OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

Industrial CASE Studentship Advertisement – 2020-21

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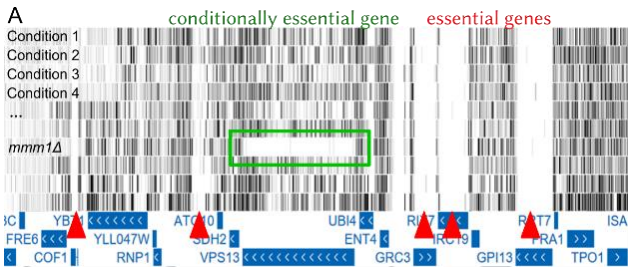
Project Title: Transposons to discover drug resistance mechanisms and their evolutionary cost

Brief description of project:

A major pitfall in the generation of novel antifungal compounds is the **emergence of resistance** caused by strong selective pressure for **mutations evading drug action**. Systematically identify such mutations will be the way forward to design drugs or combinations thereof alleviating resistance emergence.



Saturated Transposon Analysis in Yeast (SATAY) is a novel approach that allows high-throughput generation and analysis of loss-, gain- and separation-of-function mutations in *S. cerevisiae*. SATAY couples saturated transposon mutagenesis (millions of mutants with one transposon each, achieving 10-20 bp resolution genome-wide; vertical black/grey bar in Fig. A) with high-throughput sequencing, to reveal essential genes in which a transposon insertion is lethal (Fig. A, red arrowheads), as well as genes required for growth in particular conditions (Fig. A, green box). In preliminary efforts, we screened 20 antifungal compounds using SATAY.

This preliminary effort firmly established SATAY as a method of choice to unveil drug resistance mechanisms. It is now timely to exploit its full potential by tailoring it to the needs of antifungal compounds screening.

The specific questions asked herein are:

1. **What is the response of a drug-efflux-impaired *S. cerevisiae* to drug treatment?** *S. cerevisiae* is not a favoured model for drug screening because of its efficient drug efflux system. Mutant strains exist with crippled efflux that better mimic pathogenic fungi.

   Here, the student will perform antifungal screens in an efflux-crippled background and compare with previously obtained results. Any difference will point to resistance mechanisms that are relevant to (phyto-) pathogenic fungi.

2. **What is the resistance evolutionary cost?** Resistance to a drug must come at a cost. Identifying this cost will reveal potential Achille's heels in resistant strains. As we have observed, many resistance mechanisms are common to multiple drugs. Thus, their costs might

also be common. The student will perform SATAY screens on strains resistant to one or several drugs, guided by the results of our exploratory screens (i.e. strains overexpressing Pdr5, with truncated YAP1, or mutated in other pathways like Hog1, causing resistance to several compounds), with/without drug treatment. Genes normally not required for growth that become essential in resistant strains are Achille's heels to target in future combination therapies.

In that context the student will learn: Cloning, state-of-the-art molecular yeast genetics, high-throughput sequencing, Bioinformatics analysis with the R language, data analysis with machine learning, antifungal mode of action.

Most of the work will be undertaken in Oxford at the Department of Biochemistry. During the course of the studies the student will spend more than twelve weeks in Stein (Switzerland) at the Syngenta research facilities.

Attributes of suitable applicants:

We are looking for a motivated student interested in fungal plant pathogens and the appearance of resistance. The student must have a strong genetics background and the will to learn enough informatics to perform their own data analyses and code their own script.

Funding notes:

This project is funded for four years by the Biotechnology and Biological Sciences Research Council BBSRC. BBSRC eligibility criteria apply (https://www.ukri.org/files/legacy/publications/rcuk-training-grant-guide-pdf/ Annexe 1). EU nationals who do not meet BBSRC residence criteria are encouraged to contact the programme administrator to check their eligibility for BBSRC funding before submitting a formal application. Successful students will receive a stipend of no less than the standard RCUK stipend rate, currently set at £15,009 per year, which will usually be supplemented by the industrial partner.

This project is supported through the Oxford Interdisciplinary Bioscience Doctoral Training Partnership (DTP) studentship programme. The student recruited to this project will join a cohort of students enrolled in the DTP's interdisciplinary training programme, and will be able to take full advantage of the training and networking opportunities available through the DTP. For further, details please visit www.biodtp.ox.ac.uk.