Internship proposal FOR THE EMHE PROGRAM

(From February 2018)

Project #	Department	Lab name/Head	Project name	Advisor	Lab website
1	Neuroscience	**Perception and Memory** Pierre-Marie LLEDO	Olfactory dysfunction associated to early neurodegenerative processes in a mouse models of Alzheimer's disease	Mariana ALONSO malonso@pasteur.fr	https://research.pasteur.fr/fr/team/perception-and-memory/

PROJECT 1

OLFACTORY DYSFUNCTION ASSOCIATED TO EARLY NEURODEGENERATIVE PROCESSES IN A MOUSE MODELS OF ALZHEIMER'S DISEASE

Keywords: olfactory system, neurodegeneration, tau protein
Department: Neuroscience
Name of the lab: Perception and Memory.
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***Doctoral school affiliation and University*:** ED3C-UPMC

PRESENTATION OF THE LABORATORY AND ITS RESEARCH TOPICS:

The Perception and Memory laboratory focuses its research on the neural basis of sensory perception, learning, and memory. Our group applies a top-down approach to decipher mechanisms involved in adult brain plasticity using olfaction in rodents as a model system. The laboratory has acquired a strong expertise in cellular and synaptic analysis of circuit function at the early stages of the olfactory system and in revealing the link between neuronal circuit activity and behavioral responses in normal and pathological conditions.

DESCRIPTION OF THE PROJECT:

Many neurodegenerative diseases are characterized by an early loss of olfactory function. Particularly, in Alzheimer's disease (AD) olfactory deficit (OD) is an early symptom that usually precedes cognitive decline[2], nonetheless the mechanisms underlying such dysfunction remain elusive. Deciphering the molecular pathways leading to OD symptoms is essential to elucidate the progression of AD pathology, develop non-invasive methods for diagnosis and find new therapeutic targets.

AD and related dementias are characterized by the presence of insoluble neurofibrillary tangles (NFTs) in the brain of patients[1], due to the accumulation of abnormal tau protein. The presence of NFTs was found in the olfactory bulb (OB) at very early stages of AD[3], suggesting that tau accumulation might begin in this region. On the other hand, the process of adult neurogenesis generates thousands of new neurons in the adult OB and contributes to the functional plasticity of this system in mouse models. Being this process dependent on tau function[9], we propose that deficits in tau metabolism in the central relay of olfaction may be responsible of early OD. Moreover, we hypothesize that the accumulation of abnormal tau protein in the OB might contribute to spreading tau pathology to other brain areas. In this context, our main objective is to investigate a direct causal relationship between tau dysfunction and early deficits in olfaction, using mouse models of tauopathy. The specific objectives of this PhD internship project are: 1) To analyze the consequences of constitutive loss or gain of tau function over olfaction, in a TAU-knockout mouse model (TAUKO) and in transgenic mice overexpressing the human tau protein (hTAU); 2) to correlate ODs with the presence of abnormal tau in brain regions of the olfactory system; 3) to study the impact of TAU dysfunction on adult neurogenesis in the OB of TAUKO and hTAU mice.

We expect to identify the brain nuclei of the olfactory system potentially affected by tau pathology, determining the onset and time course of related OD phenotypes in correlation with altered adult neurogenesis and/or neurodegeneration rates in those brain areas. The comparative analysis of the hTau and the TAUKO models will clarify if such phenotypes are whether due to tau loss of function or the gain of toxic effects of tau due to overexpression and/or isoforms imbalance. Modulating tau

isoforms by trans-splicing in defined brain structures, as previously described[10,11], will provide a proof of concept that the tau isoforms imbalance in these areas is sufficient to produce DOs. On the other hand, by inhibiting tau gene expression we would be able to demonstrate that the increase in toxic isoforms is necessary for the generation of such deficits.. Our work will clarify the molecular mechanisms leading to early OD in tauopathies. These results might contribute to set the grounds for the development of accurate preclinical diagnosis tests and new therapeutic approaches for AD and related dementias.

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EXPECTED PROFILE OF THE CANDIDATE:

We are looking for highly motivated and talent PhD candidates who have a substantiated interest and experience in stereotaxic injections, viral vectors manipulation and animal behavior in the field of Neuroscience. Laboratory research experience is a prerequisite. The candidate needs to exhibit a good amount of inquisitiveness, initiative and independent thinking.