Equipe DSIMB, UMR-1134, Paris (www.dsimb.inserm.fr)
Contact: catherine.etchebest@inserm.fr

Post-doc recruitment

Keywords: molecular dynamics simulations, 3D modeling, membrane protein, channel, transport

Candidate profile and skills: The candidate should preferably have a PhD in structural bioinformatics, with expertise in advanced molecular dynamics simulations.

Pre-requisites:
Knowledge of a programming language
Knowledge of data analysis methods
Experience of advanced methods in molecular dynamics simulations

Qualities: Dynamism, curiosity, autonomy, imagination.

Project: Understanding impact of mutations in KCNQ1 channel and their role in tumor progression using computational biophysics approaches.

This project supported by INCA is an interdisciplinary project that aims to understand how somatic mutations carried by ion channel-encoding genes participate in tumour progression by altering associated signalling pathways. It is conducted in partnership with electrophysiologists and pathophysiologists.

Context: The potassium channel KCNQ1 was characterised as a gatekeeper of colonic epithelial integrity acting through the restriction of Wnt/ β-catenin signalling pathway. Aberrant activation of this intracellular signalling pathway is the main driving force for colorectal carcinogenesis. Several mutations on the KCNQ1 gene were identified in colon cancer databases. Thus, it is hypothesized that colorectal cancer (CRC)-associated mutations carried by KCNQ1 promote Wnt signalling activity and participate in CRC pathophysiology. Therefore, the present consortium aims at i) defining how each CRC-associated KCNQ1 mutation affects the channel structure-function relationships and biophysical properties and ii) understanding the effects of representative CRC-associated KCNQ1 mutations on the Wnt signalling activity.

The post-doc will be in charge of:

i) *Predicting how CRC-associated KCNQ1 mutations affect the channel structure using bioinformatics and computational biophysics methods.*

To clearly understand how mutations impact channel gating we will have to consider important partners of KCNQ1: PIP_2 , KCNE3 and CaM. The systems will include the different partners as a whole but also sequentially in order to better characterize the impact of each of them for each mutation. As a main hypothesis, *we assume that the mutations do not impact significantly KCNQ1 3D structure,* but they modify *the dynamics and the network of interactions between the different partners.* We will focus on six mutations and examine how the dynamics of each system is affected. Impact of mutation on the binding free energy between partners and on the ion transport will be further studied by calculating the potential of mean force (PMF) of the K+ ion along the channel.

ii) *Studying the interaction between KCNQ1 and β-catenin:*

By its interaction with β-catenin, KCNQ1 channel acts as a fine regulator of the Wnt pathway. It is a critical protagonist in carcinogenesis. Consequently, we will study the interaction between KCNQ1 and β-catenin at the structural level. First, the 3D structures of the complex will be predicted guided by experimental data. Based on the structural data, our main aim will consist in providing a list of putative residues that could be further experimentally tested. Then, we will explore how the mutations affect this list of interacting residues by examining the different mutated complexes.

Starting date: July, 1st 2023