

GRAL Research proposal for PhD projects

Institute and Group: IBS- Viral Infection & Cancer Group

Supervisor I: PETOSA Carlo

Contact information: carlo.petosa@ibs.fr

Co-Supervisor II: GOVIN Jérôme

Contact information: Jerome.Govin@univ-grenoble-alpes.fr

Title of the thesis project: Investigating an epigenetic antifungal target: the RSC chromatin remodelling complex

Keywords: Invasive fungal infection, epigenetics, chromatin, nucleosome remodelling, molecular machine

Summary of the project:

Invasive fungal infections are a major global health concern, comparable in scale to malaria or tuberculosis. We recently identified an epigenetic reader domain, the bromodomain from the fungal transcription factor Bdf1, as a potential new target for antifungal therapy. Subsequent analysis of the fungal proteome and of the published literature led us to identify another epigenetic player, the RSC complex, as an alternative, potentially superior, antifungal target. In *S. cerevisiae*, the RSC complex is a 16-subunit, 1 MDa assembly that mediates numerous chromatin-related processes by sliding or ejecting nucleosomes. Several RSC subunits are essential for viability or proper fungal growth and contain druggable ligand-binding pockets, including six bromodomains. Our long-term goal is to structurally and functionally characterize the RSC complex in *Candida albicans*, a major human fungal pathogen, and to identify small-molecule inhibitors for translational development into an antifungal drug. Towards this end, the present project aims to characterize the *C. albicans* RSC complex in terms of subunit composition and nucleosome-binding activity and determine its cryoEM structure in the unbound and nucleosome-bound states. The project is a collaboration of four partner labs with complementary expertise in fungal genetics and epigenetics, proteomics, biochemistry and structural biology.