cima
CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

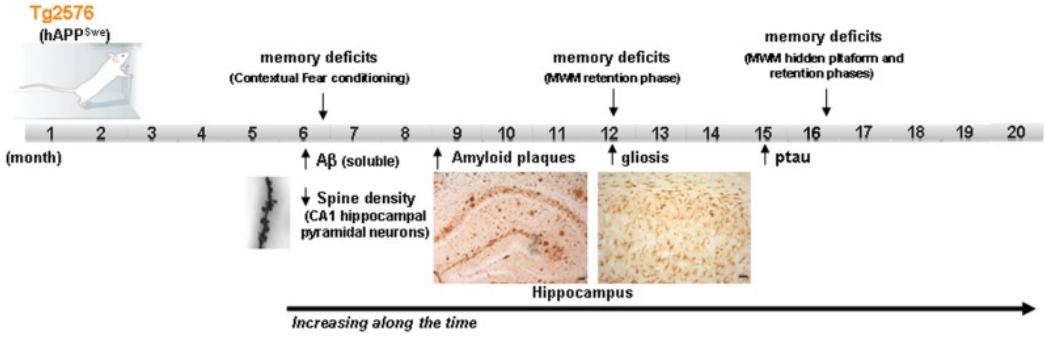
Alzheimer´s Disease: Animal Models

Alzheimer´s disease (AD) is particularly devastating disease since there is no cure, no way to prevent it and no proven way to slow its progression. Currently, approximately 18 million people worldwide are afflicted with this disease and it is projected to reach over 30 million by 2025. AD is characterized by a gradual **decline in cognitive function** and the presence in the brain of pathological inclusions such as **amyloid plaques** and **neurofibrillary tangles** composed of **phosphorylated-tau**. These are the two main hallmarks of the disease and focus of most current therapeutic strategies.

The development of transgenic models of AD has focused in these two pathological markers. Although none of them completely recapitulate the disease process, they have already contributed to the understanding of the pathogenesis of AD as well as have been provided as valuable tools in preclinical studies. Most of the AD-mouse models do not present the extensive neuronal loss observed in the brain of AD patients, nevertheless, the loss of synapses which is the best correlate of the cognitive impairment in patients with AD, is present in both of these AD-models.

Some researchers have proposed that benefits with a new therapeutic intervention should be demonstrated in at least two different animal models, thus in most of the projects at the Neurobiology of Alzheimer´s Disease Lab at CIMA we confirm results in the two different transgenic models of AD (Tg2576 and APP/PS1 transgenic lines) available.

- ✓ **Tg2576: Tg(APPSWE)2576Kha (C57BL/6* SJL mice):** Tg2576 mice overexpress a mutant form of amyloid precursor protein (APP), APPK670/671L, linked to early-onset familial AD, developing **amyloid plaques** and progressive **cognitive deficits**. Mice show impaired cognitive functions in the contextual fear conditioning test, coinciding with the increased cortical and hippocampal soluble beta amyloid levels, starting from 6 months of age. The increased insoluble beta amyloid levels and the amyloid plaques are evident at 10-12 months of age. Thus, Tg2576 transgenic model corresponds to a late onset model with an established phenotype presented at the age of 16-18 month of age (see scheme below). This allows researchers to take into account the contribution of aging to the AD phenotype.



Development of the different AD signs in Tg2576 mice over time. Scheme showing the time point of main AD features apparition in Tg2576 mice. At the age of 16month, although no neuronal loss is presented in the brain of Tg2576 mice, the AD-phenotype is well established. MWM: Morris water maze.

- ✓ **APP/PS1: Tg(APPswe,PSEN1dE9)85Dbo(C57BL/6 mice):** Double transgenic mice express a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695Swe) and a mutant human presenilin 1 (PS1-dE9) both directed to CNS neurons by the mouse prion promoter. The APP/PS1 mouse corresponds to a form of early-onset of AD, with amyloid plaques and synaptic deficits appearing even when the animals are 2–4months old. The advantage of using these early models, with their early onset of symptoms, has the disadvantage of compromising the age factor. However, they are very valuable for electrophysiological studies where long-term potentiation (LTP: the electrophysiological correlate of learning and memory) is used.

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