INTRODUCTION
Pathological hyperphosphorylation and aggregation of Tau is observed in Alzheimer’s disease (AD). The toxic role of amyloid β peptide (Aβ) has now shifted from insoluble Aβ fibrils to smaller, soluble oligomeric Aβ aggregates. Aβ oligomers (AβO) promote hyperphosphorylation of Tau mainly through the GSK-3β (AT8 and AT100), which directly participates in the neurodegenerative process. In addition, glutamatergic system, and in particular NMDA receptors, is a key player in the neurotoxicity observed in AD and is involved in one part to the AβO toxicity. DAPK1 (Death-Associated Protein Kinase 1) is overexpressed in brains of AD patients. DAPK1 is known to phosphorylate Tau protein on different sites, such as Thr231 and Ser262. The effects of a DAPK1 inhibitor (CAS 315694-89-4, 100 nM) on neuronal survival and on hyperphosphorylation of Tau protein were investigated in two in vitro AD models consisting in primary cortical neurons injured with glutamate or AβO oligomers.

RESULTS
Hyperphosphorylation of Tau after AβO and glutamate injuries

Inhibition of DAPK1-mediated Tau phosphorylation is neuroprotective

CONCLUSIONS
- AβO-injury induced a large hyperphosphorylation of Tau protein on different epitopes, mediated by GSK3β (AT100) as well as DAPK1 (Thr231; Ser262).
- Glutamate-excitotoxicity increased the phosphorylation of Tau protein on AT100, but not on the site phosphorylated by DAPK1 (Thr231; Ser262).
- DAPK1 inhibition (in neurons stressed by AβO) decreased the phosphorylation of Tau on Thr231, partially on Ser262 and surprisingly on AT100 (Thr212, Ser214).
- DAPK1 inhibition delayed neurite network loss but did not show any significant effect on the survival of cortical neurons.
- These results suggest that DAPK1-mediated phosphorylation participates in the loss of neuronal connectivity in AD.