4.1 *FINAL PUBLISHABLE SUMMARY REPORT*

PUBLISHABLE SUMMARY

A cell's survival depends on its ability to mount a successful stress response when challenged by exposure to damaging agents. Oxidative stress caused by an excess of reactive oxygen species, is known to damage cellular components. Coordination of the complex and rapid stress response is central to the cell's viability after acute exposure. In humans, oxidative stress is involved in aging, cancer, atherosclerosis, Alzheimer's and Parkinson's disease among others.

PhenOxiGEn investigates the mechanisms that regulate the oxidative stress response by associating genetic factors to phenotype when the cell is challenged by oxidative stress. The project exploits different strains of fission yeast using a range of genome-wide analyses to interrogate the stress response and its regulation at different levels and under diverse genetic backgrounds. A large and coordinated body of heterogeneous quantitative data is being generated and integrated with published information. Using these data, we not only describe the cellular stress response at a much more comprehensive and detailed level than before, but also we address fundamental biological questions such as how natural genetic variability affects a cell's ability to cope with stress, contributing to a systems-level understanding of the oxidative stress response.

An increasingly effective way of studying the interactions between genome and environment is through genome-wide association studies (GWAS), which are used for investigating genetic association with complex traits. PhenOxiGEn is taking such an approach by correlating molecular and cellular traits with genetic variation in order to identify genomic regions impacting on a cell's ability to cope with oxidative stress. At the heart of PhenOxiGEn is a library of genetically diverse fission yeast strains. The ability of these strains to respond to oxidative stress has been investigated using continuous growth assays and measuring a wide range of molecular properties, such as RNA and protein concentrations. These data have been the basis of a large integrative quantitative trait locus (QTL) analysis, allowing the identification of genetic factors explaining phenotypic variability between the individual strains. The consortium has established numerous innovative technologies enabling these measurements at an unprecedented scale beyond initially planned goals. The group of J. Bähler (UCL) has established RNA sequencing using deep sequencing technology, making it possible to simultaneously genotype a large number of segregant strains and measure RNA concentration at much higher precision as compared to microarrays. Another example is the development and advancement of targeted proteomics in the laboratory of R. Aebersold (ETH), which has enabled the measurement of much more proteins as initially planned. The group of C. Workman (DTU) has tested and established a robot-assisted automatic phenotyping method allowing time-resolved precise measurements of growth phenotypes. Here, PhenOxiGEn also goes beyond the initial plans, which did not consider time-resolved phenotyping. Finally, the group of A. Beyer (TUD) has developed new computational methods for the analysis of RNA-seq data, for the prediction of protein interactions, and for the identification of genetic loci that affect the respective phenotypes (i.e. QTL mapping). These computational methods have been applied to relatively small budding yeast (*S. cerevisiae*) datasets revealing novel insights into the impact of natural genetic variation on post-transcriptional regulation.

PhenOxiGEn is the most comprehensive project of its type studying how natural genetic variation impacts on molecular and cellular traits. The project has created the foundation for similar work in higher organisms, especially humans. The experimental and computational technologies that have been developed will be applied to human GWAS and new insights have been obtained into how an individual's ability to cope with cellular stress might be affected by its genotype.