Age-modified forms of Amyloid-? as initiator of Alzheimer Disease pathogenesis and mediator of A?-tau interaction: a study in a Drosophila model and A? immunized human Alzheimer patients

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Age-modified forms of Amyloid-? as initiator of Alzheimer Disease pathogenesis and mediator of A?-tau interaction: a study in a Drosophila model and A? immunized human Alzheimer patients

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Research Abstract
Alzheimer Disease (AD) is the commonest form of dementia, with ageing as the main risk factor. There are currently over 6 million people with dementia in the European Union (EU). The increasingly ageing population makes AD an economic and social burden for our society, thus investigating the pathological mechanisms of AD and the characterization of the pharmacological targets are research priorities. Aggregation of amyloid-Beta (A?), upstream of tau phosphorylation, is considered a driving force in AD pathogenesis, and the major target of the clinical trials of immunotherapy. The first clinical trial at Southampton University (UoS) showed A? removal but also reduced phospho-tau, supporting a link between these proteins. Similar evidence emerged in bigenic tau/A? Drosophila, a neurodegeneration model. During ageing in humans, the molecules of AD pathogenesis undergo ageing processes resulting in amino acid modifications that influence protein folding, functionality and interactions. Specially, pyroglutamate-modi?ed A? (pEA?) seems to be a key participant in AD pathology. Accordingly, the identification of markers of protein ageing is important to comprehend AD pathogenesis with relevance in therapies. Indeed, A? immunotherapy did not improve the cognition in the treated patients, potentially due to the absence of clearance of aged-modified A? implicated in pathological pathways. I propose to exploit the bigenic tau/A? drosophila to determine if pEA? increases with ageing, driving AD pathogenesis; and whether pEA? is the major A? form mediating A?/tau interaction. Taking advantage of the unique cohort of human unimmunized and immunized AD brains at UoS, I will investigate if pEA? formation and its interaction with tau have been modified by A? immunotherapy. The results will expand the A? characterization as a pharmacological target, and support the rational design of a second generation of “A? immunotherapies”. This project sustains the EU strategies to tackle AD.

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