# Postdoctoral Position in Biomolecular Modeling

**Project Title** : Enhanced molecular dynamics simulations of PEGylated agonist and antagonist binding to cardiac $\beta$-adrenergic receptors

**Supervisor** : Pr Tâp HA-DUONG

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**Duration** : 18 months, starting January 2024

**Project Description** :

In the framework of an ANR project, named CARDIOPEG, the objective of the proposed research will be to characterize and compare the interactions of PEGylated ligands *versus* free ligands with $\beta$-adrenergic receptors ($\beta$-ARs), by using enhanced molecular dynamics (MD) simulations of their binding and unbinding processes.

The cell membrane of cardiac myocytes is characterized by invaginations of the surface membrane, occurring primarily perpendicular to myocyte longitudinal edges, that form a complex interconnected tubular network penetrating deep into the cell interior (Fig. 1A). Like the cardiac cell outer surface membrane (OSM), the transverse tubule membrane (TTM) contains many receptors, channels or enzymes, including $\beta$-ARs which are key players in the regulation of cardiac function. Nevertheless, biochemical assays have provided indirect evidence that $\beta$-ARs may have different properties and/or activity whether located in TTM or OSM [1].

Classical pharmacology using $\beta$-AR agonists or antagonists allows to explore the function of $\beta$-ARs in the whole cell membrane but not separately in OSM *versus* TTM compartments. Therefore, chemistry and biology collaborators have developed PEGylated ligands that can differentiate the function of $\beta$-ARs according to their location on the cell membrane : While free agonists or antagonists have access to all cell membrane (OSM+TTM), a PEGylated ligand will only access to OSM due to its increased size which prevents it to penetrate the TT network (Fig. 1B). This innovative chemical biology tool will allow to characterize and compare the respective roles of OSM *versus* TTM $\beta$-ARs in intact cardiomyocytes.

However, the precise mechanism of action of PEGylated agonists or antagonists of $\beta$-ARs is not known compared to that of their free counterparts. In particular, the impact of the PEG

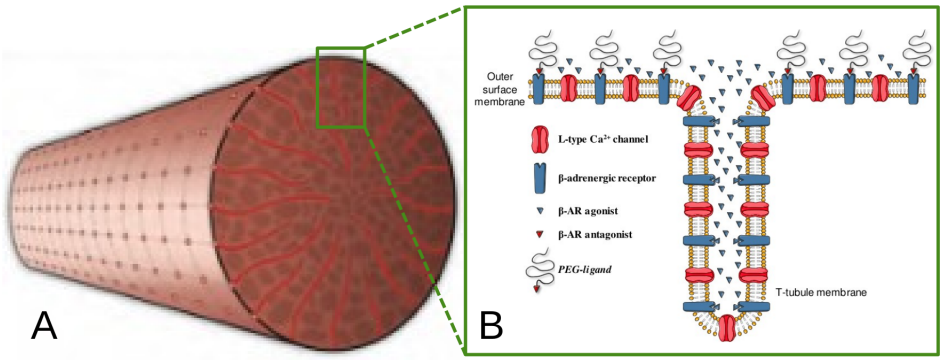


FIGURE 1 – (**A**) Transverse tubule network (red lines) in ventricular myocytes. (**B**) Illustration of the strategy to selectively activate OSM versus TTM $\beta$-ARs by using PEGylated agonists.

chain on the ligand binding to the activation site and on the activated receptor conformational dynamics have never been documented to date. In this context, we propose to employ enhanced MD simulations, including steered MD and umbrella sampling, to investigate the binding process of five PEGylated ligands to $\beta$-ARs and the latter conformational response. Receptors will be embedded within explicit lipid bilayers and all biomolecules will be solvated by explicit water molecules and ions. MD simulations will be performed with the CHARMM36m force field [2] and the GROMACS software [3]. The postdoctoral research will provide valuable information at the atomic scale about the structure-dynamics-activity relationship of $\beta$-AR-PEG-ligand complexes.

**Profile** : Candidates must have a PhD in computational biophysics or biochemistry with strong skills in molecular dynamics (MD) simulations.

**Application** : tap.ha-duong@universite-paris-saclay.fr (attach a single PDF file including cover letter, curriculum vitae, and list of publications).

## Références

[1] Barthé, M. ; Lefebvre, F. ; Langlois, E. ; Lefebvre, F. ; Lechêne, P. ; Iturrioz, X. ; Llorens-Cortes, C. ; Ha-Duong, T. ; Moine, L. ; Tsapis, N. ; Fischmeister, R. Distinct functions of cardiac $\beta$-adrenergic receptors in the T-tubule vs. outer surface membrane. *bioR$\chi$iv* **2022**. doi :10.1101/2021.04.28.441732.

[2] Huang, J. ; Rauscher, S. ; Nawrocki, G. ; Ran, T. ; Feig, M. ; de Groot, B.L. ; Grubmüller, H. ; MacKerell, A.D. CHARMM36m : an improved force field for folded and intrinsically disordered proteins. *Nature Methods* **2017**, *14*, 71–73.

[3] Abraham, M.J. ; Murtola, T. ; Schulz, R. ; Páll, S. ; Smith, J.C. ; Hess, B. ; Lindahl, E. GROMACS : High performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX* **2015**, *1–2*, 19–25.