ANTI-ABETA LIPOSOMAL VACCINE, ACI-24.060, RETAINS MEMORY IN AN AGGRESSIVE MOUSE MODEL OF ALZHEIMER'S DISEASE

Poster P0215 / #1422

Emma Fiorini, Chiara Babolin, Catherine Morici, Aurelie Guillaume Gentil, Fabiana Tione, Harishini Balachandiran, Maxime Ayer, Marie-Gabrielle Beuzelin, Rakel Carpintero, Stefania Rigotti, Andrea Pfeifer, Marie Kosco-Vilbois and Marija Vukicevic - AC Immune SA - Lausanne (Switzerland)

Introduction

ACI-24.060 is a Phase 2 clinical stage anti-Abeta active immunotherapy that, in preclinical studies, induces sustained antibody responses targeting pathological Abeta species (Vukicevic, 2022). Here, we report the ability of ACI-24.060 to maintain neuronal health using a cognitive test for learning and memory in the 5xFAD model of Alzheimer's disease.

SupraAntigen® platform

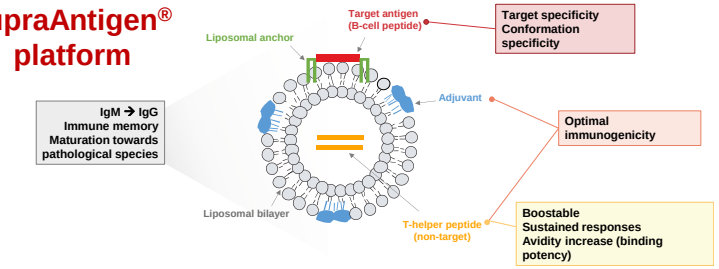


Figure 1: ACI-24.060 is an optimized liposomal SupraAntigen® vaccine formulation

ACI-24.060 induced a strong and sustained polyclonal response in 5xFAD mice

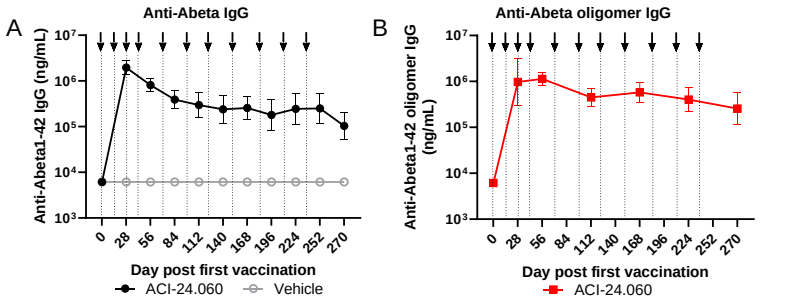
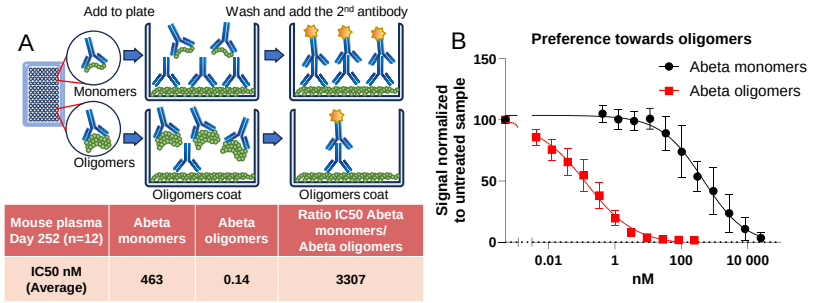


Figure 2: Mice received eleven injections with ACI-24.060 (8µg/dose) or vehicle over a period of 9 months (arrows indicate injections), starting at 1.5 month of age (n=15/group). A) Anti-Abeta and B) anti-Abeta oligomer IgG in mouse plasma (n=15/group) at predose and postdose. Data are shown as geometric mean with 95% confidence interval (CI).

ACI-24.060 induces antibodies with a 3-log preferential recognition of Abeta oligomers vs monomers



Mouse plasma Day 252 (n=12)	Abeta monomers	Abeta oligomers	Ratio IC50 Abeta monomers/ Abeta oligomers
IC50 nM (Average)	463	0.14	3307

Figure 3: A) Scheme of the assay set-up (Soderberg, 2022). B) Mouse plasma (n= 12) (collected after 11 injections with ACI-24.060) at 1/200 were incubated with increasing concentration of Abeta oligomers (squares) or monomers (circles). The signal in the presence of Abeta species is normalized to the untreated sample. IC50 was calculated and used to obtain the monomer vs oligomer ratio. Graph shows the mean inhibition of individual mice ±SD.

ACI-24.060 maintained both learning and memory capacities comparable to animals without disease

DAY	LEARNING TRIAL				PROBE TRIAL	Platform
	Trial 1	Trial 2	Trial 3	Trial 4		
1	SE	SW	NW	SW	-	NE
2	NW	SE	SW	NW	-	NE
3	SW	NW	SE	NW	-	NE
4	SE	SW	NW	SE	-	NE
5	-	-	-	-	SW	Removed

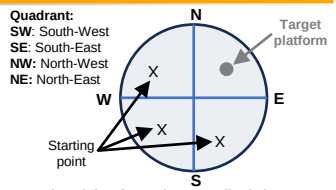


Figure 4: Set up of the Morris-Water Maze Test: Mice were trained for four days to find the hidden platform (learning trial, Day 1-4) , and then on the fifth day the platform was removed, and the memory capacity was assessed (probe trial, Day 5).

Learning capacity during training (learning trial)

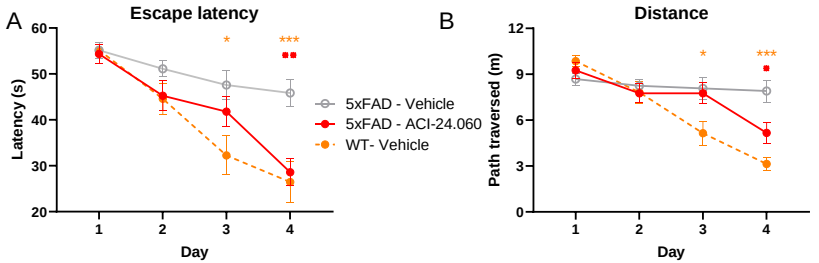


*Figure 5: A) Escape latency and B) swim distance in the Morris Water Maze (n=15/group) with wild-type (WT) or 5xFAD mice at the age of ~11 months. Results are shown as group means ± SEM. Statistics: Repeated measures two-way ANOVA followed by Bonferroni's multiple comparisons test, using vehicle treated 5xFAD mice as a reference group. *(5xFAD - Vehicle vs. WT- Vehicle) or *(5xFAD - Vehicle vs. 5xFAD- ACI-24.060). */* p<0.05, **p<0.05, ***/* * * p<0.001*

Post-training memory evaluation (probe trial)

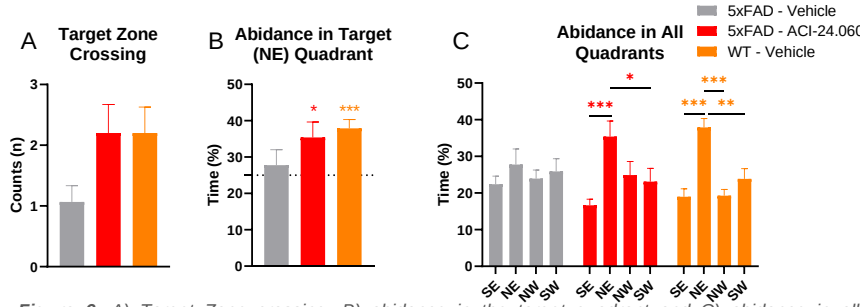


*Figure 6: A) Target Zone crossing, B) abidance in the target quadrant and C) abidance in all quadrants. Results are shown as group means ± SEM. Statistics: (A) Mann-Whitney tests; (B)One sample t-test against a random abidance in the target quadrant of 25%; (C) Two-way ANOVA followed by Bonferroni's multiple comparisons test (within each group). *p<0.05,**p<0.05, *** p<0.001*

Cognitive score of training and probe trial

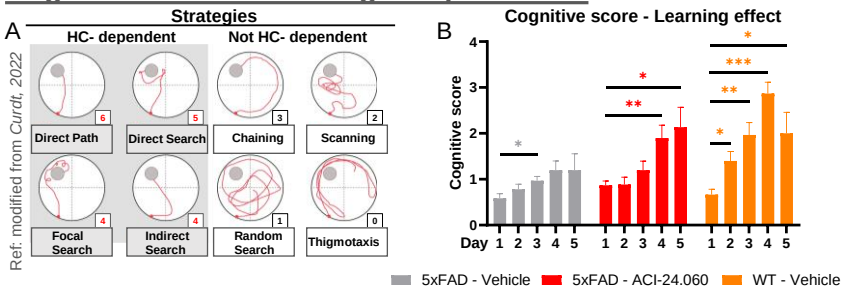


*Figure 7: A) Hippocampus (HC)-related cognitive scores in Water Maze test. B) Results are shown as group means ± SEM. Statistics: Repeated measures two-way ANOVA followed by Bonferroni's multiple comparisons test. * p<0.05, **p<0.05, *** p<0.001*

Conclusions

- ACI-24.060 induced antibody responses in an aggressive mouse model, 5xFAD, with robust and sustained titers against Abeta pathological oligomers
- ACI-24.060 immunization maintained:
  - ✓ Learning capacities at the levels of non-diseased animals
  - ✓ Memory capacities mirroring the performance of animals without disease
- The safety and efficacy of the ACI-24.060 vaccine is currently being evaluated in the clinical trial Abate (CT.gov # NCT05462106)