**PhD PROPOSAL FOR THE**

**PASTEUR - PARIS UNIVERSITY INTERNATIONAL DOCTORAL PROGRAM**

Time for applicants to contact host laboratories: September 13 – November 2, 2017

Deadline for full application: November 13, 2017

Interviews: January 30, February 2, 2018

Start of the Ph.D.: October 1, 2018

**Title of the PhD project:** The role of nicotinic receptors in Alzheimer’s Disease pathology and treatment

**Keywords:** Alzheimer’s Disease, nicotinic receptor, mouse models, in vivo imaging

**Department:**  Neuroscience

**Name of the lab:** Integrative Neurobiology of Cholinergic Systems

**Head of the lab:** Uwe Maskos

**PhD advisor:** Uwe Maskos

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**Web site address of the lab:** <https://research.pasteur.fr/en/team/integrative-neurobiology-of-cholinergic-systems/>

***Doctoral school affiliation and University*:** ED3C at UPMC

Presentation of the laboratory and its research topics:

We are studying the crucial role of nicotinic acetylcholine receptors in the central nervous system. They are expressed by all neurons, and modulate the release of every other neurotransmitter like dopamine, glutamate, GABA etc. Over the last decade, we have dissected the role of nicotinic receptors in nicotine addiction, see references below (1, 2).

We have now started to dissect their role in cortical function, see our *Nature Medicine* paper below (3). We are using an integrated approach to neural function, including transgenic mice and rats, molecular biology, electrophysiology, imaging, iPS stem cells, and collaboration with clinical psychiatrists.

Description of the project:

Alzheimer's Disease (AD) is the most common neurodegenerative disorder. AD is the major form of senile dementia, and characterised by neuronal loss, extracellular deposits, and neurofibrillary tangles. It is accompanied by loss of cholinergic tone, and so far medication is restricted to enhancing cholinergic signalling. The nicotinic acetylcholine receptor (nAChR) is one of the two main receptors for acetylcholine (ACh) in the brain. We want to elucidate how the interaction of amyloid beta (Aβ) with the nAChR contributes to AD pathology, and can potentially serve as a therapeutic target, including in non-neuronal cells.

The identification of the molecular mechanisms and brain circuits involved in potential neuroprotection and the development of novel tools to allow genetic and molecular manipulation is vital. A direct binding interaction was discovered between Aβ and nicotinic acetylcholine receptors (nAChRs) that may take place in the normal physiology of the cells, and also in AD pathology. In our work, we aim to elucidate which is the main neuronal cell type that is affected by the Aβ peptide by developping adeno-associated viral vectors (AAV) that are able to target specific cell types. This will allow us to understand the role of the different nicotinic subunits that have been found in specific neuronal types. This will be combined with *in vivo* two-photon imaging in the wake behaving mouse, in the cortex and hippocampus, to follow up on our first publications (4), and patent.

References:

1. *S Tolu, R Eddine, F Marti, V David, M Graupner, S Pons, M Baudonnat, M Husson, M Besson, C Reperant, J Zemdegs, C Pagès, YAH Hay, B Lambolez, J Caboche, B Gutkin, AM Gardier, J-P Changeux, P Faure & U Maskos (2013) Co-activation of VTA DA and GABA neurons mediates nicotine reinforcement. Mol Psychiatry 18, 382-393.*
2. *C Morel\*, L Fattore\*, S Pons, A Hay, F Marti, B Lambolez, M De Biasi, M Lathrop, W Fratta, U Maskos\* & P Faure\* (2014) Nicotine consumption is regulated by a human polymorphism in dopamine neurons. Mol Psychiatry 19, 930-936.*
3. *F Koukouli, M Rooy, D Tziotis, KA Sailor, HC O’Neill, J Levenga, M Witte, M Nilges, JP Changeux, CA Hoeffer, JA Stitzel, BS Gutkin, DA DiGregorio & U Maskos (2017) Nicotine reverses hypofrontality in animal models of addiction and schizophrenia. Nature Medicine 23, 347-354.*
4. *S Lombardo, J Catteau, M Besson & U Maskos (2016) A role for ß2\* nicotinic receptors in a model of local amyloid pathology induced in dentate gyrus. Neurobiology of Aging 46, 221-234.*

Expected profile of the candidate (optional):

Very motivated and willing to work hard in a team effort.

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