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UNIVERSITÉ CÔTE D'AZUR

Master Project: Cytoplasmic crowding during morphogenesis and virulence in a human fungal pathogen

The fungus *Candida albicans* is normally a harmless commensal found on mucosal surfaces of the gastrointestinal and urogenital tract in most healthy individuals. In response to alterations of its environment, this fungal pathogen can cause superficial as well as life-threatening systemic infections, particularly aggressive in immuno-compromised individuals, including chemotherapy patients and organ transplant recipients. As an opportunistic pathogen it colonizes and infects different body sites and is responsible for one of the most predominant fungal nosocomial infections. The ability of this fungal pathogen to switch from an ovoid form to a filamentous form is critical for its virulence, in particularly its ability to invade host tissues as well as evade/escape host immune cells. Given limited available antifungal drugs, drug resistance and tolerance can lead to unsuccessful treatment and recurrent infection, that can be particularly problematic. Antifungal drug tolerance is not due to genetic changes but rather the ability of the fungus to undergo limited growth in high drug concentrations.

We have been investigating the biophysical changes in *C. albicans* cytoplasm associated both with morphogenesis and antifungal drug tolerance. In particular, we observed dramatic changes in the cell cytoplasm during filamentous growth as well as during tolerant growth in the presence of antifungal drugs target ergosterol biosynthesis, such as the widely used azole drug class. We have optimized and applied different biophysical approaches to analyze the onset and maintenance of morphogenesis and of antifungal drug tolerance, taking advantage of a range of live-cell time-lapse microscopy approaches with high spatial and temporal resolution including TIRF (total internal reflection fluorescence) and FRAP (fluorescence recovery after photobleaching). In addition, by using these approaches in strains expressing different labelled cellular compartments, taking advantage of spectrally distinct fluorescent proteins, as well as fluorescent azole drugs, we will correlate cellular changes with distinct responses to antifungal drugs and cell shape changes.

The goal of this project is to quantitate alterations in the cell with specific morphogenetic responses, responses to antifungal drugs, including growth rate, protein translation and stress responses. This project will use a combination of molecular biology, microbiology and live cell microscopy to investigate antifungal tolerance in this human pathogen.

Objectives:
- Determine the temporal order of changes in the cytoplasm during these different processes.
- Establish the causality of these cytoplasmic changes with respect to morphogenesis and drug tolerance.
- Investigate the roles of transcription and translation in cytoplasmic changes during onset filamentous growth and antifungal drug tolerance.

In this collaborative project, we aim specifically to determine the link between morphogenesis, antifungal drug tolerance and host interactions, and cytoplasmic crowding at the single cell level. The project will take advantage of cutting-edge imaging approaches, micro-fabrication, molecular genetics and image analysis to investigate relationship between the physical characteristics of the cytoplasm and fungal pathogen physiology as well as tolerance to antifungal drugs.

We are seeking highly motivated candidates with a background in Cell Biology and/or Biophysics and previous experience in live-cell imaging, image analysis or microbiology is a plus.

Interested candidates contact R. Arkowitz (robert.arkowitz@univ-cotedazur.fr)

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2) A. Serrano, C. Puerner, E. Plumb, L. Chevalier, J. Elferich, S. Diggs, L.R. Sinn, N. Grigorieff, M. Ralser, M. Delarue, M. Bassilana & R. A. Arkowitz. *Nature Microbiology*. 2026. **11**:169.
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4) R. Garcia-Rodas, H. Labbaoui, F. Orange, N. Solis, O. Zaragoza, S. G. Filler, M. Bassilana, & R. A. Arkowitz. *mBio.* 2022. **13**:e0387321.