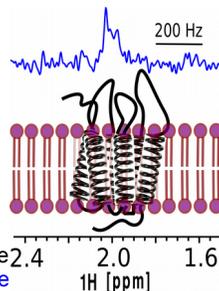


Study of the energy landscape of G Protein-Coupled Receptors in lipid discs



A 2-year funded postdoctoral position is available in the [Laboratory of Biology and Physico-Chemistry of Membrane Proteins in Paris \(UMR 7099 CNRS, Université Paris Diderot ; IBPC, 13, rue Pierre et Marie Curie\)](http://www.ibpc.fr/). This project aims at exploring the energy landscape of GPCRs, large family of proteins present in most of the membrane of eukaryotic cells that are known to behave as complex allosteric machines. The research program is focused on the study of the molecular bases, structural and dynamics, of receptor activation to provide insights in major functional processes such as ligand binding, coupling to signaling partners, biased signaling, and allosteric modulation.

Location : IBPC, Paris

<http://www.ibpc.fr/>

<http://www.ibpc.fr/UMR7099/>

http://www.ibpc.fr/UMR7099/systemes/Theme2/study_of_signal_transduction.html

Start : december 2018

Supervisor : Laurent Catoire

Grant : ANR ALLOSIG

Keywords : Energy Landscape, GPCR, Allostery, NMR, Lipid Nanodiscs

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Scientific context: the majority of hormones and neurotransmitters communicate information to cells via G protein-coupled receptors (GPCRs). The large number of biological functions they control also makes these membrane receptors one of the most prominent families of pharmacological targets in biomedicine. GPCRs exhibit complex signaling behaviors as a single receptor can activate more than one G protein subtype as well as G protein-independent pathways. As a consequence, a given drug can possess distinct intrinsic efficacies towards these different pathways, a concept described as ligand bias. Allostery further increases the complexity of GPCR functioning. Indeed, many substances can act as allosteric modulators of GPCR signaling. These include synthetic ligands, signaling proteins, lipids, or dimerization partners. It has been proposed that the remarkable functional versatility of GPCRs is associated to their intrinsic dynamic properties. In this model, GPCRs are considered as flexible proteins that can visit multiple conformational states linked to distinct functional outcomes. Signaling modulation can then be seen as an alteration of the equilibrium between such states, with the relative amount of the different populations modulated by coupling to orthosteric or allosteric ligands, to intracellular protein partners, by receptor oligomerization, or by alterations in membrane composition. Although major progresses have been made in structural biology of GPCRs thanks to numerous crystal structures, we are nevertheless only beginning to appreciate the role of these dynamics in GPCR signaling. Hence, answering the question of how GPCRs dynamics can control their downstream signaling pathways still requires a variety of additional cutting-edge biophysical methods. In this context, we propose to illuminate how dynamics govern signaling through an integrated, multidisciplinary analysis that will combine innovative tools in biochemistry to state-of-the-art experimental (NMR) and computational methods. Two different GPCRs, the ghrelin (GHSR) and low affinity leukotriene B4 (BLT2) receptors, will be considered. Besides being prototypical class A GPCRs, both are prominent pharmacological targets. GHSR and ghrelin are involved, among others, in the control of growth hormone secretion, of food intake, and of reward-seeking behaviors in alcohol and drug abuse. BLT2 is implicated in pro- and anti-inflammatory pathways. The proposed program will therefore provide unprecedented insights into the role of dynamics in major functional processes such as ligand binding, receptor activation, coupling to downstream signaling partners, biased signaling, and allosteric modulation. This is of more than academic interest since stabilization of receptor states is likely the key to modulating GPCR function in drug design.

Required skills: the candidate should have a good knowledge of biochemistry of membrane proteins (production & purification) and surfactants (detergents, lipids,...). Additional skills in biophysics, in particular NMR will be appreciated.

Net salary/month : ~2100 euros

Required diploma : Ph.D

For any additional information or to apply (with cover and recommendation letters), please contact Laurent Catoire at laurent.catoire@ibpc.fr

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