NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Reg. No. 200604393R

Research Theme:

Research Project Title: Identify Essential Genes to Construct a Functional Unfolded Protein Response Programme Using Synthetic Biology

Principal Investigator/Supervisor: Guillaume Thibault

Co-supervisor/ Collaborator(s) (if any):

Project Description

a) Background: Stress pathways monitor intracellular systems and deploy a range of regulatory mechanisms upon stress. One of the best characterised pathway with wide implications in diseases, the unfolded protein response (UPR), is the endoplasmic reticulum (ER) guarding to maintain homeostasis. In eukaryotes, the UPR comprises of three highly conserved transducers leading to the regulation of hundreds of gene targets by activating UPR-specific transcription factors. Developed UPR inhibitors to treat diseases have serious potential long term side effects on the functions of the pancreas, the immune system, and the liver as the UPR programme is too broad to be inhibited from the upstream players. Thus, being unable to inhibit a subset of downstream players part of the UPR programme might yield better success but the characterisation of such players, in different stress conditions, is still poorly understood. We propose to reconstruct the human minimal pathway required to restore homeostasis in a synthetic Saccharomyces cerevisiae system based on inter-species network alignments and identification of the conserved components of the programme. We aim to identify and validate the minimum conserved components of the three human UPR branches (ATF6, Ire1α, and PERK) to restore ER homeostasis. The minimal UPR programme will be incorporated in yeast using the Synthetic Chromosome Rearrangement and Modification by LoxP-Mediated Evolution (SCRaMbLE) system. This system is highly flexible allowing constant alteration to optimise the minimal UPR programme. Findings from our novel synthetic yeast system will be critical to develop targeted therapeutic approaches to prevent chronic ER stress while maintaining homeostasis.

b) Proposed work: The candidate will develop, test and validate the humanized UPR programme in yeast in an attempt to identify the minimal UPR circuit required to restore ER homeostasis.

Supervisor contact:

If you have questions regarding this project, please email the Principal Investigator: thibault@ntu.edu.sg

SBS contact and how to apply:

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Please apply at the following:

http://admissions.ntu.edu.sg/graduate/R-Programs/R-WhenYouApply/Pages/R-ApplyOnline.aspx

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