

## Titre du stage

Rôle des lipides dans la fusion mitochondriale / Lipid determinants of outer mitochondrial membrane fusion

## Lieu

Labo Trafic membranaire dans le cerveau normal et pathologique  
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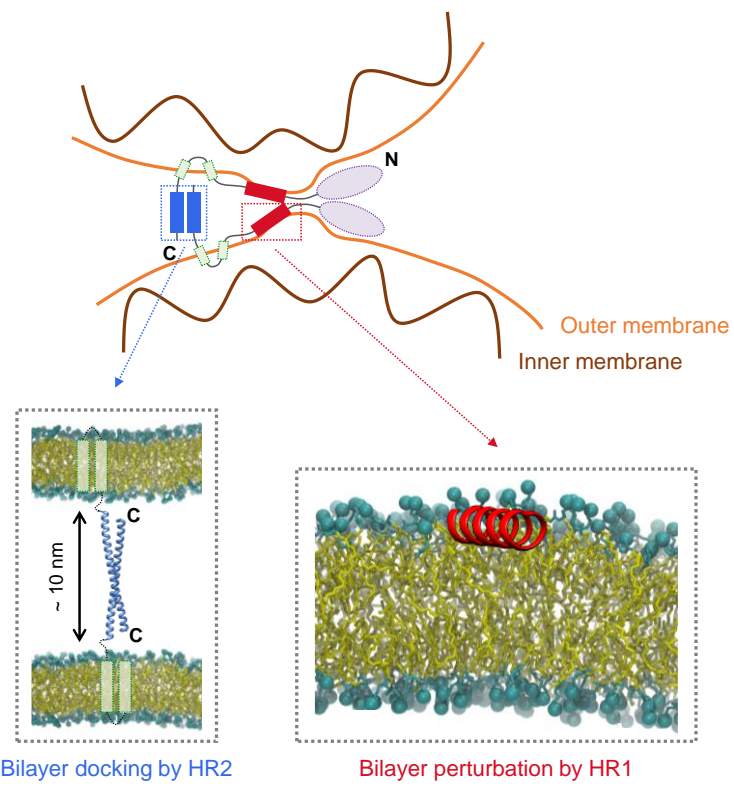
**Durée du stage** : 3 à 6 mois avec prolongation en thèse possible (financement ANR)

## 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<sup>1</sup>. 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<sup>2</sup>. *In vitro* reconstitution studies by us and others<sup>3,4</sup> 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<sup>5</sup>. 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 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 domain in green).