PhD thesis project

Institution: INSA Toulouse, University of Toulouse

Laboratory: Toulouse Biotechnology Institute (TBI), INSA, UMR CNRS 5504 & INRAE 792, Toulouse

Team: Integrated physiology and functional genomics of microbial systems (PHYGE) (Co-head: Nathalie Gorret, DR INRAE, and Jean-Pascal Capp, MCU INSA)

Title: Mapping metabolic burden to develop resilient yeast bioproduction strains

Project description:

Achieving commercially viable microbial bioproduction of valuable heterologous small molecules depends on maintaining the integrity of highly productive engineered microbial strains throughout the complex stages of industrial scale-up. However, the invasive nature of drastically altering a microorganism's native metabolism frequently induces significant cellular stress. This physiological burden often triggers strain deterioration through the emergence of non-productive sub-populations that can outcompete their high-producing counterparts, thereby compromising or completely abolishing product accumulation.

The aim of this doctoral research project is to systematically investigate the physiological effects of common strain engineering manipulations. Specifically, the candidate shall examine how 1) the overexpression of multiple heterologous biosynthetic genes, 2) the redirection of carbon flux to boost precursor metabolites, and 3) the downregulation of competing native pathways introduces cellular stresses and impacts cellular fitness and strain integrity. By understanding these relationships, we aim to develop optimized engineering regimes preventing strain heterogeneity and deterioration.

To achieve this, the candidate will construct an extensive array of engineered *Saccharomyces cerevisiae* strains based on previously established terpenoid-producing engineered strains spanning a gradient of genetic modifications, covering different intensities of heterologous and native gene expression or repression. The candidate will then collect a comprehensive multi-omics data set to map the effects of these invasive manipulations. This analytical approach will employ transcriptomic analysis to monitor established stress markers and identify novel indicators of metabolic burden, alongside metabolomic analysis of products, intermediates and native precursors to assess metabolic perturbations. Furthermore, flow cytometry-based methods will be utilized to monitor real-time strain heterogeneity and population fitness.

The resulting multi-factorial data will be utilized to construct a predictive model to identify risks to production integrity. Ultimately, this project seeks to transform these insights into the development of robust, high-performance production strains capable of meeting the rigorous demands of industrial biomanufacturing.

Keywords: **Microbial bioproduction, yeast strain engineering, metabolic burden, heterologous gene expression.**

Expected skills: The candidate should hold a master's degree or equivalent in biotechnology, biochemistry, microbiology or similar. Mandatory: Plasmid construction, microbial culture. Additional: Analytical chemistry, gene expression analysis, statistical modelling. A good level of written and spoken English is required.

Application: Candidates are invited to submit their CV, a covering letter and two academic references by July 1st, 2026 to **capp@insa-toulouse.fr**.

Starting date: 1 October 2026.