Universitat Pompeu Fabra Barcelona

Master in Bioinformatics for Health Sciences

Master project 2021-2022

Personal Information

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Project

Structural bioinformatics

Project Title:

Unraveling signaling bias at G protein-coupled receptors (GPCRs)

Keywords:

G protein-coupled receptors, molecular dynamics, data analysis, drug design

Summary:

G protein-coupled receptors (GPCRs) are the most abundant class of receptors in the human organism. They are present in almost every type of cell, and govern almost every process in the human body (i.e. cognitive and inflammatory processes or control of the cardiovascular system). Owing to their ubiquity, they are targets of more than 30% of current drugs, and every day new GPCRs are revealed to be pharmacological targets for existing diseases. GPCRs can initiate signalling through binding with several intracellular partners, which in turn elicit distinct signalling cascades. It is established that in physiological conditions, a receptor binds to each of the partners in equal proportion. Interestingly some drugs act by altering the GPCR structure so that it preferentially binds to one specific partner - a phenomenon known as signaling bias. Such ligands, named biased ligands, offer great promise, as they enable to modify pathways associated with symptoms while not modifying other pathways - which could cause side effects. However, the molecular requirements for a molecule to act as a biased agonist within a receptor are still poorly understood. Molecular dynamics (MD) is a novel and sophisticated technique that enables to simulate protein behaviour in a physiological environment. The Master student will apply this approach to study time-resolved molecular mechanisms underlying signaling bias induced by small drug-like molecules. For this, the student will be trained on setting up simulated systems, running production simulations as well as the application of a wide range of analysis tools that allow capturing subtle structural events related to signaling bias. Structural insights will be exploited for the design of a novel class of GPCR modulators with a tailored signaling profile. We expect that the results of the analysis will be published in a high impact journal, and the expertise acquired by the student will make her/him a valuable asset for pharma companies in future. We are looking for a highly motivated and skilled student with exceptional academic records that allows pursuing a PhD afterwards.

References:

Rodríguez-Espigares & Torrens-Fontanals et al. GPCRmd uncovers the dynamics of the 3D-GPCRome, Nature Methods 2020, DOI: 10.1038/s41592-020-0884-y

Expected skills::

Experience in structural biology, programming in python/bash, molecular dynamics engines (GROMACS, NAMD, etc.), analysis tools/packages (VMD, Chimera, MDtraj…) and high level of English, oral and written.

Possibility of funding::

To be discussed

Possible continuity with PhD: :

Yes