| Title of Project: | Rest and reactivation in a major fungal pathogen: quantitative analysis of gene regulation in growth-state transitions |
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| Cell Mechanism Supervisor Name | Elizabeth Bayne |
| Quantitative Supervisor Name | Edward Wallace |


Summary of project

Cells spend long periods of time in “quiescent” states, where an apparent low level of activity hides an internal organization poised to spring into action when stimulated. RNA transcription, processing, and translation, are all crucial to enable transitions between quiescence and activity. This PhD project will address RNA regulation and growth-state transitions in the fungal pathogen *Cryptococcus neoformans*, which is a major cause of mortality in immunocompromised people and an emerging model organism. Our hypothesis is that RNA interference (RNAi) and translation regulation are employed by *Cryptococcus* to manage quiescence and reactivation. The project will be a new collaboration building on the supervisors' work, on mechanisms of RNAi (Bayne), and on translation regulation and stress responses (Wallace).

The first goal of the project is to find how RNA content and cell features change during *Cryptococcus* growth and quiescence. Highly multiplexed RNA-seq will measure RNA in wild-type and RNAi mutant cells, each grown in multiple media, over days-long timecourses. Bioinformatic analyses applied to this rich dataset will assess the major drivers of differential RNA levels including the impact of RNAi. These will be complemented by classical growth and mutant assays as well as new functional genomics tools: a library of gene deletion mutants, CRISPR/Cas9 transformation to generate new mutants, novel reporter gene systems, and ribosome profiling to measure protein synthesis. The combination of big data and new methods should produce a step change in our understanding of how fungal pathogens use RNA processing to navigate environmental transitions, generating new hypotheses for antifungal treatments.


What quantitative skills will the student acquire or develop during their PhD project?

Cell biology: fundamental microbiology, RNA methods, high-throughput sequencing, transformation including CRISPR-Cas9, modular cloning.
Quantitative skills: bioinformatics for transcriptomic analysis, statistics including multiple hypothesis testing and regression for motif analysis, data visualization, quantitative growth rate assays.