PhD thesis proposal:
Structural modeling of multidrug resistance transporters in cancer

Keywords: cancer, multidrug resistance, membrane transport protein, structural bioinformatics, molecular simulation, conformational changes, high dimensional spaces, dynamics, dynamical systems, thermodynamics.

Context: Cancer development is a complex process combining an accumulation of mutations with dynamic changes, as well as a complex cross-talk between the various types of cells involved in tumors. Unfortunately, the cellular mechanisms underlying the regulation of cancer (stem) cells (self-renewal, maintenance, differentiation, crosstalk with the tumor microenvironment) and their resistance to treatments are poorly understood, jeopardizing therapies and confusing prognosis. Uncovering these mechanisms is a pre-requisite to develop curative cancer treatments based on chemo and immunotherapies. This PhD thesis complies with this perspective, as the work envisioned ambitions to advance our understanding of multidrug resistance in cancer stem cells (CSCs), by unveiling the structural mechanisms accounting for drug efflux.

Goals: The Hedgehog (Hh) signaling pathway controls cell differentiation and is involved in the progression and metastasis of many aggressive cancers. Two mechanisms involving Hh proteins and their receptor Patched (Ptc) are key. The first one is the interaction between the Hh morphogen and Ptc, which activates CSC proliferation. Therefore, preventing this interaction is a promising strategy to inhibit CSCs proliferation. The second one is the drug efflux of Ptc which was recently discovered in our lab [BTM+12, FTS+15], an activity which may critically contribute to the resistance of CSCs to chemotherapeutic agents. Both mechanisms have remained elusive due to the lack of structural information. Ptc is indeed a protein with 12 transmembrane domains and two large extracellular domains (involved in Hh binding), whose production and crystallization still challenges experimentalists.

In this context, state-of-the-art molecular modeling techniques and experiments will be combined to unveil the aforementioned mechanisms, targeting successively structural and dynamical aspects. The models developed will benefit from state-of-the-art algorithms developed in our lab [CDM+15, RDRC16], available within the Structural Bioinformatics Library [CD17] (http://sbl.inria.fr), a software environment offering a unique spectrum of complementary building blocks to tackle multi-scale modeling of large molecular systems.

If successful, this project will make Ptc a new target for anti-cancer therapy, via the identification of interaction sites that may be targeted by novel therapeutics.

Scientific environment: This project is part of UCancer, a consortium involving 14 research groups within the newly funded IDEX UCA\textsuperscript{JEDI} (http://univ-cotedazur.fr/fr). UCancer spans all major disciplines involved in cancer studies (fundamental biology, modeling, chemistry, clinics), and offers a vibrant environment to tackle complex multidisciplinary problems.

Background: Master in structural bioinformatics or biophysics or bio-mathematics or computational chemistry.

Salary: Competitive salary 2000+ € net/month.
References


