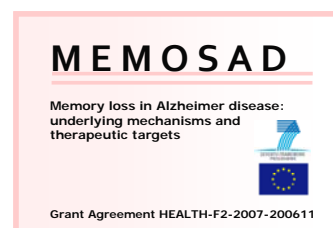


PROJECT INFO SHEET

Title: Memory loss in Alzheimer disease: underlying mechanisms and therapeutic targets

Acronym: MEMOSAD
Contract number: HEALTH-F2-2007-200611
EC contribution: Euro 2.998.696
Starting date: 01.01.2008
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Instrument: Collaborative project



Summary

The first task to be accomplished within **MEMOSAD** will be the identification of toxic Abeta and tau species responsible for memory loss in Alzheimer disease (AD). As for Abeta, we will start with the generation and characterization of Abeta preparations from various sources. The different Abeta preparations will be thoroughly characterized biochemically and biophysically using techniques standardized throughout the centres. The data generated will help to elucidate the mechanisms of Abeta-mediated toxicity that are at the basis of memory loss. As for tau, the research largely relies on the availability of models of tauopathy including cellular models, brain slices, as well as zebrafish models, C.elegans models and mouse models. Data obtained in the respective studies will help to identify the toxic tau species and the mechanism of toxicity that are also at the base of memory loss in AD. The next task to be accomplished will be to find out how toxic Abeta oligomers affect tau metabolism, what are the combined effects of Abeta and tau pathology in mouse and zebrafish models, and how relevant tau is for the Abeta-induced toxic effects. The data obtained should provide a more complete picture of the pathologic pathways going from Abeta oligomers through tau to synaptotoxicity, thereby helping to accomplish the final objective of **MEMOSAD**, namely to identify novel candidate therapeutic targets, ideally genes and proteins participating in signalling pathways essential for synaptic plasticity and memory, which are disrupted by Abeta and tau aggregates.

Background

One of the early and characteristic symptoms in AD is memory loss. This neurodegenerative disease is characterized by two histopathological hallmarks: extracellular plaques composed mostly of Abeta peptide, and intracellular neurofibrillary tangles composed of abnormally phosphorylated microtubule-binding protein tau. For decades a controversy persisted over whether abnormal Abeta or tau accumulation is the primary cause of neurodegeneration in AD. Indeed, a large body of evidence has independently linked abnormal Abeta or tau-aggregates to neurotoxicity, with the two hypotheses neglecting each other and evolving largely independently. It was not until recently that a mechanistic link between the two pathologies was identified and it is now more widely accepted that tau accumulation, although sufficient by itself to cause neurodegeneration, in AD occurs as a consequence of Abeta-induced neuronal damage. The precise interaction between Abeta and tau and more importantly, how these proteins affect synaptic function, memory loss and ultimately neuronal survival remain largely unknown. Further study is crucial to facilitate the development of therapeutic strategies and to move from symptomatic treatment towards a real disease-modifying therapy.

Aim

The **MEMOSAD** project aims at defining the molecular mechanisms of Abeta- and tau-induced synaptotoxicity and at developing disease-modifying therapeutics for the prevention of memory loss in AD. For this purpose, the pathologic pathways leading from Abeta through tau to synaptotoxicity and the interaction of these pathways will be investigated, and, thus, novel points for therapeutic intervention will be revealed. The specific objectives are (1) to define precisely the toxic Abeta and tau species responsible for memory loss in AD, (2) to elucidate the mechanisms of Abeta- and tau-mediated toxicity that are at the basis of memory loss, (3) to define at the molecular level the mechanistic link between Abeta and tau that brings about memory loss, and (4) to translate the biological findings into effective, disease-modifying therapeutic strategies. For this investigation primary neuronal cultures and animal models (C. elegans, zebrafish, mouse) will be employed.

Expected results

Initial **MEMOSAD** experiments will reveal the effects of well-defined Abeta species on long-term potentiation, synaptic morphology, gene expression, tau phosphorylation/ aggregation, axonal transport and behaviour. Parallel investigations will uncover the functional consequences of tau malfunction, aggregation, hyperphosphorylation and missorting in various cell culture systems (retinal ganglion cells, primary hippocampal neurons, organotypical slices) and animal models, especially with regard to intraneuronal trafficking and synaptic function. Once the toxic Abeta and tau species are known and their mechanism of toxicity is defined, the interaction between these two pathways will be studied. Following the track that leads from Abeta through tau to synaptotoxicity and memory loss should reveal novel points for therapeutic intervention. It is planned to deliver 3 or 4 validated therapeutic targets and at least 2 compounds with demonstrated therapeutic efficacy in AD mouse models.

Potential applications

MEMOSAD is expected to go considerably beyond the state-of-the-art knowledge of the molecular events that are triggered by abnormal Abeta and tau aggregates and that lead to synaptic impairment, memory loss and ultimately neurodegeneration. Investigation of the mechanistic link between Abeta and tau that is at the basis of the synaptotoxic effects in AD will help to identify novel candidate therapeutic targets. Thus, the project has the potential not only to gain new knowledge on the brain functions and dysfunctions, from molecules to cognition and from synaptic impairment to neurodegeneration, but also to foster the application of this new knowledge in the development of therapeutic drugs for the prevention of memory loss in AD. Large-scale drug screening efforts focusing in the validated targets will be done in a follow-up phase of **MEMOSAD**, in collaboration with the pharmaceutical industry. The consortium will aim for optimal use of its combined intellectual property as to promote drug development in this field.

Project web-site: www.verum-foundation.de/memosad

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