New Alzheimer models for drug screening based on improved human amyloid beta (1-42) oligomer preparations

Poster #54152

Julie Colin, **Ahmad Allouche**, Sophie Hidalgo, Estelle Lager, Sandrine Lemoine, Christophe Muller, Pascale Rozan, Jean-François Bisson, Nicolas Violle
ETAP-Lab, Vandœuvre-lès-Nancy, France. Email: a.allouche@etap-cell.com

Background

A growing body of literature suggests that amyloid beta oligomers (AβO) are the root cause of Alzheimer's disease (AD). These oligomeric forms are the predominant neurotoxic species in brains during the early stages of the disease and provide a target to treat AD. Oligomers show a high selectivity to synapses where they impair neuronal synaptic plasticity by disrupting both long-term potentiation and long-term depression. They also induce calcium dyshomeostasis, synapses deterioration, axonal dysfunction, neurogenesis impairment, oxidative stress, neuroinflammation and cell death.

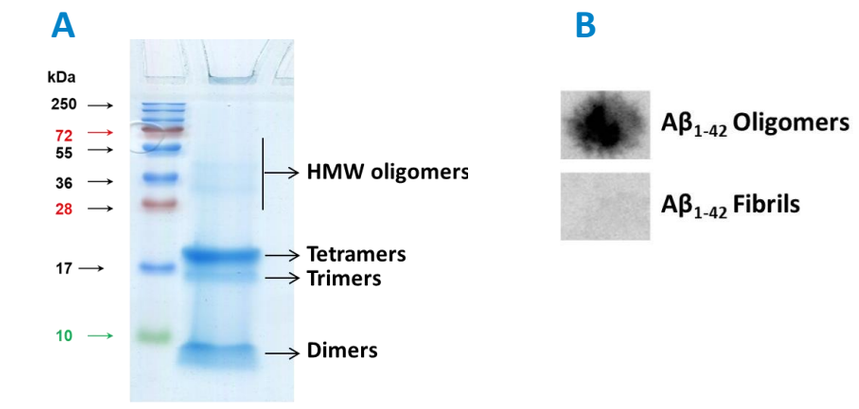
ETAP-Lab describes new translational *in vitro* and *in vivo* models of AD, induced by minute amount of in-house prepared of human AβO.

Methods

AβO were prepared from human $Aβ_{1-42}$ monomers. The oligomeric preparations were characterized by SDS-page and dot-plot assays. Rodent primary neurons were used to assess the neurotoxic activities of AβO *in vitro*. *In vivo*, aged wild-type mice (18-months-old) were used to test the effects of a single intracerebral injection of AβO (1 nM) on memory performances. The Novel Object Recognition (NOR) test was assessed on D5 to evaluate episodic memory performances and the Morris Water Maze (MWM) test was performed from D10 to D15 to evaluate spatial memory performances. Donepezil (DPZ) was used as a reference drug for pharmacological validation (1 mg/kg, i.p.). At the end of the study (D16), brain were sampled and used for evaluation of neuronal and astrocyte functions and apoptotic signal by ELISA in hippocampus.

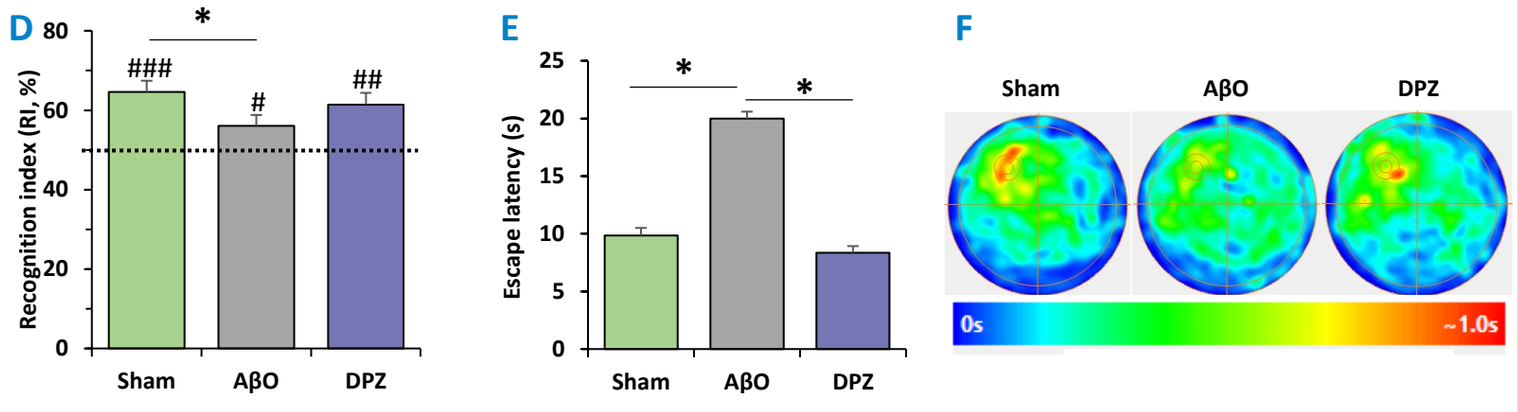
Key findings

Characterization of human β-amyloid$_{1-42}$ oligomers



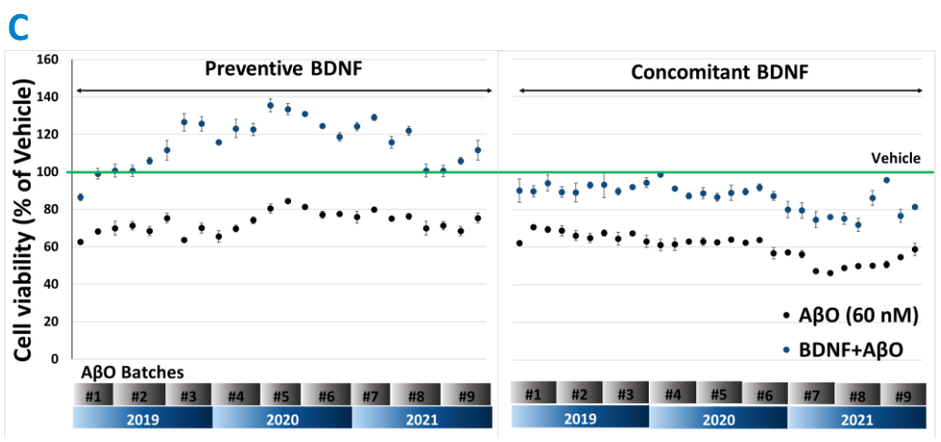
From beta-amyloid$_{1-42}$ monomers, ETAP-Lab generates soluble oligomers. They are stable for more than two years. These oligomers contain a mixture of dimers, trimers and tetramers, as well as traces of high molecular weight oligomers (**A**). AβO were detected using A11 antibody, which recognizes all types of oligomers, but not fibrils (**B**).

AβO induce cognitive decline in aged wild-type mice



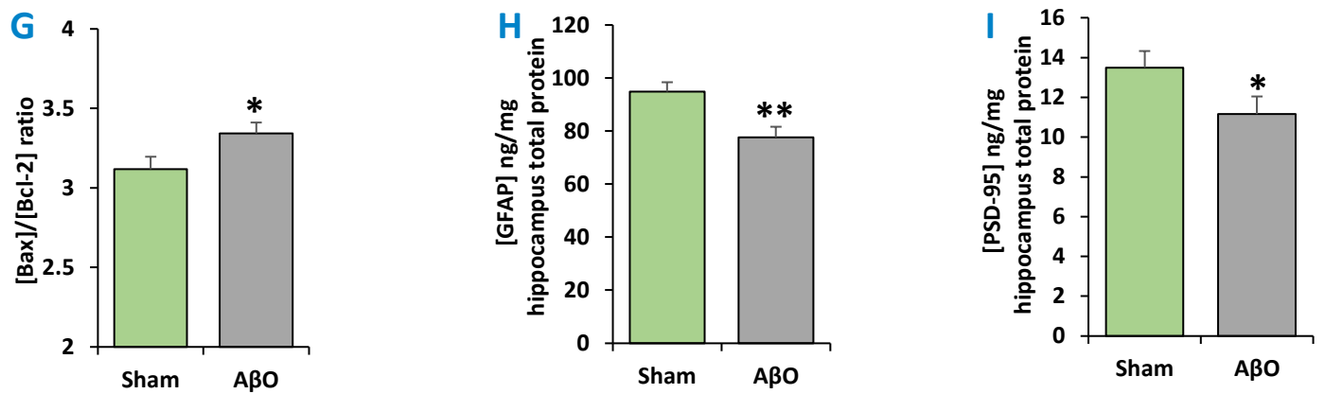
In vivo, a single intracerebral microinjection of $AβO_{1-42}$ in 18-month-old wild-type mice leads to a significant memory impairment. Learning deficits are observed in both episodic short-term memory (**D**, NOR) and spatial long-term memory (**E-F**, MWM) tests. DPZ partially alleviates episodic memory deficits (**D**) and totally reverses spatial memory deficits (**E-F**). *Statistical significance level : * P < 0.05 (1-way ANOVA followed by Tukey's test), # P < 0.05, ## P < 0.01, ### P < 0.001 (comparison to chance RI = 50%, t-student test), n = 14-17/group.*

AβO-induced neurotoxicity in rodent primary neurons



In vitro, AβO induce a reproducible neurotoxic effect on primary neurons (**C**). Moreover, brain-derived neurotrophic factor (BDNF) significantly attenuated AβO-induced neurotoxicity in each experiment.

AβO promote neuronal apoptosis and induce synaptic loss and astrocyte atrophy



In hippocampus, AβO promote neuronal apoptosis by disrupting pro- and anti-apoptotic signaling (**G**), induce a decline in synaptic function (**H**) and functional alterations in astrocytes (**I**). GFAP reduction is likely related to astrocyte atrophy and contributes to synaptic deficit during early stages of AD. Further investigations of neuronal and astrocyte functions are in progress. *Statistical significance level : * P < 0.05, ** P < 0.01 (Mann-Whitney U test), n = 14-17/group.*

Conclusions

- Human AβO produced by ETAP-Lab remain soluble and stable for more than two years.
- AβO are well characterized and induce a significant neurotoxicity in rodent primary neurons, which is reversed by reference compound (BNDF).
- In aged mice, a single intracerebral injection of AβO results in dramatic impairment of cognitive functions, disruption pro- and anti-apoptotic signaling and synaptic impairment.
- This non-inherited AD model is a new tool for preclinical testing of both disease modifying and symptomatic drugs.
- ETAP-Lab's *in vitro* and *in vivo* models are also valuable to study the mechanisms underlying AD.

Contact

ETAP-Lab
etap-lab.com
www.etap-lab.com
contact@etap-lab.com
+33 (0) 383 444 635
13 rue du bois de la Champelle,
54500 Vandœuvre-lès-Nancy, FRANCE
Follow us

Grand Est ALSACE CHAMPAGNE-ARDENNE LORRAINE

This project is co-financed by the "Region Grand-Est" and the European Union through the operational programme "FEDER-FSE Lorraine et Massif des Vosges 2014-2020".

UNION EUROPÉENNE
Fonds Européen de Développement Régional