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) : UMR_S 938, Centre de Recherche Saint-Antoine
Research Unit Director : Pr Bruno Fève
Research Team Director : Dr Guillaume Dorothée
Team name : Immune System and Neuroinflammation

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2. Internship project title:

Involvement of neutrophils in the pathophysiology of Alzheimer's disease: mechanistic aspects and prognostic value

3. Internship Description :

Accumulating evidence emphasizes an instrumental role of peripheral immunity and systemic inflammation in the pathophysiology of Alzheimer's Disease (AD). Neutrophils (PMNs) are key components of innate immunity and contribute to uncontrolled systemic inflammation if not tightly regulated. A recent study in mouse models of AD-like pathology reported that PMN depletion reduces both amyloid- and Tau-related pathophysiology and improves memory in mice with already established pathology, suggesting the involvement of PMNs in AD pathophysiology. Importantly, in AD patients with dementia we recently evidenced an altered homeostasis of peripheral PMNs characterized by the expansion of the harmful hyperactive senescent or "aged" PMN subset together with decreased immunosuppressive PMN subset. Such alterations were greater in fast decliners than slow decliners AD patients, strongly suggesting that PMN phenotype might be associated with the rate of cognitive decline. Intriguingly, our preliminary results suggest that patients with non-AD Tau pathologies do not exhibit phenotypic and functional alterations of PMNs, supporting that altered PMN homeostasis associated with the expansion of senescent subsets may be related to amyloid rather than Tau pathology.

These results underline the need for better understanding the mechanistic bases driving altered PMN homeostasis in AD, i.e. the enhanced ratio of senescent/immunosuppressive peripheral PMNs, as well as the consequences of such alterations on disease pathophysiology, with a particular focus on the role of senescent PMNs on vascular inflammation. The objectives of our study are to :
1) Better characterize the impact of amyloid and Tau pathology on PMN homeostasis, This comparative analysis will include:

- *in vivo* studies investigating PMN phenotype and functions in a large cohort of AD patients and patients with non-AD Tauopathies.
- *in vitro* studies investigating the effect of Aβ1-42 peptide or Tau protein on the phenotype and functions of PMNs from healthy donors.

2) Evaluate the contribution of aged PMN to vascular inflammation. To achieve this goal, we will analyze the effect of PMN subsets purifed from healthy donors, AD patients and patients with Tauopathies on the integrity of the blood brain barrier (BBB) by using an *in vitro* model of BBB.

3) Evaluate the usefulness of PMN phenotype as an innovative prognostic biomarker of disease progression. To achieve this goal, we will investigate the potential correlations between all the combined measured PMN indicators, i.e. the ratio of senescent/immunosuppressive PMN, and the rate of disease progression according to CDR score.

This work help better understand the role of PMNs in the pathophysiology of AD and other Tau-related pathologies. Our data should also open new perspectives in the development of innovative immunotherapy strategies based on either PMNs modulation, e.g. for rebalancing senescent and immunosuppressive PMNs subsets, and/or by decreasing their basal hyperactivation state.