In silico Tau aggregates as tool for design and synthesis of aggregation disruptors related to Alzheimer's Disease

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Alzheimer's disease is a slow neuronal degeneration characterized by short-term memory troubles, executive performance disruptions and time and space orientation function disturbance. Brain study of patients with Alzheimer's disease has shown two types of damages: amyloid plaques and neurofibrillary tangles. Each of those two types of lesions is associated to one protein compound: beta-amyloid peptide (Aβ) for senile (amyloid) plaques and hyperphosphorylated tau protein for neurofibrillary tangles. For both of these proteins, key-peptide sequences were identified as responsible for early oligomerization initiating the whole amyloidogenic process [1,2]. In this process, these peptides shape in a beta sheet structuration. We are aiming to design and synthetize small molecules as protein-protein interaction disruptors in order to prevent oligomerization.

The present study was initiated by a conformational analysis of the Tau key peptide sequences implied in aggregation. Various aggregates were built (one example is shown on Figure1), their stabilities were assessed through Molecular Dynamic (MD) simulations and the analyses of intra- and intermolecular interaction in various aggregate cores were carried out and will be presented. Furthermore, MD simulations of Tau aggregates with palmatine, a Tau aggregation disruptor [3], were launched and mechanisms of aggregation disruption will be proposed.

In parallel, similarity screening of our in-house chemical library [4] based on palmatine scaffold and *in vitro* tests made as a part of collaboration with Bari University provided 40 scaffolds as starting points for rational design of abiotic foldamers that could disturb the interactions between amyloid fibrils.

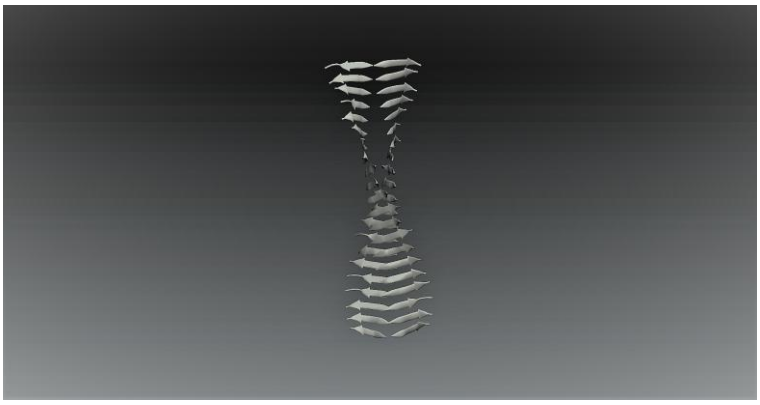

Figure 1. Average fibrillar structure of one Tau protein hexapeptide implied in Tau aggregation

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