Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MSc RESEARCH SCHOLARSHIP 2020-2021

RESEARCH INTERNSHIP PROPOSAL

Institute / Group

IRIG / IBS - VIC

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Research Project Title

Investigating an epigenetic pathway in a deadly emerging fungal superbug

Description of the project

Background. Invasive fungal infections cause over 1 million deaths annually worldwide, posing an urgent need for novel antifungal drugs. This is especially true for a deadly, rapidly emerging, multidrug-resistant fungal "superbug" – Candida auris – that is attracting increasing media attention (including by the BBC, CNN, CBS, New York Times, Le Parisien, Libération). **Preliminary data.** We have previously shown that an epigenetic reader module, the bromodomain (BD), is a valid antifungal target in Candida albicans (Mietton et al., 2017) and Candida glabrata (unpublished) and identified small-molecule BD inhibitors that inhibit the growth of these fungal species. **Aims.** The long-term goal is to validate BD inhibition as a suitable antifungal strategy in C. auris. Specific aims are to: (i) functionally and structurally characterize C. auris BDs in the unbound state and bound to small-molecule BD inhibitors; and (ii) assess the effect of BD inhibitors on the growth, phenotypic and virulence characteristics (e.g., biofilm formation, ability to filament) of C. auris cells. The project is a collaboration with Jérôme Govin's team at the Institute for Advanced Biosciences (IAB). **Techniques.** Protein purification, FRET-based assays, X-ray crystallography, light microscopy. **Recommended background.** Structural biology, nanosciences, biochemistry or cell biology.

Keywords

Invasive fungal infection, Candida auris, epigenetics, bromodomains, antifungal therapy

Relevant publications of the team

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*. (2017) Selective BET bromodomain inhibition as an antifungal therapeutic strategy. Nature Comm 8:15482.

Petosa C, Govin J, Mietton F. (2018) A new hope to fight invasive fungal infection. Med Sci 34:123-125.

Garcia-Saez I, Menoni H, Boopathi R, Shukla MS, Soueidan L, Noirclerc-Savoye M, Le Roy A, Skoufias DA, Bednar J*, Hamiche A*, Angelov D*, Petosa C*, Dimitrov S*. (2018) Structure of an H1-bound 6-nucleosome array reveals an untwisted two-start chromatin fiber conformation. Mol Cell 72:902-915.