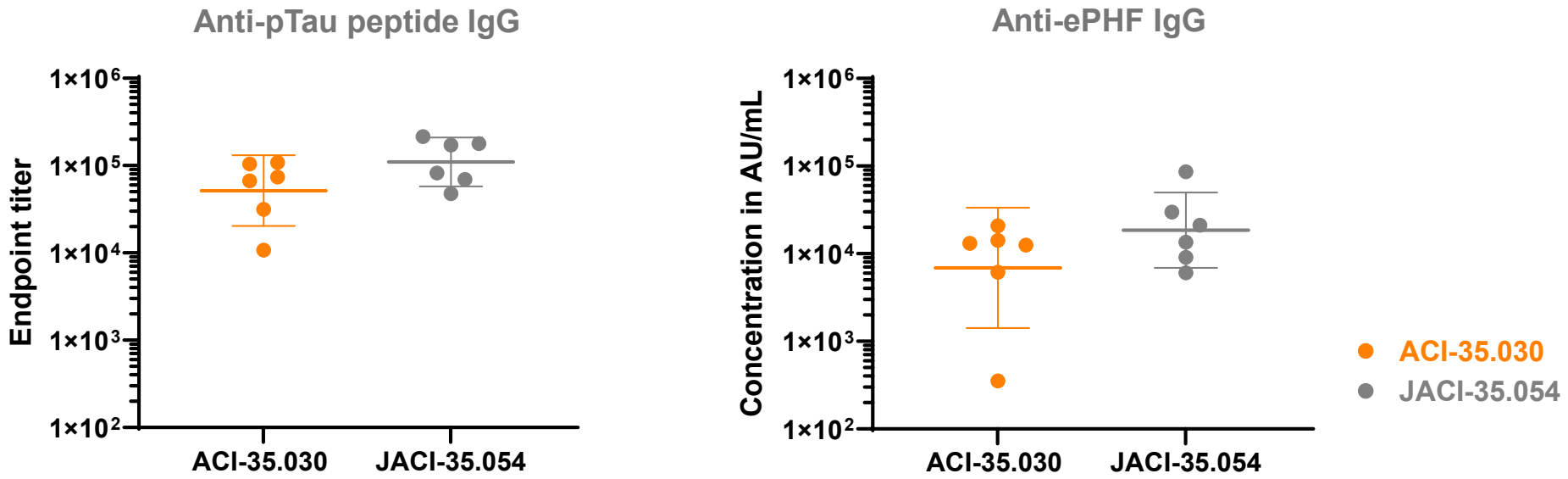

**SupraAntigen® liposomal ACI-35.030 vaccine**

**Carrier protein-conjugated JACI-35.054 vaccine**

- Targeting Tau with pTau peptide in two vaccine formulations:
  - Liposome based ACI-35.030
  - Carrier protein based JACI-35.054

# Liposomal ACI-35.030 and conjugate JACI-35.054

## Strong Ab response binding the antigenic pTau peptide and pathological brain-derived ePHF in NHPs



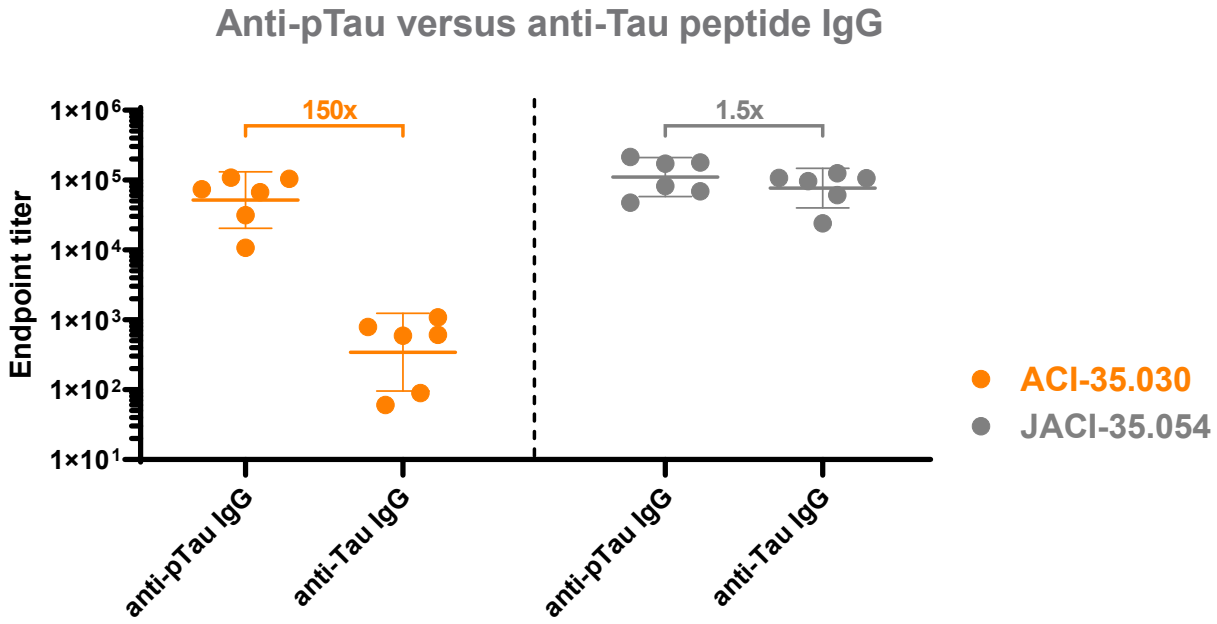

NHP: non-human primates
Immunization schedule: Day 1, 29, 85 and 169
Analysis: Day 190 (3 weeks after the 4th immunization)

ePHF, enriched paired helical filaments

- ACI-35.030 liposomal vaccine and JACI-35.054 conjugate vaccine induce similar IgG titers towards pTau peptide as well as the pathological human AD brain-derived form of Tau (ePHF)

# Liposomal ACI-35.030 and conjugate JACI-35.054

## PhosphoTau-preference of antibodies for induced by ACI-35.030 in NHPs




NHP: non-human primates
Immunization schedule: Day 1, 29, 85 and 169
Analysis: Day 190 (3 weeks after the 4th immunization)

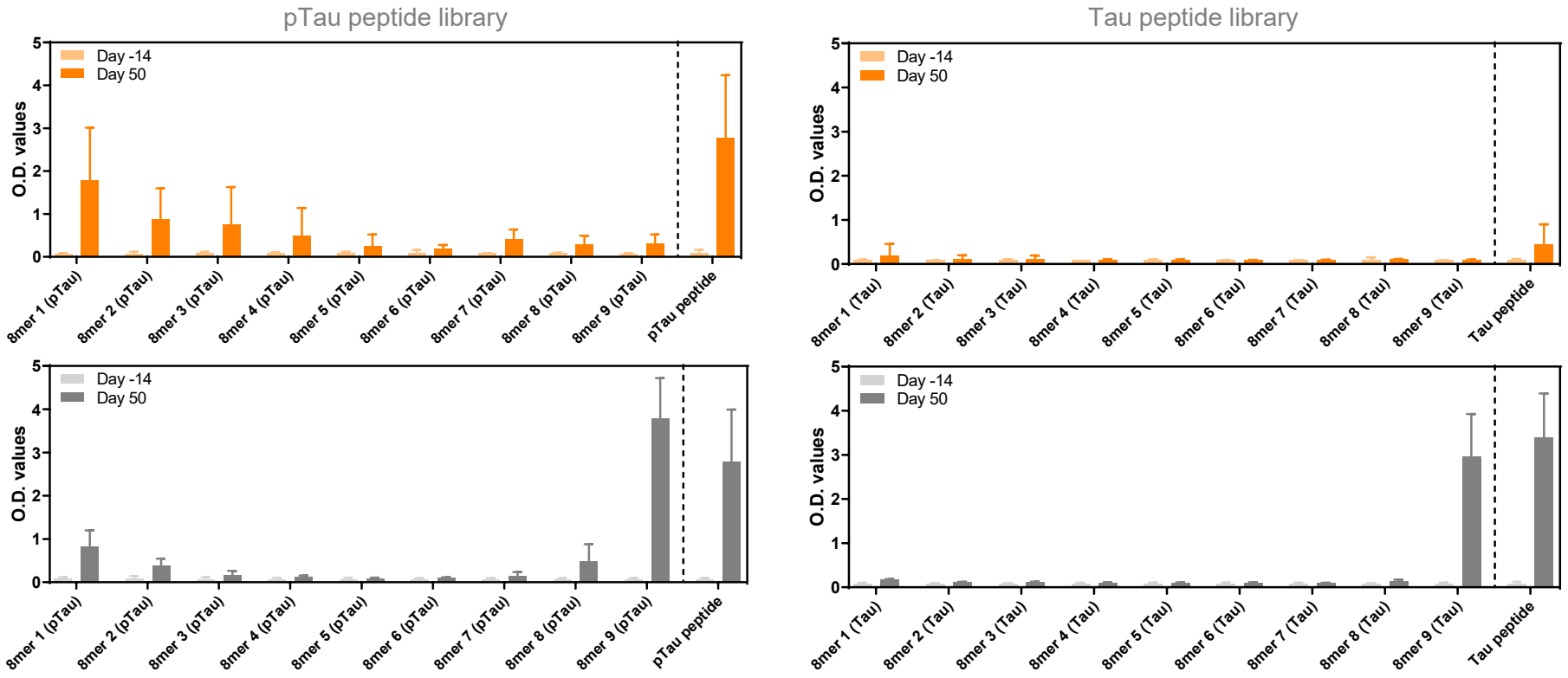
- ACI-35.030 vaccine induces antibodies with a strong specificity towards the pTau peptide with a very low to absent binding to the non-pTau peptide
- JACI-35.054 induces antibodies binding similarly to the pTau and non-pTau peptides

# Characterizing the epitope coverage

## Level of phospho-specific binders differentiates ACI-35.030 and JACI-35.054 in NHPs

ACI-35.030

JACI-35.054

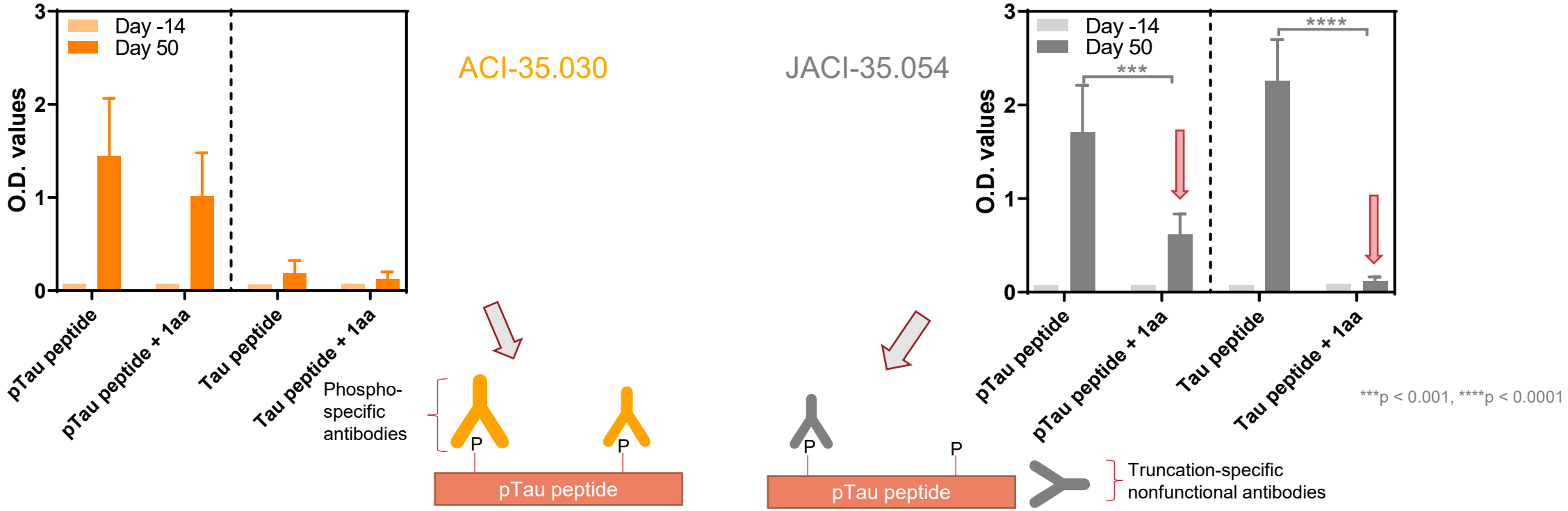



NHP: non-human primates
Immunization schedule: Day 1 and 29
Analysis: Day 50 (3 weeks after the 2nd immunization)

- ACI-35.030 vaccine induces wide range of Abs covering the pTau antigenic sequence
- JACI-35.054 induces antibodies mostly binding to the very C-terminus of the peptide in a non-phospho-specific manner

# Characterizing further epitope coverage

## Truncation specific antibodies differentiate ACI-35.030 and JACI-35.054 in NHPs

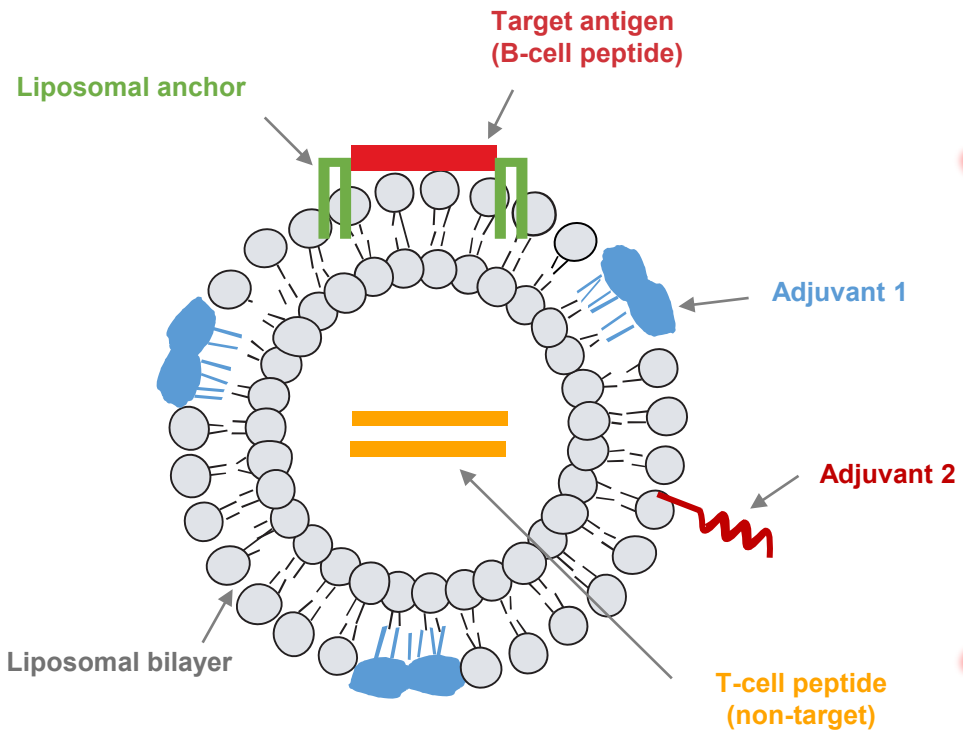



NHP: non-human primates; aa: amino acid
Analysis: Day 50 (3 weeks after the 2nd immunization)

- Addition of one amino acid to the antigenic peptide does not change the binding of ACI-35.030 induced Abs
- Addition of one amino acid to the antigenic peptide decreases the binding of JACI-35.054 induced Abs, suggesting the abundance of truncation-specific irrelevant antibodies

# Disruptive potential of SupraAntigen® based vaccines

## Safe, efficient and patient convenient dosing vaccines to prevent and treat NDD




**Drives the characteristics of an effective immune response to fight disease**

| | |
|---|---|
| Immunogenicity | ++++ |
| Target specificity | ++++[1] |
| Conformation specificity | +++ |
| Avidity increase over time | +++ |
| Sustainability of response | +++ |
| Boosting | +++ |
| Class switching IgM to IgG | +++ |
| Evidence of memory B cells | +++ |

- Optimized ACI-24 induces a unique polyclonal Ab profile, binding to the pathological oligomers and pyroglutamate species of Abeta
- ACI-35.030 generates a polyclonal antibody response with specificity towards phosphoTau

(1) Increases over time

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# AC Immune

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

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