ACI-35.030, a novel anti-phospho Tau vaccine for the treatment of Alzheimer's Disease: Interim data on safety, tolerability and immunogenicity

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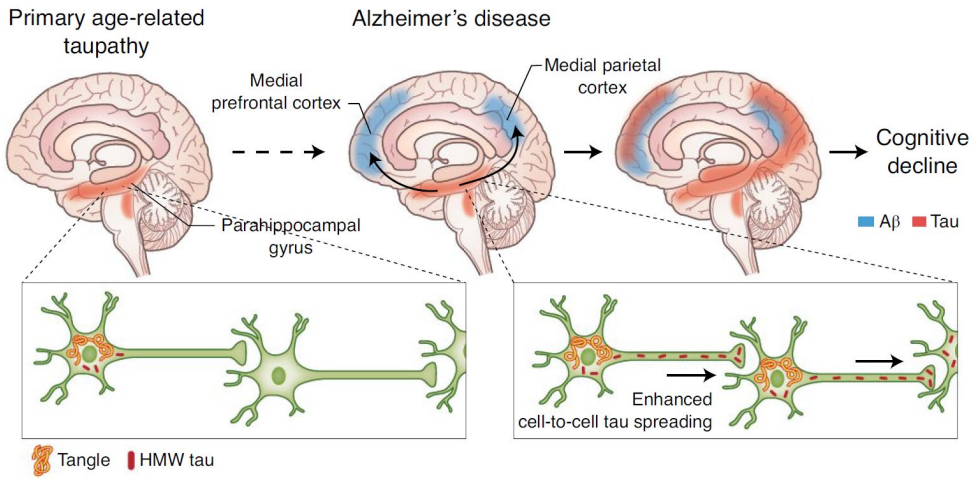
Conflict of interest disclosure

Johannes Streffer is an employee of AC Immune entitled to stock options.

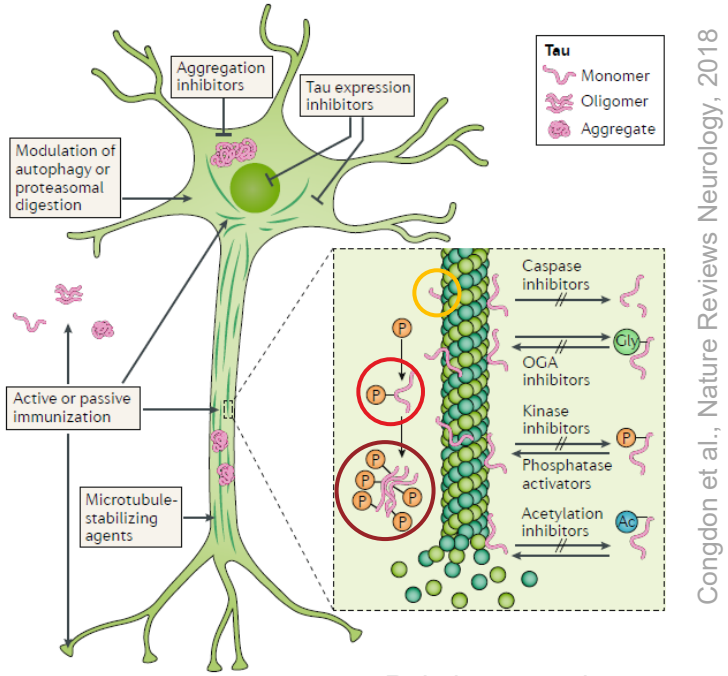
Aβ plaques accelerate Tau spreading and Tau-related cognitive decline in human AD

Synergy between amyloid-β and tau in Alzheimer's disease

Marc Aurel Busche[1] ✉ and Bradley T. Hyman[2]



Busche et al., Nature Neuroscience, 2020



Congdon et al., Nature Reviews Neurology, 2018

Relation to study measures:
Antibodies against:
Non-phosphorylated Tau protein
Phosphorylated Tau protein
Enriched Paired Helical Filaments (ePHF)

- Targeting Tau is well validated by neuro-pathology and pre-clinical results
- Tau hyperphosphorylates and aggregates in Alzheimer's disease

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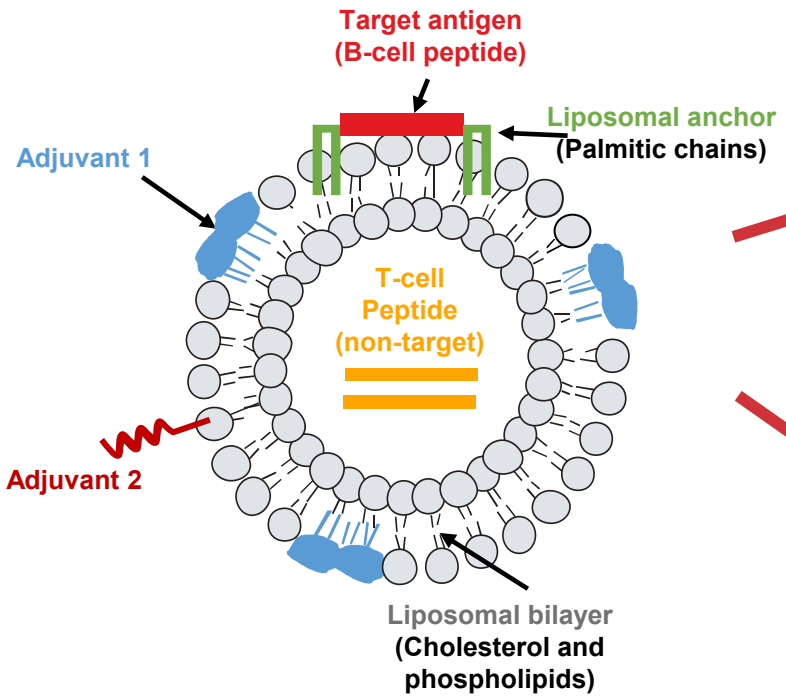
Targeting Amyloid Plaques and Pathological Tau with Immunotherapy

Biologicals: Vaccines and monoclonal antibodies

Proprietary SupraAntigen® platform

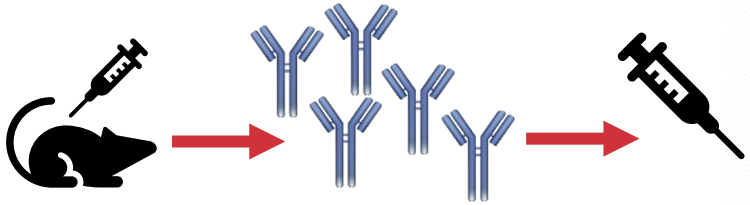


Adjuvants and other liposome components are optimized for each specific application

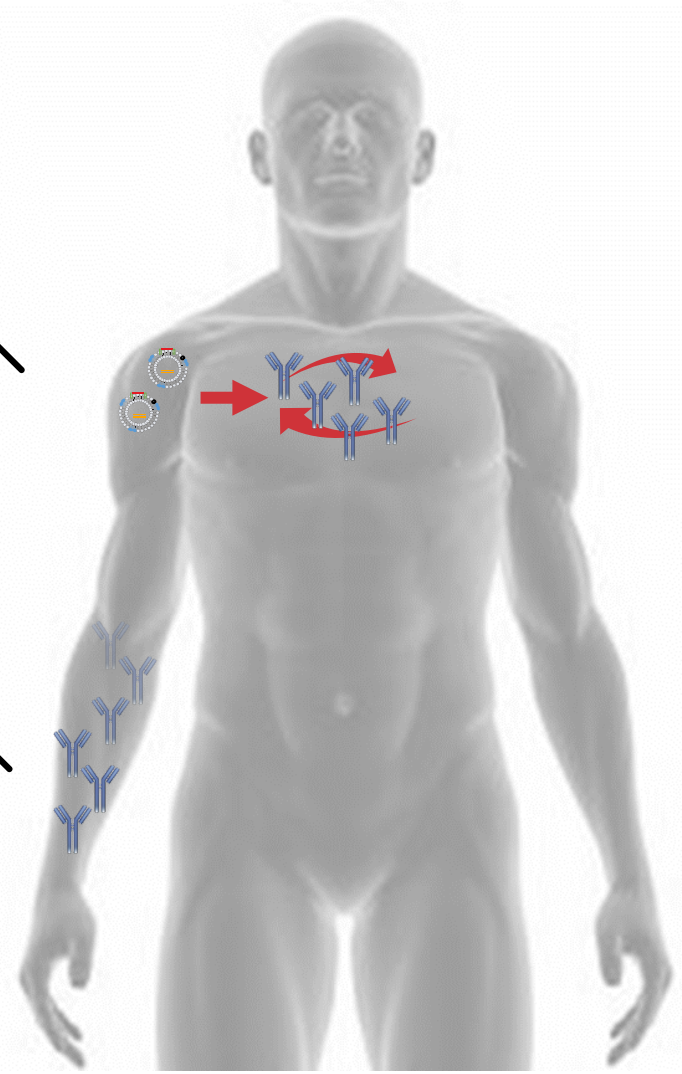
SupraAntigen®-V

Vaccines: Active immunization
(immune system produces antibodies)

SupraAntigen®-A



Antibodies: Passive immunization
(external antibody production)

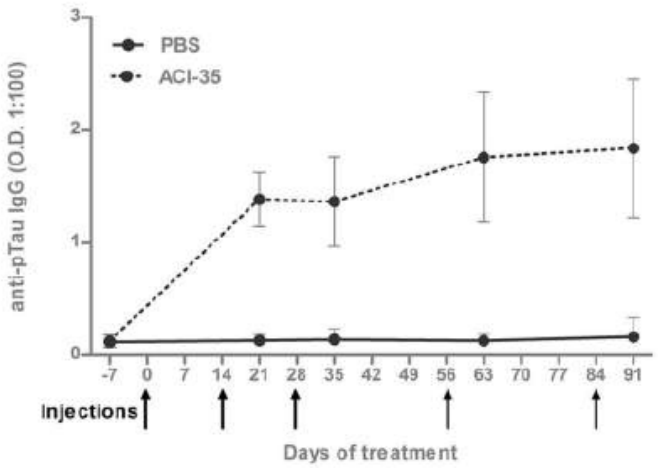


ACI-35 (1st generation – pre-clinical)

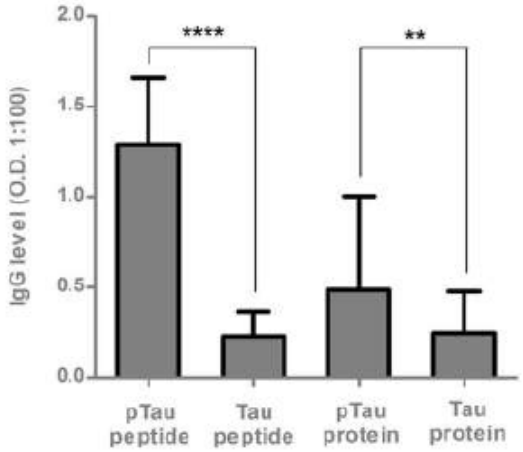
Strong phospho-Tau specific antibody response in pre-clinical species, with staining of pathological Tau aggregates on transgenic mouse brain sections

ACI-35 in Tau.P301L mice

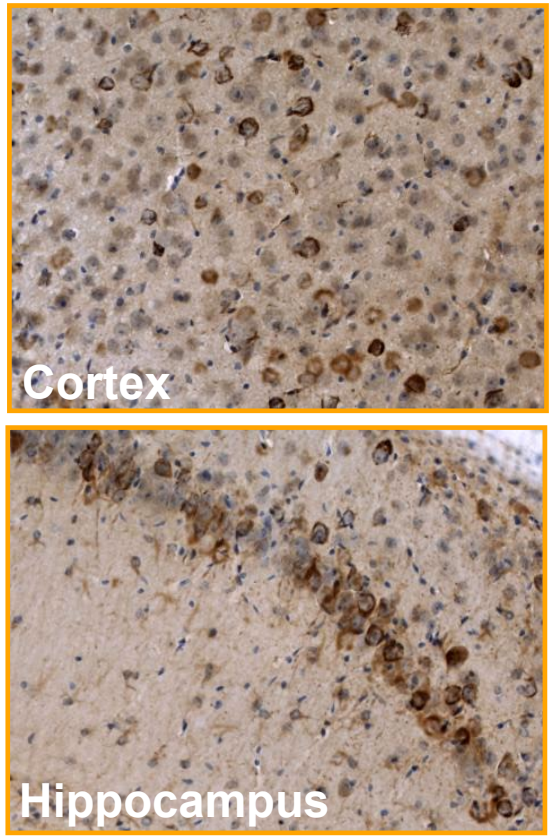
pTau IgG titers



pTau specificity (d35)



Taupir Staining (d35)



Theunis et al., PlosONE, 2013

ACI-35 (1st generation – clinical)

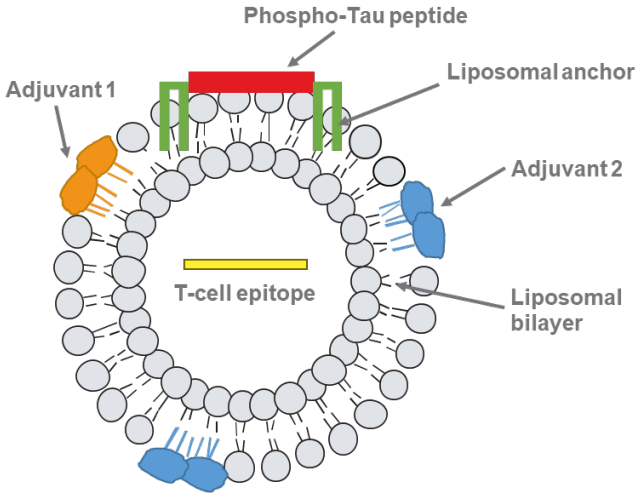
Phase 1b study in Alzheimer's disease

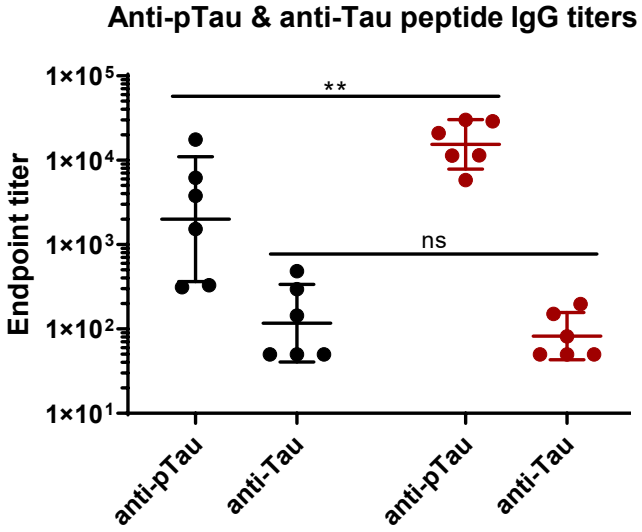
- Double-blind, randomized, placebo-controlled study for the safety, tolerability and immunogenicity of ACI-35 in patients with mild to moderate Alzheimer's disease
  - Safe and well-tolerated at all doses and treatment regimens
  - Mild and self-limiting injection site reactions; no other treatment related adverse events observed
  - Rapid induction of a target-specific antibody response against phospho-Tau after the first injection
  - Limited boosting of anti-phospho-Tau responses

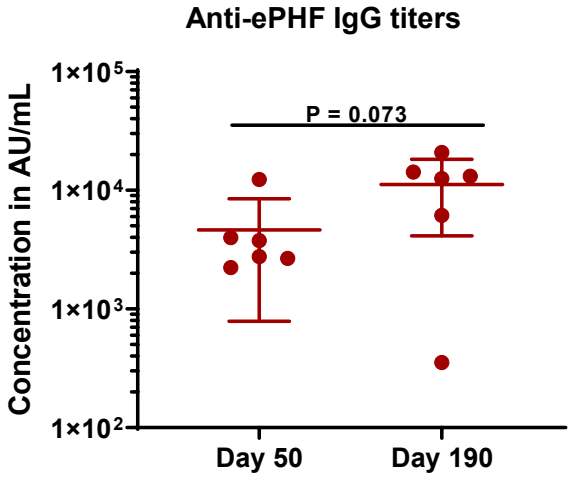
- Conclusion from ACI-35 first generation evaluation:
  Develop a 2nd generation vaccine with the aim to optimize the antibody response

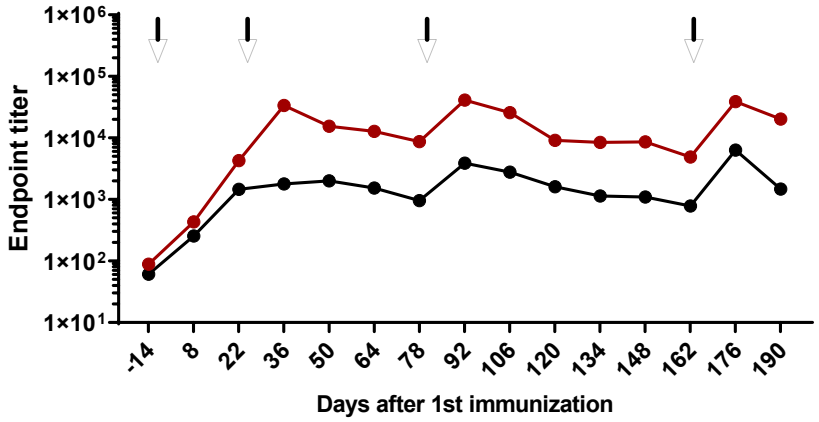
2nd generation of the anti-pTau vaccine: ACI-35.030

Addition of Tau independent T-cell epitope to increase immunogenicity in Rhesus monkeys









● 1st gen. ACI-35
● 2nd gen. ACI-35

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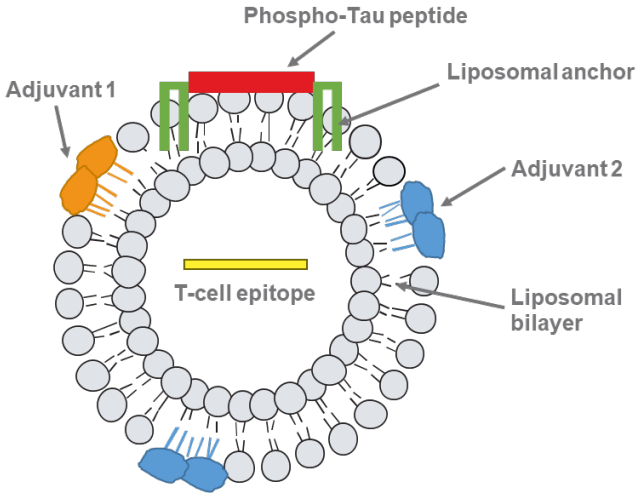
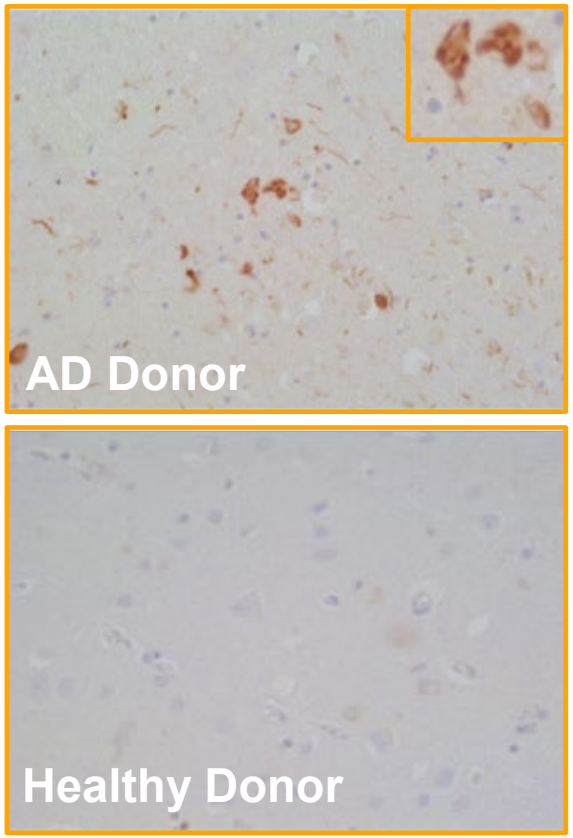
2nd generation of the anti-pTau vaccine: ACI-35.030

Addition of Tau independent T-cell epitope to increase immunogenicity in Rhesus monkeys



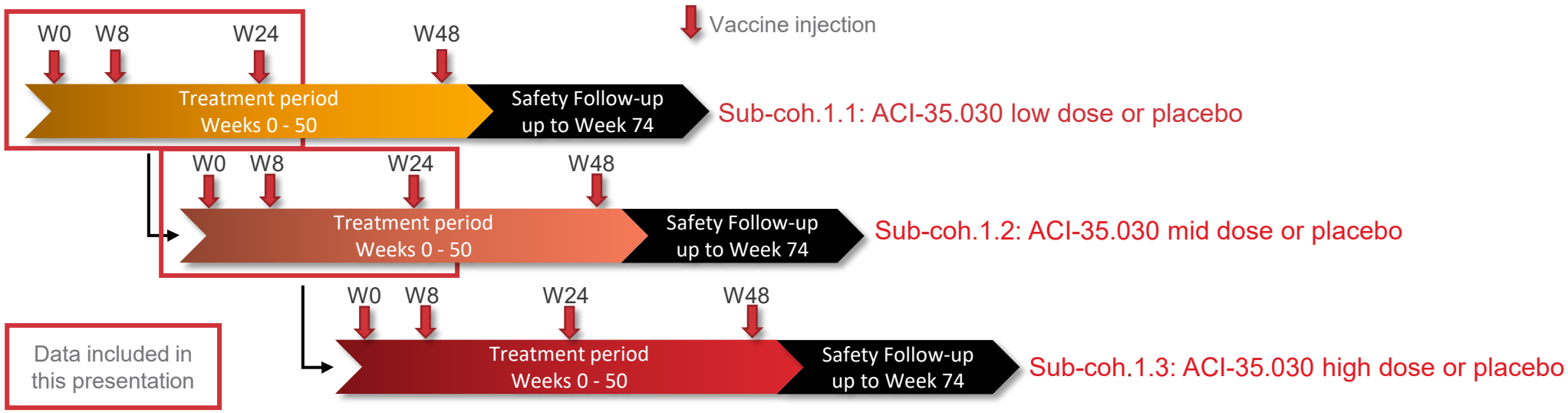
Immunostaining of Human cortical brain tissue



- Second generation ACI-35 results in Rhesus monkeys
  - Strong prime, boost and maintenance of antibody response in non-human primates
  - Phospho-Tau specific antibody response
  - Over time increase in IgG specific for pathological species (ePHF)
  - Strong staining of pathological Tau in human brain

Phase 1b/2a study ACI-35-1802

Study design for Cohort 1 (ACI-35.030 or placebo)



- Design features
  - Mild AD or MCI due to AD (NIA-AA criteria)
  - Sequential dose cohorts with escalating doses
  - 8 AD subjects per study sub-cohort (active/placebo ratio: 3:1)
  - Sub-cohorts can be expanded to a total of 24 AD subjects
- Primary Objectives
  - Safety and tolerability
  - Immunogenicity
- Study status
  - Study sub-cohorts 1.1 to 1.3 are fully recruited
  - Sub-cohort 1.2 is in expansion to a total of 24 AD subjects

(1) ClinicalTrials.gov Identifier: NCT04445831

Good safety and tolerability

Sub-cohort 1.1 & 1.2 (Data cut end of September 2021)

- ACI-35.030 was safe and well tolerated with no study vaccine-related safety concerns observed to date
- No withdrawals due to adverse events
- No adverse events of severe intensity
- Two SAEs considered unlikely related to the study vaccine reported in the study to date in the first 2 sub-cohorts
  - episode of acute diverticulitis
  - sick sinus syndrome (requiring pacemaker)
- No CNS inflammation or other significant changes reported on MRI
- Two safety unrelated study withdrawals in sub-cohort 1.1
  - resulting study data from cohort 1.1 can only be shown until week 10 (2 weeks after 2nd vaccination) to keep study blind

	Sub-cohort 1.1	Sub-cohort 1.2
Age (Years) {Range}	65,3 {61-75}	65 {51-71}
Sex (F/M)	5/3	4/4
MMSE (Mean) {Range}	26,3 {22/29}	26,4 {24/29}
Ethnicity	All participants white non-hispanic	

High response rate as early as 2 weeks post first vaccination

	Sub-cohort 1.1		Sub-cohort 1.2		
	Week 2	Week 10	Week 2	Week 10	Week 26
Anti-Tau IgG	83.3%	33.3%	83.3%	100%	50%
Anti-pTau IgG	100%	100%	100%	100%	100%
Anti-ePHF IgG	66.7%	83.3%	100%	100%	100%

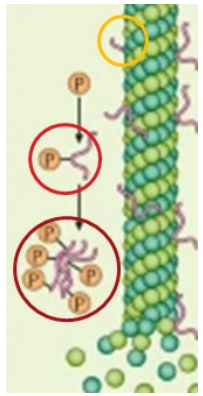
- High responder rates after first and all following vaccinations
- 100% response rate for pathological (ePHF) and phosphorylated Tau at the higher dose
- Rapid class-switching observed from IgM to IgG, with indication for memory building

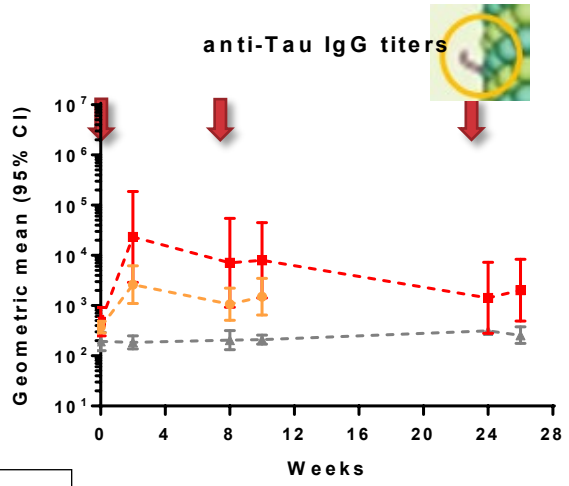
Prespecified responder definitions: Responders were defined as higher than a pretreatment value multiplied by a threshold factor (>~2x)

ACI-35.030 induces potent antibody response with preference for pathological species

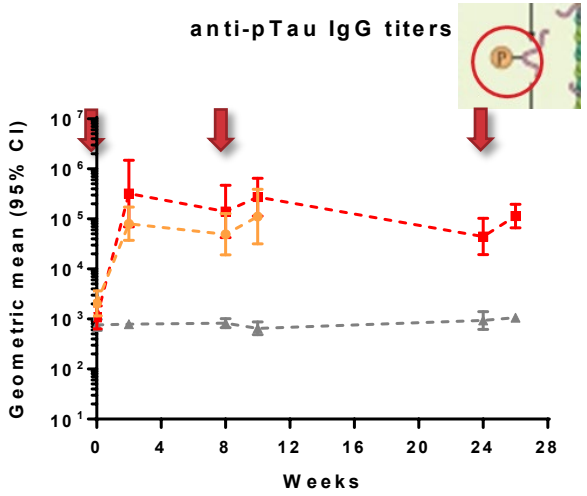
Fast, high, phospho-Tau-specific, and boost-able antibody response

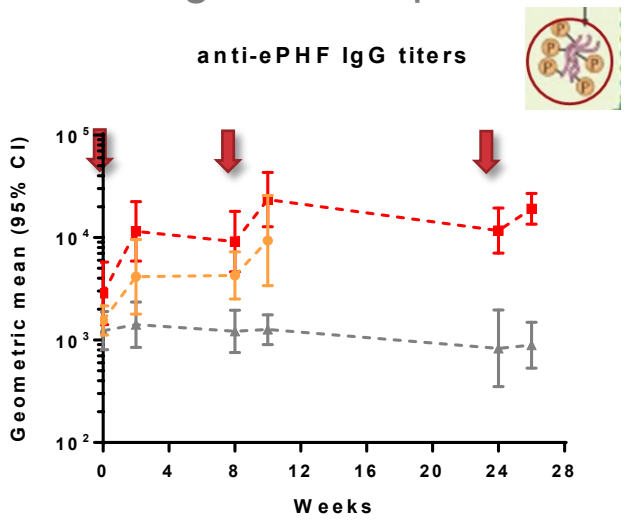
Non-Phosphorylated Tau





Phosphorylated & Pathological Tau species





Vaccine injection

Low dose
Mid dose
Placebo

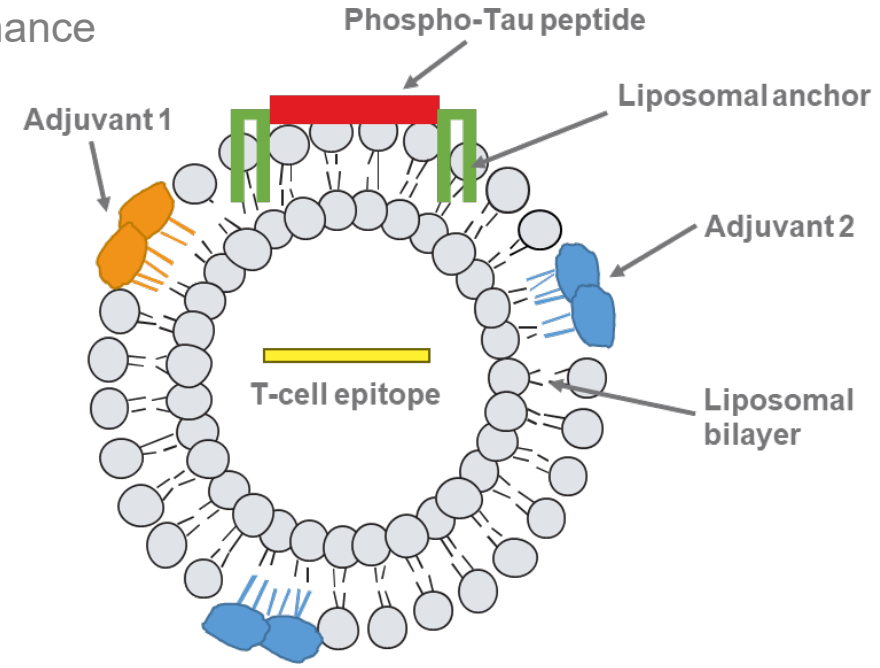
- Potent antibody response to all measured Tau species
- Developing preference for pathological Tau
  - Boostable anti-ePHF IgG
  - Very high anti-pTau IgG titers observed following injection
  - Maintained anti-pTau IgG
  - Over time lower anti-Tau IgG

Safe and potent anti-Tau Vaccine

Optimized SupraAntigen® vaccine delivering superior results

- ACI-35 is a clinical stage Tau vaccine generating target/phospho-Tau-specific antibody response
- ACI-35 optimized formulation engages safely target-unrelated T-cells to enhance and maintain antibody response
- Strong translation of pre-clinical results in current clinical study seen with
  - Strong target specific immunogenicity
  - Sustainability and boosting of antibody response
  - High ePHF/confirmation specific antibodies
  - Early class switch from IgM to IgG with evidence for memory B cells

- **Robust immunogenicity and no safety concerns to date in humans**
- **Evidence for lasting immune response in the initial 26-week period supporting a disease prevention approach**



We want to thank the study participants, their families and caregivers for their participation and commitment, as well as all Investigators and Site personnel for their active participation and support.

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