Internship title
Lipid determinants of outer mitochondrial membrane fusion

Laboratory
Membrane Traffic in Healthy and Diseased Brain
Institute of Psychiatry and Neuroscience of Paris (UMR_S1266 INSERM-Université Paris Descartes)
102-108, rue de la santé 75014 Paris
https://sites.google.com/site/insermu950/Biophysics-of-membrane-fusion

PhD supervisor
David Tareste
david.tareste@inserm.fr

Internship duration
3-6 months with the possibility to continue for a PhD (ANR funding available)

Project summary
Mitochondria are double-membrane bound organelles that constantly move, fuse and divide within cells. The balance between fusion and fission events defines mitochondrial morphology and is crucial for normal mitochondrial and cellular function[1]. Outer mitochondrial membrane fusion is mediated by Mitofusin proteins, whose molecular architecture consists of an N-terminal GTPase domain, a first heptad repeat domain (HR1), a transmembrane (TM) region, and a second heptad repeat domain (HR2). Mutations in any of these functional domains impair Mitofusin function, but their exact role in mitochondrial fusion remains elusive[2]. *In vitro* reconstitution studies by us and others[3,4] suggest that the HR2 domain of Mitofusin mediates short distance (~10 nm) membrane docking by forming homotypic antiparallel dimers, while its HR1 domain – owing to its amphipathic nature – triggers fusion by perturbing the lipid bilayer structure (Fig. 1). Mitochondrial fusion is also regulated by specific lipids such as cardiolipin (CL), phosphatidylethanolamine (PE) and phosphatidic acid (PA). Reduction in CL and/or PE level in mitochondrial membranes impairs mitochondrial fusion, and increase of PA level promotes close apposition of mitochondrial membranes, which is a necessary step of the fusion event[5]. However, the exact mode of action of these regulatory lipids in Mitofusin-mediated fusion is not fully understood. This project aims at elucidating how Mitofusin-mediated fusion is regulated by lipids. To this end, we will use a combination of approaches including cell-free *in vitro* liposome docking and fusion assays, as well as live cell imaging of mitochondrial fusion *in situ*, and morphological analysis of liposomes and mitochondria by electron microscopy.

References
1. Chan, D. C. Mitochondrial fusion and fission in mammals. *Annu Rev Cell Dev Biol* **22,** 79–99 (2006).
2. Cohen, M. M. & Tareste, D. Recent insights into the structure and function of Mitofusins in mitochondrial fusion. [version 1; referees: 2 approved]. *F1000Res* **7,** (2018).
3. Koshiba, T. *et al.* Structural basis of mitochondrial tethering by mitofusin complexes. *Science* **305,** 858–862 (2004).
4. Daste, F. *et al.* The heptad repeat domain 1 of Mitofusin has membrane destabilization function in mitochondrial fusion. *EMBO Rep* **19,** (2018).
5. Frohman, M. A. Role of mitochondrial lipids in guiding fission and fusion. *J Mol Med* **93,** 263–269 (2015).

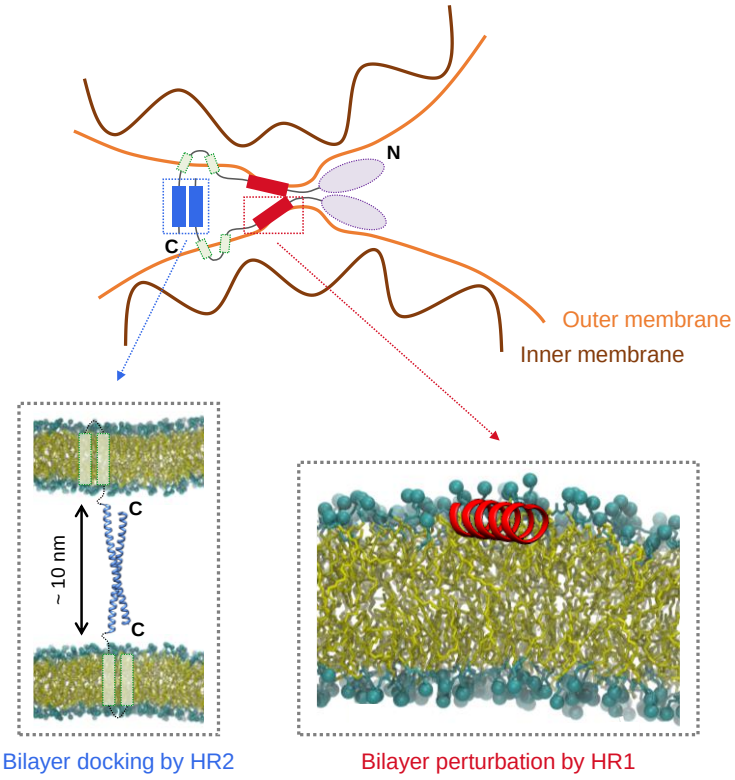

Figure 1. Working model for the role of the heptad repeat domains of Mitofusin in outer mitochondrial membrane fusion (GTPase domain in purple, HR1 domain in red, HR2 domain in blue, and transmembrane domains in green).