Molecular basis of successful therapies to delay progression to Alzheimer's disease.

S-01.5-1

J. Viña[I], C. Borrás[II]

[I]FACULTAT DE MEDICINA. DPTO. DE FISIOLOGÍA, Valencia, Spain, [II]University of Valencia. Depart. of Physiology Faculty of Medicine., Valencia, Spain

Alzheimer's disease has, as it is well known, devastating effects on the individual health, that of the caregivers and finally, on the whole of society, not only in personal terms, but also in huge economic terms. Any attempt to delay the onset of Alzheimer's dementia deserves full attention.

It is well known now that brain damage, including plaque deposition and even changes in brain volume start well before the onset of clinical symptoms. The lack period may be as long as one or even two decades. On the other hand, Alzheimer's pathology is of such seriousness that it involves not only one mechanism, but a series of molecular mechanisms leading to amyloid-β accumulation and tau hyperphosphorylation.

Attempts to treat Alzheimer's by delaying the onset of dementia, i.e. changing the course of the disease, must be multimodal, because the pathogenetic mechanisms leading to the disease are also multimodal.

Of critical importance is that the fact that oxidative stress, inflammation and probably senescence, are all involved in the pathogenetic mechanisms of Alzheimer's pathology.

Another important condition for the treatment of a disease that has to be performed over the course of decades is that the interventions be practically devoid of side effects. For instance, intravenous effects of substances that are meant to last for twenty years may not be indicated as they are inconvenient for the patients.

In the past twenty years, we have analysed the characteristics of oxidative stress associated with Alzheimer's disease and found that these changes in redox signalling contribute to link amyloid-β pathology with tau hyperphosphorylation.

Some time ago we realised that genistein, a soya isoflavone that binds to PPAR-γ, activates a production of ApoE, which in turn clears amyloid-β from brain. We tested this hypothesis in an animal model, i.e. the APP-PS1 and observed that genistein very significantly lowers the amount of amyloid-β in brain, decreases brain inflammation associated with Alzheimer's and improves cognition in animal tests.

Now, we wish to report the results of a pilot clinical trial that show that genistein is effective in delaying the transition of minimal cognitive impairment patients to dementia. The mechanisms for this results will be discussed.