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SEMINAR

The Alzheimer's disease pathophysiology: a longitudinal multi-tracer PET imaging study in a rat model of AD

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by the abnormal accumulation of amyloid-b (Ab) plaques and Tau neurofibrillary tangles (NFTs) in the brain, giving rise to widespread synaptic loss, inflammation, oxidative damage and neuronal death. Some of these processes begin decades before the onset of clinical symptoms, constituting a unique opportunity for the early diagnosis of the disease and eventual evaluation of the response to treatment. However, to date, there is no effective treatment for AD available in the market nor is there any reliable option for the early assessment of the disease. The diagnosis is therefore mainly based on clinical symptoms, which occur at later stages of the disease, when it is much too late for successful medical intervention. To overcome this growing problem and provide AD patients with better treatment options, there is an urgent need to identify new disease biomarkers to (i) enable longitudinal and non-invasive monitoring of disease progression, (ii) enable a targeted approach for new treatment, diagnostic and theragnostic strategies and (iii) provide with new tools for treatment response evaluation.

Alzheimer's pathophysiology can be investigated non-invasively by the means of positron emission tomography (PET) imaging, using specifically designed radiotracers to detect biological hallmarks of the disease in vivo. At the same time, even though animal models of AD lack on recapitulating the complete spectra of the disease, they offer a true understanding of the underlying mechanisms of the disease and have proven to be invaluable in the preclinical evaluation of potential therapeutic interventions and diagnostic tools. In this sense, the Tg-F344 AD rat model manifests age-dependent cerebral amyloidosis that precedes tauopathy, gliosis, apoptotic loss of neurons in the cerebral cortex and hippocampus, and cognitive disturbance. Overall, the model constitutes a step forward for the study of the disease pathophysiology compared to previously used transgenic mice models.

In this study, we looked into the longitudinal progression of some of the pathophysiological aspects of AD (e.g. Tau deposition, amyloid plaques, neuroinflammation, enzymatic levels and synaptic density) in the Tg-F344 rat model of AD, by acquiring PET images at different time points with an array of selected radiotracers. At the same time, we monitored age-matched wild type (WT) littermates under the same conditions for baseline purposes. We supported our findings with ex vivo imaging techniques (e.g. autoradiography and immunofluorescence) from harvested brain tissue and assessed the cognitive status of the animals under different behavior tests. Overall, we examined the ability of PET radiotracers to monitor disease progression overtime, while we gained a better understanding on the characterization of this model for future studies. Further steps in this project will include the use of this rat model for treatment response evaluation of potential disease modifying drug candidates.