Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

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Supervisor(s):

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Host laboratory:

Lab : Institut de Biologie Structurale (IBS)

Host group/team:

Epigenetics and Molecular Pathways Group (EPIGEN)

Title of the M2 research internship:

Deciphering the epigenetic control of virulence in a major human fungal pathogen

Project summary:

Background: Fungal infections kill an estimated 3.8 million people every year – more than the combined global deaths from tuberculosis, malaria and HIV. However, fungal pathogens remain poorly studied, with key aspects of their biology and virulence still not fully understood. Among these pathogens, *Candida albicans* is a leading cause of deadly bloodstream infections in hospitals worldwide. A key determinant of its pathogenicity is its ability to switch between two distinct forms: a unicellular yeast form that spreads through the bloodstream and an invasive filamentous form that penetrates host tissues. This morphological switch is essential for infection, yet how the fungus senses its environment and chooses between these forms remains unclear.
Our laboratory has identified a *Candida* protein called Bdf1 as a promising new antifungal target. Bdf1 is a transcriptional regulator that binds chromatin by recognizing acetylated histones (DNA-packaging proteins) through specialized modules called bromodomains. Acetylation is a common epigenetic modification of specific histone lysine residues. Unlike its human counterpart, the *Candida* protein has a uniquely structured binding pocket that allows it to recognize a less common modification of these lysines, called crotonylation. In a recent breakthrough, we discovered that this structural difference enables the fungus to respond to host-derived metabolites and influences whether it adopts the yeast or invasive form. These findings suggest that Bdf1 acts as an epigenetic sensor linking the host environment to fungal virulence.

Objectives: This project aims to define how Bdf1 controls morphotype switching in *Candida albicans*. The goals of ths M2 internship are to: (1) determine whether Bdf1 directly recognizes histone crotonylation in living cells; and (2) uncover the structural basis that allows *Candida* Bdf1 to recognize crotonylated histones.

Methodology: The project combines cell biology, biochemistry and structural biology. Using live-cell fluorescence microscopy (FRAP), the student will analyze the mobility of Bdf1 in human and fungal cells in response to changes in histone crotonylation. In addition, the student will express and purify Bdf1 bromodomains and determine how they recognize crotonylated histones by solving their 3D structure by X-ray crystallography, using diffraction data collected at the ESRF synchrotron located next to our institute. Through this work, the student will gain hands-on training in fluorescence microscopy, protein purification and structural biology within an international research environment at the interface of epigenetics and host–pathogen interactions.

Keywords:

epigenetics, fungal virulence, host-pathogen interactions, live-cell imaging, structural biology

Relevant publications of the team:

1. Cooperative binding of two acetylation marks on a histone tail by a single bromodomain.
Morinière J, Rousseaux S, Steuerwald U, Soler-López M, Curtet S, Vitte A-L, Govin J, Gaucher J, Sadoul K, Hart DJ, Krijgsveld J, Khochbin S, Müller CW, **Petosa C.**
Nature 2009, 461:664-8. https://doi.org/10.1038/nature08397

2. Bromodomains: structure, function and pharmacology of inhibition.
Ferri E, **Petosa C**, McKenna CE.
Biochem Pharmacol 2016, 106:1-18. https://doi.org/10.1016/j.bcp.2015.12.005

3. Selective BET bromodomain inhibition as an antifungal therapeutic strategy.
Mietton F, Ferri E, Champleboux M, Zala N, Maubon D, Zhou Y, Harbut M, Spittler D, Garnaud C, Chauvel M, d'Enfert C, Kashemirov BA, Hull M, Cornet M, McKenna CE*, Govin J*, **Petosa C***.
Nature Commun 2017, 8:15482. https://doi.org/10.1038/ncomms15482

4. A new hope to fight invasive fungal infection. [French]
Petosa C, Govin J, Mietton F.
Med Sci 2018, 34:123-125. https://doi.org/10.1051/medsci/20183402007

5. Humanized *Candida* and NanoBiT Assays Expedite Discovery of Bdf1 Bromodomain Inhibitors with Antifungal Potential.
Wei K, Arlotto M, Overhulse JM, Dinh T-A, Zhou Y, Dupper NJ, Yang J, Kashemirov BA, Dawi H, Garnaud C, Bourgine G, Mietton F, Champleboux M, Larabi A, Hayat Y, Indorato RL, Noirclerc-Savoye M, Skoufias D, Cornet M, Rabut G, McKenna CE*, **Petosa C***, Govin J*.
Advanced Science 2025, Jan 16:e2404260. https://doi.org/10.1002/advs.202404260