Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2019-2020

1. Host team :

Research Unit (e.g. Department or Institute) : UMRS 938 – Centre de Recherche Saint-Antoine
Research Unit Director : Pr. Bruno FEVE
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2. Internship project title:

Role of T cell immunity in the pathophysiology of Alzheimer's disease and Tauopathies

3. Internship Description :

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive loss of memory and cognitive functions. AD neuropathology is defined by extracellular deposits of Aβ amyloid peptides, and intraneuronal aggregates of hyperphosphorylated Tau proteins. Both neuropathological lesions lead to activation of microglia and astrocytes, triggering a chronic innate neuroinflammatory response. Contribution of such neuroinflammation to AD pathophysiology remains controversial, with both beneficial impacts and detrimental effects evolving along disease progression. Besides such innate neuroinflammation, neuropathological and genetic data now emphasize an instrumental role of cellular adaptive immunity in AD, although the impact on disease progression of T cell responses to pathological proteins involved in AD is poorly defined.

Most existing data on T cell immunity in AD have been related to amyloid pathology and remain contradictory, suggesting a complex implication of Aβ-reactive T cells, with either beneficial or detrimental outcomes that may depend on the magnitude and functionality of different type of T cell responses. Our recently published studies in a mouse model of AD-like amyloid pathology evidenced the therapeutic potential in AD of immunomodulatory approaches targeting regulatory T cells, and further highlighted an intricate interplay between T cell immunity and innate neuroinflammation (Dansokho et al, *Brain*, 2016). In contrast, much less is known regarding innate and adaptive immune responses associated with Tauopathy. Particularly, besides very few studies, the interplay between T cell immunity

and Tau pathology remains totally elusive. Similar to AD, genome-wide association studies suggested the involvement of T cells in the pathogenesis of frontotemporal dementia, a subtype of which are defined as Tauopathies. A recent neuropathological study reported a correlation between T cell infiltration and pTau load in the brain of AD patients. Using a mouse model of AD-like Tau pathology (THY-Tau22 mice), we contributed to describe a similar association between Tau pathology and T cell infiltration in the hippocampus of THY-Tau22 mice. Strikingly, early total T-cell depletion prevented the development of spatial memory deficits and down-modulated innate neuroinflammation in the brain of THY-Tau22 animals (Laurent et al, *Brain*, 2017). These studies suggest that Tau pathology may drive the development of T cell responses that contribute to promote disease progression. However, the nature, specificity and functionality of such detrimental T cells responses remain poorly defined, as well as the impact of their modulation on Tau-driven pathophysiology.

The proposed project will consist in better characterizing the impact of different T cell subsets on disease progression in our mouse model of AD-like Tau pathology. Experimental studies will involve immunohistochemistry, flow cytometry, gene expression analyses, and behavior studies.