Supervisor: Frédéric Cazals
Inria Sophia Antipolis Méditerranée
Web: http://team.inria.fr/abs
Email: Frederic.Cazals@inria.fr

Co-supervisor: Isabelle Mus-Veteau
Institut de Pharmacologie Moléculaire et Cellulaire / CNRS
Web: https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi
Email: musveteau@ipmc.cnrs.fr

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^{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

[BTM+12] Michel Bidet, Amandine Tomico, Patrick Martin, Hélène Guizouarn, Patrick Mollat, and Isabelle Mus-Veteau. The hedgehog receptor patched functions in multidrug transport and chemotherapy resistance. *Molecular Cancer Research*, 10(11):1496–1508, 2012.

[CD17] F. Cazals and T. Dreyfus. The Structural Bioinformatics Library: modeling in biomolecular science and beyond. *Bioinformatics*, 7(33):1–8, 2017.

[CDM+15] F. Cazals, T. Dreyfus, D. Mazauric, A. Roth, and C.H. Robert. Conformational ensembles and sampled energy landscapes: Analysis and comparison. *J. of Computational Chemistry*, 36(16):1213–1231, 2015.

[FTS+15] Laura Fiorini, Marie-Aude Tribalat, Lucy Sauvard, Julie Cazareth, Enzo Lalli, Isabelle Broutin, Olivier P Thomas, and Isabelle Mus-Veteau. Natural paniceins from mediterranean sponge inhibit the multidrug resistance activity of patched and increase chemotherapy efficiency on melanoma cells. *Oncotarget*, 6(26):22282, 2015.

[RDRC16] A. Roth, T. Dreyfus, C.H. Robert, and F. Cazals. Hybridizing rapidly growing random trees and basin hopping yields an improved exploration of energy landscapes. *J. of Computational Chemistry*, 37(8):739–752, 2016.